


REVIEW

Circular RNAs in human diseases

Yuanyong Wang^{1,2,#} | Jin Zhang^{3,4,#} | Yuchen Yang^{3,4} | Zhuofeng Liu⁵ |
Sijia Sun^{3,4} | Rui Li⁶ | Hui Zhu^{7,8} | Tian Li⁹ | Jin Zheng^{3,4,*} | Jie Li^{10,*} |
Litian Ma^{1,3,4,11,12,*} 

¹Department of Thoracic Surgery, Tangdu Hospital, Air Force Medical University, Xi'an, China

²Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), The First Department of Thoracic Surgery, Peking University Cancer Hospital and Institute, Peking University School of Oncology, Beijing, China

³Department of Traditional Chinese Medicine, Tangdu Hospital, Air Force Medical University, Xi'an, China

⁴Key Laboratory of Integrated Traditional Chinese and Western Medicine Tumor Diagnosis and Treatment in Shaanxi Province, Xi'an, China

⁵Department of Traditional Chinese Medicine, The Third Affiliated Hospital of Xi'an Medical University, Xi'an, China

⁶Department of Epidemiology, School of Public Health, Air Force Medical University, Xi'an, China

⁷Department of Anatomy, Medical College of Yan'an University, Yan'an, China

⁸Institute of Medical Research, Northwestern Polytechnical University, Xi'an, China

⁹School of Basic Medicine, Fourth Military Medical University, Xi'an, China

¹⁰Department of Endocrine, Xijing 986 Hospital, Air Force Medical University, Xi'an, China

¹¹Department of Gastroenterology, Tangdu Hospital, Air Force Medical University, Xi'an, China

¹²School of Medicine, Northwest University, Xi'an, China

*Correspondence

Litian Ma and Jin Zheng Department of Traditional Chinese Medicine, Tangdu Hospital, Air Force Medical University, Xi'an, China.

Email: malitian1234@fmmu.edu.cn; malitian1234@163.com and zjddln@163.com

Jie Li, Department of Endocrine, Xijing 986 Hospital, Air Force Medical University, Xi'an, China.
Email: wangwj1978@126.com

Funding information

Joint Research Project of the China Science and Technology Development Center of Traditional Chinese Medicine; Talent Exchange Center of the National Administration of Traditional Chinese Medicine, Grant/Award Number:

Abstract

Circular RNAs (circRNAs) are a unique class of RNA molecules formed through back-splicing rather than linear splicing. As an emerging field in molecular biology, circRNAs have garnered significant attention due to their distinct structure and potential functional implications. A comprehensive understanding of circRNAs' functions and potential clinical applications remains elusive despite accumulating evidence of their involvement in disease pathogenesis. Recent research highlights their significant roles in various human diseases, but comprehensive reviews on their functions and applications remain scarce. This review provides an in-depth examination of circRNAs, focusing first on their involvement in non-neoplastic diseases such as respiratory, endocrine, metabolic, musculoskeletal, cardiovascular, and renal disorders. We then explore their roles in tumors, with particular emphasis on exosomal circular RNAs, which are crucial for cancer initiation, progression, and resistance to treatment. By detailing their biogenesis, functions, and impact on disease mechanisms, this

[#]Yuanyong Wang, Jin Zhang contributed equally to this work and share first authorship.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2024 The Author(s). *MedComm* published by Sichuan International Medical Exchange & Promotion Association (SCIMEA) and John Wiley & Sons Australia, Ltd.

CXZH202307; Single Disease Library Project of the Air Force Medical University, Grant/Award Number: 2023LC2339; Clinical Research General Program of the Air Force Medical University, Grant/Award Number: 2023LC2330; Second Batch of Research Projects of the Science and Technology Department of Shaanxi Province, Grant/Award Number: 2024SF-YBXM-176; Natural Science Basic Research Program of Shaanxi Province, Grant/Award Number: 2021JM-245; Social Talent Fund of the Second Affiliated Hospital of the Air Force Medical University, Grant/Award Number: 2023YFJH016

review underscores the potential of circRNAs as diagnostic biomarkers and therapeutic targets. The review not only enhances our understanding of circRNAs' roles in specific diseases and tumor types but also highlights their potential as novel diagnostic and therapeutic tools, thereby paving the way for future clinical investigations and potential therapeutic interventions.

KEYWORDS

biomarker, cancers, circular RNAs, exosome, prognosis, progression

1 | INTRODUCTION

Circular RNAs (circRNAs), initially considered splicing byproducts or degradation-resistant intermediates, have gained recognition through advanced detection technologies for their diverse roles as noncoding RNAs containing hundreds to thousands of nucleotides.¹ They form closed loops by linking 3'- and 5'-terminals of linear RNAs, with biogenesis processes including reverse splicing across viral, eukaryotic, and prokaryotic genomes.² Classified into intronic circRNAs (ciRNAs),³ exonic circRNAs (EcircRNAs),⁴ and exon-intron circRNAs (EicRNAs),⁵ circRNAs play crucial roles in RNA processing and gene expression regulation, influencing various biological activities.^{6–10}

Delving deeper into their implications beyond biogenesis, circRNAs exhibit significant involvement in non-neoplastic diseases.^{11,12} They are increasingly associated with respiratory diseases, metabolic disorders such as diabetes and obesity, musculoskeletal diseases like rheumatoid arthritis (RA), cardiovascular diseases (CVDs) including heart failure (HF) and atherosclerosis, and renal diseases including kidney injury and fibrosis. This broad spectrum highlights circRNAs as potential biomarkers and therapeutic targets across diverse medical conditions.

Transitioning to cancer, circRNAs emerge as pivotal players in tumorigenesis, tumor progression, and therapeutic resistance, addressing persistent challenges in cancer diagnosis and treatment.^{13,14} Extracellular vesicles (EVs), particularly exosomes, are explored as carriers of circRNAs, offering insights into cancer biology^{15,16} and resistance mechanisms^{17–19} (Figure 1). EVs, enriched with biomolecules like proteins, nucleic acids, and lipids, hold promise for revolutionizing cancer diagnostics and treatments through liquid biopsy approaches.^{20–22}

In summary, this review comprehensively explores circRNAs' multifaceted roles across human diseases, underscoring their potential in clinical diagnostics, prognostics, and therapies. By elucidating circRNA dysregulation mechanisms and their implications, this review aims to provide valuable insights into leveraging circRNAs for improved disease management and patient outcomes.

2 | FUNCTION OF circRNAs

In this section, we explore the diverse functions of circRNAs, elucidating their pivotal roles in RNA processing and gene regulation. By examining their formation mechanisms and structural characteristics, we highlight how circRNAs serve as critical intermediates and regulators in cellular processes. This section aims to underscore the functional versatility of circRNAs and their implications across various biological contexts.

2.1 | CircRNAs origin and activity

CircRNAs represent novel endogenous ncRNAs that contain covalently closed loop structures but without 3'-polytails, 5'-caps, or polyadenylated tails.²³ CircRNAs regulate themselves independently of their linear transcripts due to their evolutionarily conserved structure and cell-specific expression profiles.^{24,25} As discovered by Li et al.²⁶ through RNA-seq, there are numerous exosomal circRNAs (exocircRNAs), and they are new, stable RNAs existing in exosomes. CircRNAs are suggested to exist in cell RNAs and migrate into exosomes; then, molecular information can be transferred to the recipient cells.^{27,28}

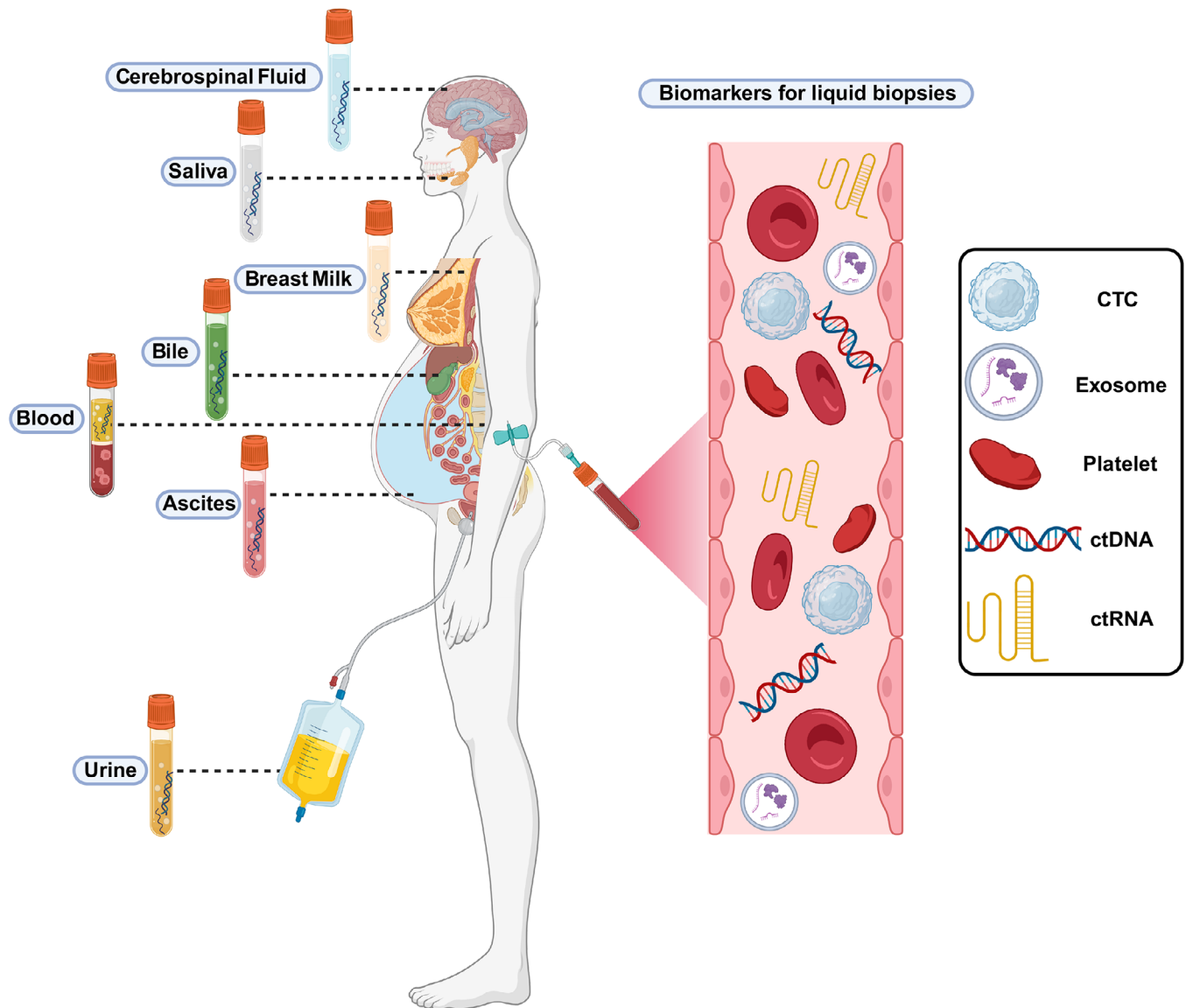


FIGURE 1 Liquid biopsy of tumors. This figure elucidates the concept and fundamental components of liquid biopsy. It delineates various bodily fluids as potential sources and underscores critical biomarkers such as ctDNA and ctRNA for the detection and monitoring of cancer. The diagram accentuates the interrelationship between bodily fluids and the human body, thereby illustrating the simplicity and convenience of liquid biopsy in the context of cancer diagnosis and surveillance. (ctDNA, circulating tumor DNA; ctRNA, circulating tumor RNA).

2.2 | miRNA sponges

CircRNAs can function as competitive endogenous RNAs (ceRNAs), which are rich in binding sites for miRNAs (also referred to as miRNA response elements [MREs]), and they show competitive binding to miRNAs, thereby removing the inhibition against downstream targets, thus affecting the transduction of intracellular signals and the expression of target genes.^{29,30} The function of circRNAs as miRNA sponges represents the classic model of their function.^{31,32} For instance, the cerebellar degeneration-

related protein 1 antisense, or circRNA sponge for miRNA (miR)-7 (ciRS-7), as identified by Hansen et al.³³ exhibited a negative regulatory effect on miR-7 levels. Additionally, over 70 binding domains for miR-7 were discovered in ciRS-7, which exhibited high expression in HEK293 cells while binding as many as 20,000 miR-7 molecules per cell. Moreover, circRNA-PVT1 silencing has been suggested to suppress sirtuin 7 by increasing miR-3666 expression, eventually inhibiting hepatocellular carcinoma (HCC) cells in proliferation and metastasis.³⁴ Furthermore, circRNAs can function as miRNA sponges in humans and in parasites including nematodes.³⁵ Additionally, circRNAs

that can sponge miRNAs have been detected in plants such as citrus,³⁶ wheat,³⁷ and *Arabidopsis*.³⁸

2.3 | Involvement in translation

Although circRNAs were once thought to be ncRNAs, they have recently been found to be associated with peptide/protein translation, refuting the widely accepted theory.^{39–42} When circRNAs contain the internal ribosome entry site (IRES), eukaryotic ribosomes are thought to initiate translation from such circRNAs.^{43,44} For instance, circ-PINT is translated through the IRES into PINT87aa polypeptide, containing 87 amino acids. PINT87aa can interact with the polymerase-associated factor complex gene, thereby inhibiting glioma occurrence.⁴⁵ In circRNAs, their IRES domains are later estimated as the binding sites for numerous RNA-binding proteins (RBPs), such as PTB and HUR, and they regulate IRES element-mediated protein translation.⁴⁶ Based on further research developments, circRNAs that do not contain IRES elements have been found to be translated into various functional proteins. For instance, N6-methyladenosine (m6A) has a certain impact on mRNA translation in the case of heat shock stress and can modulate circRNAs translation.^{42,47} This may be related to m⁶A modification via the methyltransferase like (METTL)3/METTL14–WTAP protein complex, FTO-mediated m⁶A de-modification, and the m⁶A modification-containing site that initiates protein translation through recruiting YTHDF3 and subsequent eIF4G2, thus shedding more light on circRNA chemical modifications.⁴⁸ In addition, circRNAs are found to utilize overlapping codons in protein translation, representing a unique translation approach.⁴⁹ As discovered, circ-AKT3 can produce the new functional protein AKT3-174aa using overlapping codons. The latter can bind to p-PDK1 to impact AKT2/3 phosphorylation, thereby exerting negative regulation on the PI3K/AKT pathway and suppressing brain tumor genesis and progression.⁵⁰ This unique translation process is significant for investigating the novel activities of circRNAs.

2.4 | Protein–circRNA interactions

To regulate protein levels, circRNAs function as protein sponges and can bind to RBPs to form RNA–protein complexes.^{51,52} For instance, MBL, an RNA splicing factor, can bind to the parent gene at the second exon, thereby promoting its cyclization to form circ-MBL in *Drosophila*.⁵² Meanwhile, many sites exist in circ-MBL, which can bind to MBL protein and reduce MBL's effective content.⁵² Additionally, circRNAs interact with specific target pro-

teins, playing roles in cellular division, proliferation, and apoptotic processes.⁵³

For instance, circ-Foxo3, in combination with cyclin-dependent kinase 2 (CDK2) and cyclin-dependent kinase inhibitor 1 (p21), forms the circ-Foxo3–p21–CDK2 ternary complex, thereby inhibiting CDK2 activity and blocking the cell cycle. Furthermore, endogenous circ-Foxo3 knockdown enhances cell proliferation.⁵⁴ As discovered in another study, circ-ANRIL binds with PES1 protein, which suppresses the binding to pre-rRNA and the exonuclease-regulated maturation of rRNA. Therefore, circ-ANRIL decreases ribosomal biogenesis, thereby activating p53, subsequently increasing apoptosis, and decreasing proliferation.⁵⁵ AKT and cardiomyocyte survival can both be improved by the upregulation of circAmotl1 in neonatal cardiac tissue. AKT1 and PDK1 are bound by circAmotl1, which activates nuclear translocation and phosphorylation of AKT.⁵⁶ As proteins possess numerous activities, further investigations are needed to explore the protein-binding activity of circRNAs.

2.5 | Gene transcriptional regulation

EIcRNAs and ciRNAs exhibit competitive regulation of parental gene transcription via linear splicing. CiRNAs act as active regulatory factors for RNA polymerase (Pol) II, which in turn can regulate parental gene transcription.⁵⁷ EIcRNAs interact with U1 small nuclear RNA (snRNP) to form the EIcRNA–U1 snRNP complex, which further interacts with the RNA Pol II transcriptional complex, affecting parental gene expression.^{5,52} Noncoding intron transcripts, like ci-ankrd52, can positively regulate the transcription by RNA Pol II, and exhibit cis-regulation of the parental coding genes; moreover, they are associated with the RNA Pol II extension mechanism.³ According to a 2020 study, circ-DAB1 increases the recombinant signal-binding protein level of the immunoglobulin kappa J region (RBPJ), thereby enhancing RBPJ's binding to the promoter of DAB adaptor protein 1 (DAB1) and promoting DAB1 transcription⁵⁸ (Figure 2).

2.6 | Exosomal-circRNAs in cancer

Most types of cells release exosomes, which are small EVs originating from endocytosis.^{59,60} Exosomes function as mediators of intercellular communication throughout tumorigenesis. Additionally, circRNAs can be loaded into exosomes to create exosomal-circRNAs (exo-circRNAs), which transport their cargo molecules horizontally to recipient cells, communicating with nearby or distant cells.⁶¹ Exo-circRNAs modify biological signaling path-

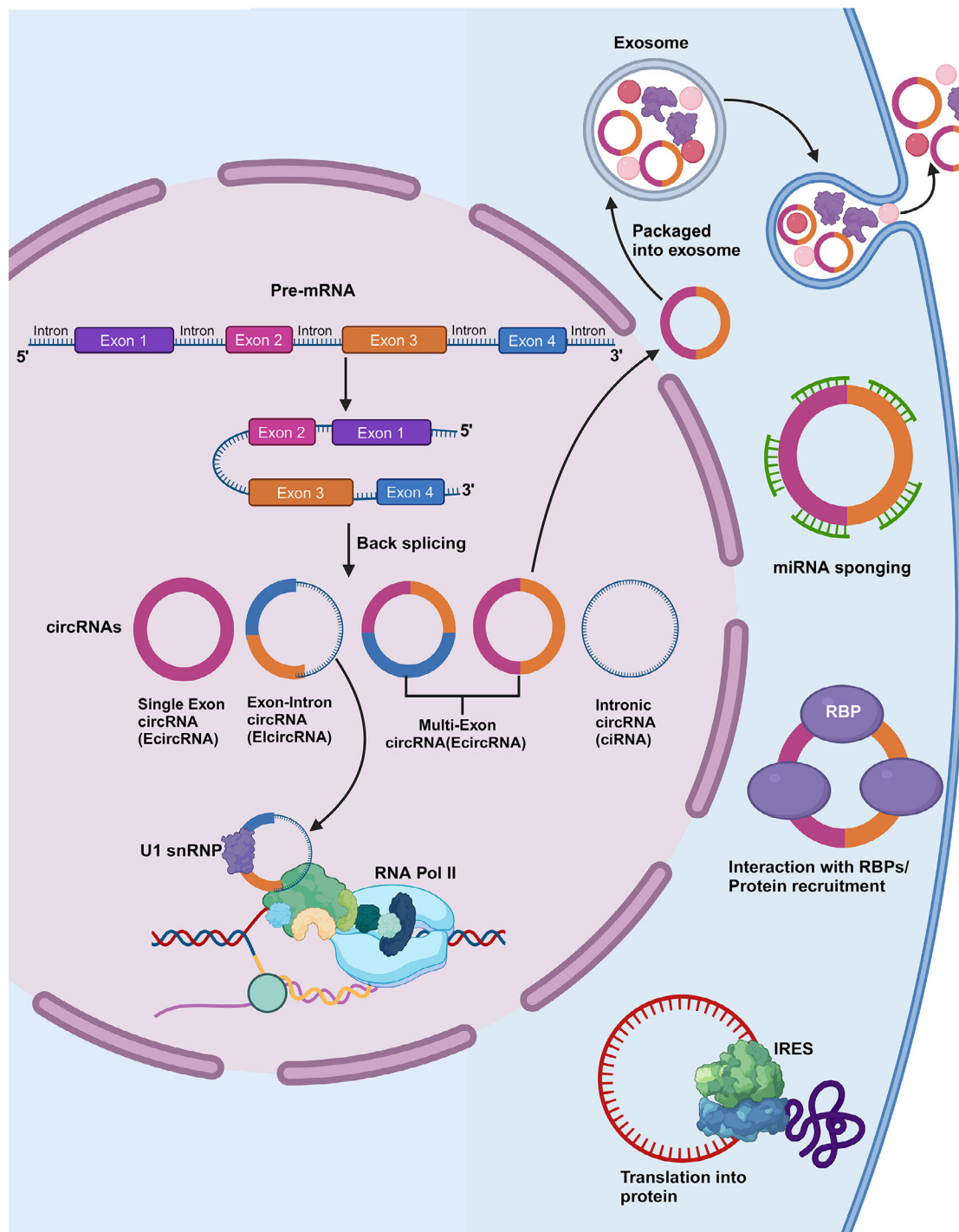


FIGURE 2 Major activities of circRNAs. This figure elucidates the multifaceted processes involved in eukaryotic gene expression, encompassing transcription within the nucleus and translation in the cytoplasm. It underscores critical stages such as pre-mRNA splicing, miRNA sponging, interactions with RBPs, packaging into exosomes, and ultimately, protein translation. The illustration emphasizes the intricate interplay of molecular machineries and regulatory mechanisms that govern these processes. (RBPs, RNA binding proteins).

ways, affecting the onset and progression of cancer. According to a recent study, circLPAR1 levels are reduced in colorectal cancer (CRC) tissues and are encapsulated in exosomes. Additionally, the level of circLPAR1 in plasma exosomes is considerably lower during CRC progression but reverts postoperatively.⁶² Currently, two theories may

elucidate how exo-circRNAs function: circRNA clearance and cell communication.^{63,64} According to Huang et al.,⁶³ exocircRNA-100338 increases the metastatic capacity of HCC cells when delivered to recipient cells inside EVs. Conversely, since circRNAs are more abundant than linear forms in EVs, Lasda and Parker⁶⁴ proposed

TABLE 1 Methods for detecting and quantifying circRNA.

Method	Sensitivity/accuracy	Throughput	Advantages and disadvantages	References
Northern blotting	Low	Low	Gold standard analysis of circRNA validation; insensitive to low expression of circRNA	3,69–72
RT-qPCR	Medium-high	Low-medium	Provide quantitative data; false positive signal may be generated	70,73,74
RCA	High	Medium	Simple operation, no need for high-precision temperature cycle and additional separation steps.	75,76
NanoString Technologies nCounter assays	High	Medium-high	Quantify circRNA; requires special equipment and is expensive	77
Microarrays	Medium	High	High throughput and high detection efficiency; difficult to compare between different studies	69,78,79
FISH	High	Low	Forming stable DNA-RNA hybrid; highly affected by personnel operations and instrumentation and costly	80,81
RNA-seq	Medium-high	High	Widely used in the discovery of novel circRNAs; overlap with linear molecular signals, data processing capabilities are required	82–85

Abbreviations: FISH, fluorescence in situ hybridization; RCA, rolling circle amplification; RNA-seq, RNA-sequencing; RT-qPCR, reverse transcription quantitative real-time PCR.

that exosomes may use EVs to remove endogenous cellular circRNAs. Nevertheless, Alhasan et al.⁶⁵ hypothesized that exosomal exonucleases are responsible for circRNA enrichment in exosomes. Exosomes are easily accessible and protect the RNAs in different human biofluids from degradation, irrespective of the mechanism involved. All of these discoveries suggest that exo-circRNAs may be useful biological markers and treatment targets for human diseases.

2.7 | CircRNA detection and characterization

Over the past few decades, researchers have identified over 100,000 distinct human circRNAs.^{66,67} Nevertheless, due to their distinct circular morphology, low abundance, and absence of 5'-caps and 3'-poly (A) tails, circRNAs are challenging to accurately identify and detect using standard approaches.⁶⁸

The initial identification and characterization of circRNAs involved using Northern blotting and PCR methods (Table 1).⁶⁹ The most accurate method for validating circRNA is Northern blotting, which utilizes RNA probes for hybridization and denatured polyacrylamide gel electrophoresis to separate circRNAs into their linear counterparts.^{3,70,71} However, low-abundance circRNAs are difficult to identify by Northern blotting, and there is no high-throughput detection method available.⁷² The most popular technique for circRNA analysis is RT-qPCR,

which uses a series of primers to amplify circRNA fragments and detect circRNA at the position flanking the BSJ locus.^{70,73} CircRNA molecules may yield false positive results in reverse transcription due to rolling circle replication and strand displacement.⁷⁴

The circular morphology of circRNAs makes for a perfect template for the process of rolling circle amplification (RCA), making rolling RCA, a recently established technology, highly appropriate for circRNA analysis.⁷⁵ The benefits of the reverse transcription RCA approach are ease of use and low cost while selectively amplifying target circRNAs.⁷⁶ CircRNA detection using enzymes eliminates the requirement for primers. A DNA/circRNA hybrid is digested by duplex-specific nucleases, which release a fluorescent probe fragment and circRNA that enhances the fluorescence signal when exposed to target circRNA.⁸⁶ The most recent technique for precise and sensitive circRNA detection is the nCounter assay from NanoString Technologies. Without enzymatic reactions or bias, NanoString correctly quantifies circRNA using dual-probe hybridization containing biotinylated capture probes as well as distinctive color-coded reporter probes.⁷⁷ Nonetheless, this approach necessitates expensive specialized equipment. Microarrays are a popular high-throughput assay with strong sensitivity and accuracy for circRNA identification. These tests are appropriate for circRNA expression research since they are unaffected by lower transcript expression levels.^{78,79} Nevertheless, it might be challenging to compare microarray data from different investigations.⁶⁹ Fluorescence in situ hybridization is a popular method

for studying the subcellular localization of RNA, using fluorescently labeled DNA probes.^{80,81} However, this method takes a lot of time and costly signal-detecting apparatus.⁶⁹

The discovery of circRNAs and advances in biological research have both been considerably accelerated by the advent of RNA-seq technology.^{82,83} Before short-read deep sequencing, circRNAs had to be biochemically enriched due to their low abundance in vivo and the absence of poly(A) tails.⁶⁸ RNase R treatment significantly enriches circRNAs in samples.^{73,87} For preliminary circRNA analysis, rRNA depletion is often utilized instead of poly(A) screening and transcriptomic sequencing before sequencing and building circRNA libraries.⁸⁴ Numerous circRNAs have been discovered using ribo-RNA sequencing, which also provides data on the expression profiles of coding and noncoding RNAs.⁸⁸ Ribo-RNA-seq allows for direct quantitative comparison of the expression levels of circRNAs and their cognate linear RNAs.⁸⁹ However, this method results in overlapping circRNA and linear RNA signals that cannot be distinguished in exonic areas.⁸⁵ Numerous human genes that produce circRNA isoforms have been identified using the poly(A)-RNA-seq method, which is suitable for circRNAs lacking poly(A) tails.⁹⁰ Small circRNAs might not be detected by this method, and it may also struggle to accurately detect and quantify unusual circular isoforms.⁹⁰ Compared with ribo- or poly(A)-RNA-seq, the RNase R RNA-seq approach may detect a greater number of individual circRNAs, thereby maximizing circRNA enrichment.^{70,71} A straightforward, accurate, sensitive, and efficient technique for the analysis and detection of circRNA is still needed.

2.8 | Application of CircRNAs

CircRNAs have attracted more attention due to their distinctive structure, immunogenicity, stability, and potential biological benefits. CircRNAs represent a stable alternative to mRNA-based treatments and may serve as a complement using adeno-associated vector technology.^{91,92} Nanoformulations of circRNA delivery containing IRES have demonstrated a prolonged translational period.^{91,93} The SARS-CoV-2 circRNA vaccine demonstrated long-lasting antigen synthesis and the ability to generate neutralizing antibodies.⁹⁴ The team from Peking University, led by Prof. Wei, developed a circRNA vaccine for COVID-19's Delta variant for the first time. The vaccine provided broad-spectrum defense against several novel coronavirus strains.⁹⁴ However, developing methods to enhance circRNA synthesis and transport, and to attenuate the cellular

immune response caused by circRNA, remains a challenge and requires further investigation and improvement.^{95,96}

Numerous diseases, including autoimmune disorders, cancer, liver disorders, neurological disorders,^{97–99} cardiovascular disorders, and diabetes, are accompanied by dysregulated circRNA expression.^{85,100–103} Numerous DNA, RNA, and protein-based biological markers are currently used in clinical settings as tools for disease diagnosis.¹⁰⁴ CircRNAs are excellent candidates for biological markers, as they are not readily broken down by nucleic acid exonucleases and have a significantly longer half-life compared with linear RNAs.¹⁰⁵ CircRNAs are abundantly expressed in the urine, saliva, gastric juice, and blood of prostate cancer patients, suggesting they could serve as biological markers for early cancer detection.^{66,106–109} Prostate cancer diagnosis was significantly enhanced in clinical studies by combining circRNA detection with prostate-specific antigen testing.¹¹⁰

CircRNAs have also been identified as potential clinical treatment targets for a variety of diseases. F-circRNA, for instance, promotes cellular survival, transformation, and therapy resistance in acute promyelocytic leukemia, thus representing a potential therapeutic target for disease management.¹¹¹ CircSLC8A1 is abundantly present in the heart, and its suppression in vivo alleviates myocardial ischemia–reperfusion (I/R) injury and cardiac hypertrophy caused by stress overload.^{112,113} CircRNA treatments are still in the early stages of development, and numerous challenges still need to be addressed. Designing and optimizing circRNA overexpression vectors, enhancing cyclization, creating effective delivery methods, improving chemical production processes, and controlling process development are significant challenges.⁸⁴ Although much remains to be learned about circRNAs, they are anticipated to become a powerful tool for clinical diagnosis and treatment in the near future.

3 | CircRNAs IN NONCANCER DISEASES

This section delves into the involvement of circRNAs in non-neoplastic diseases, ranging from respiratory and metabolic disorders to musculoskeletal and cardiovascular conditions. By exploring specific examples and underlying mechanisms, we illuminate how dysregulated circRNAs contribute to disease pathogenesis and their potential as diagnostic biomarkers and therapeutic targets. This discussion aims to provide a comprehensive understanding of circRNAs' roles beyond cancer biology.

3.1 | CircRNAs in respiratory diseases

3.1.1 | CircRNAs in COVID-19

COVID-19 research on differentially expressed circRNAs (DEcircRNAs) is sparse, but holds promise for shedding light on DEcircRNAs post-SARS-CoV-2 infection and their distribution across various samples. A genome-wide dynamic analysis identified over 5000 circRNAs at diverse genomic locations in human lung epithelial cells infected with SARS-CoV-2.¹¹⁴ In addition, DEcircRNAs were detected in whole-blood samples from recurrent COVID-19 cases compared with healthy controls.¹¹⁵ Infection with SARS-CoV-2 may disrupt the expression of host circRNAs in the blood. A distinct expression profile of circRNAs has been observed in cerebrospinal fluid among COVID-19 cases, healthy controls, and neurological disease cases.¹¹⁶ It is essential to investigate potential overlaps or differences in DEcircRNA types between neural cells and blood cells, given the tissue- and cell-specific expression of circRNAs. Using techniques such as single-cell RNA sequencing and spatial transcriptomics sequencing, we could gain a deeper understanding of SARS-CoV-2's systemic effects.

Possible mechanisms of circRNAs underlying SARS-CoV-2 infection

CircRNAs sponge miRNAs to influence viral replication. CircRNAs, which show a high evolutionary conservation degree, exhibit tissue- and cell-specific expression patterns.^{117–119} CircRNAs containing miRNA-responsive elements are the vital components of ceRNA network, which can modulate the expression of downstream target genes through sponging microRNAs (miRNAs), swiftly binding to specific miRNAs, and alleviating their inhibition against messenger RNAs (mRNAs) translation. Clearly, circRNAs containing miRNA-responsive elements can effectively sponge miRNAs in the ceRNA network in order to impede the miRNA-dependent target gene modulation.^{33,120} CircRNAs are verified to have higher sponging activities than long noncoding RNA (lncRNA) transcripts and linear miRNAs.^{70,121} Arora et al.¹²² recently detected the ceRNA network within SARS-CoV-1-infected cells, which comprised a lncRNA (Gm26917), a miRNA (MMU-miR-124-3p), a mRNA (Ddx58), a transcription factor (TF) (Stat2), together with two circRNAs (C330019G07Rik, Ppp1r10). The RIG-I/Ddx58 receptor in this ceRNA network interacts with SARS-CoV-1 nsp13, which initiates the viral life cycle (Figure 3A). Ddx58 also participates in mRNA splicing and miRNA biosynthesis. The increased expression can result in miRNA splicing reprogramming, which decreased miRNA expression. miR-124-3p upregulation induces Ddx58 degradation,

leading to decreased viral replication. Moreover, miR-124-3p can regulate Toll-like receptor (TLR)-dependent innate immunity via Stat3, therefore downregulating TNF- α and IL-6.¹²³ The above findings indicate a potential similar role of miR-124-3p in modulating Stat2, impacting viral life cycle. In the ceRNA network, two circRNAs (C330019G07Rik and Ppp1r10) execute crucial modulating functions as the miR-124-3p sponges to inhibit Ddx58 degradation, which can affect SARS-CoV-1 replication. Additionally, as observed by Zhang et al.,¹²⁴ host circRNAs mainly served as the miRNA sponges to influence MERS-CoV replication. From Figure 3B, hsa_circ_0067985 originates in FNDC3B gene, which sponges hsa-miR-1275, while hsa_circ_0006275 originates in CNOT1 gene and sponges hsa-miR-2392. These two circRNAs show significant upregulation during MERS-CoV infection, thereby regulating the expression of key downstream target genes including MYO15B, MAP3K9, MEF2C, SPOCK1, ZBTB11, and USP15. Collectively, the findings provide novel insights into the circRNA regulation and associated signaling pathways, presenting potential host-targeted antiviral measures to resist SARS-CoV-2 infection.

CircRNAs affect cytokines to regulate the immunity against SARS-CoV-2 infection. CircRNAs exert a vital role in preventing viral damage by regulating the immunity in host-virus interaction.¹²⁵ According to Li et al.,¹²⁶ NF90/NF110, originating in human interleukin-enhanced binding factor 3 (ILF3), made a direct impact on governing back-splicing and collaboration with circRNA generation during viral infection. In the case of viral invasion, NF90/NF110 translocates into nucleus, which partly contributes to a reduction in circRNA production. The accumulation of NF90/NF110-circRNP complexes in the cytoplasm probably affects the host immunity. Based on the obtained results, circRNAs compete against viral mRNAs to bind to NF90/NF110, which potentially serve as the NF90/NF110 molecular reservoir to achieve rapid immunity during viral infection.^{126,127} According to Chen et al.,¹²⁸ self-splicing introns-derived circRNAs could bind to retinoic acid-inducible gene I (RIG-I) receptor to efficiently activate immune signaling during viral infection. It has been recently suggested that hsa_circ_0000479 upregulation among COVID-19 patients modulates RIG-I and IL-6 levels through sequestering hsa-miR-149-5p.¹²⁹ Furthermore, circRNAs regulate immunity by mediating signaling pathways and cytokine production. Recently, an integrative analysis of protein transcription demonstrates significant modulation of hypoxia-inducible factor-1 (HIF-1), epidermal growth factor receptor (ErbB), tumor necrosis factor (TNF), and mammalian target of rapamycin (mTOR) signaling pathways through SARS-CoV-2 infection.¹³⁰ For DEcircRNAs, their parental genes associated with the above pathways are involved in various

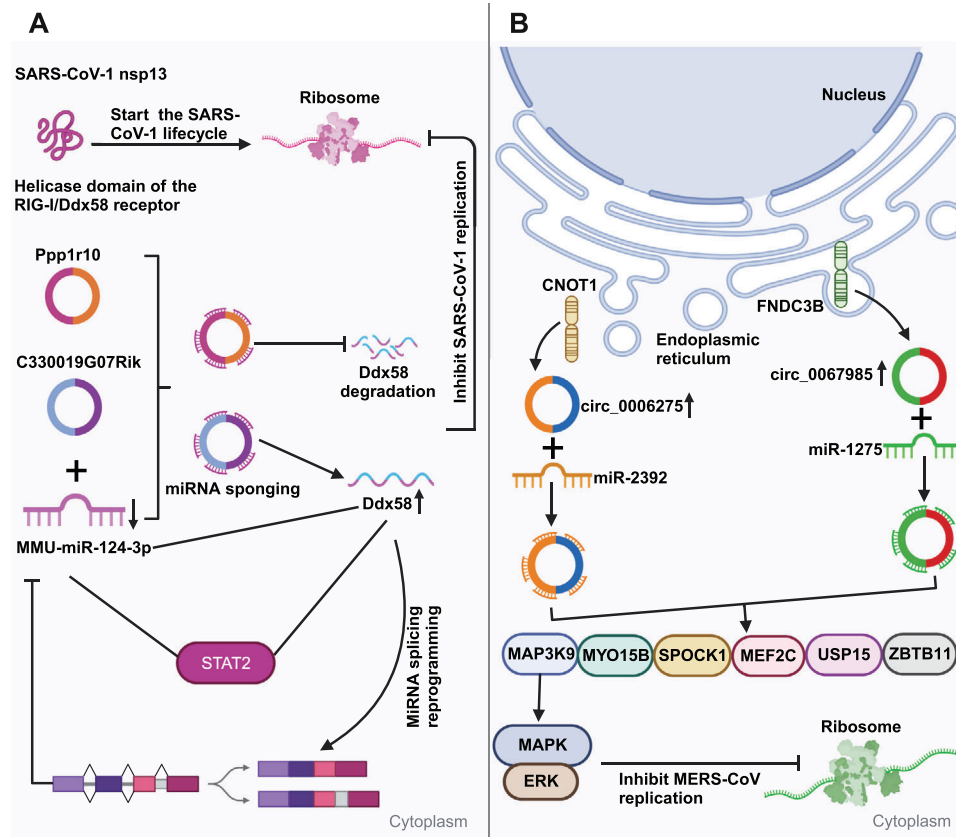


FIGURE 3 Regulation of viral replication by RIG-I/Ddx58 and circRNA-mediated miRNA sponging. (A) RIG-I/Ddx58 receptor interacts with SARS-CoV-1 nsp13, initiating viral replication. miR-124-3p degrades Ddx58, reducing replication. CircRNAs Ppp1r10 and C330019G07Rik act as miR-124-3p sponges, preserving Ddx58. (B) circRNAs hsa_circ_0067985 and hsa_circ_0006275 are upregulated in MERS-CoV infection, sponging hsa-miR-1275 and hsa-miR-2392, respectively, and regulating key viral replication targets. These circRNAs may be potential antiviral targets.

antiviral signaling pathways, including chemokines, interferon (IFN), RIG-I-like receptors, and mitogen-activated protein kinases (MAPKs).¹¹⁷ Therefore, circRNAs can regulate cellular signaling and immuno-inflammatory responses in SARS-CoV-2 infection.

Small molecular polypeptides, cytokines and glycoproteins produced via various cells, exert vital effects on numerous physiological events, including immuno-inflammatory response regulation. Acting as immunomodulators, cytokines are related to endocrine, paracrine, and autocrine signaling, contributing to the immune response against viral infections.^{131,132} Viral infections can induce cytokine production, which is of great importance for immune response control, antiviral defense, and target cell capacity to support viral replication.¹³³ The infection with SARS-CoV-2 induces auto-immunity by activating specific immune factors, including Th1 chemokines CXCL9/10/11, interferon-inducible proteins, and 2′–5′ oligoadenylate synthase (OAS1-3).¹³⁴ Additionally, it decreases ribosomal protein transcription.¹³⁴ OAS activation necessitates the par-

ticipation of viral genome dsRNA, leading to 2′–5′ oligoadenylate (2′–5′A) generation. Then, 2′–5′A markedly enhances RNase L activity to execute the antiviral activity, thereby degrading viral RNA whereas impeding viral protein production.¹³⁵ As discovered by Liu et al.,¹⁰⁰ dsRNA-activated protein kinase R (PKR) inhibitors are generated by endogenous circRNAs (16–26 bp) duplexes. In addition, circRNAs undergo global degradation via endonuclease RNase L, activating PKR antiviral pathway.

3.1.2 | CircRNAs in asthma

CircRNAs and airway smooth muscle cells

In general, mild asthma can be efficiently treated, while severe asthma will bring significant burdens on the economy and society. It usually entails notable alterations of airway smooth muscle cells (ASMCs), including hypertrophy, hyperplasia, as well as changes of fibrosis- and inflammation-associated proteins.¹³⁶ These aberrations in

ASMCs make significant contributions to airway remodeling in severe asthma.¹³⁷ Regrettably, there still lack such strategies for addressing such changes in ASMCs. Hence, it is imperative to thoroughly understand the asthma pathogenesis to develop efficient ways for mitigating the influence on ASMCs caused by severe asthma and improve patient prognosis.

The development of next-generation sequencing has made it possible to identify many circRNAs in different types of cells and species.⁸⁸ In asthma, there are few studies investigating the effect of circRNAs on ASMC dysfunction. The role of circRNAs in regulating the biological and cellular processes of ASMCs during asthma has recently been revealed in numerous studies. These processes, such as growth, invasion, apoptosis, extracellular matrix (ECM) generation, and inflammatory factor production, are primarily mediated through their role as ceRNAs for miRNAs, thereby regulating target gene mRNAs.

CircERBB2, originating at ERBB2 locus, is a notable circRNA in this context and is correlated with tumor genesis. CircERBB2 upregulation can be detected within bronchial biopsy tissues in patients with asthma and ASMCs treated with platelet-derived growth factor BB (PDGF-BB), the *in vitro* model of asthma.¹³⁸ PDGF-BB has been the factor implicated in inflammation and airway remodeling during asthma,¹³⁹ which can stimulate ASMCs growth and invasion.^{140,141} Noteworthy, PDGF-BB upregulation is closely related to asthma severity, with increased ASMC proliferation and invasion being observed in asthma patients.¹⁴² CircERBB2 silencing with small hairpin RNA (shRNA) significantly alleviates the proliferation, invasion and inflammation of ASMCs caused by PDGF-BB.¹³⁸ From the mechanism perspective, circERBB2 can sponge miR-98-5p to regulate the expression of insulin-like growth factor 1 receptor (IGF1R) and facilitate ASMC growth and invasion after PDGF-BB administration.¹³⁸

Another circRNA of interest, circHIPK3, also called circ_0000284, shows upregulation in ASMCs upon PDGF-BB stimulation.^{143,144} CircHIPK3 can enhance the growth and invasion of PDGF-BB-treated ASMCs and inhibit their apoptosis by interacting with miR-326 for regulating stromal interaction molecule 1 (STIM1).¹⁴³ STIM1 is an endoplasmic reticulum membrane protein exerting a role of the calcium sensor as well as the stimulatory factor for airway hyperresponsiveness (AHR) and ASMC remodeling during asthma.^{145,146} In addition, circHIPK3 enhances ASMC growth, migration, and invasion after PDGF administration, which is achieved by regulating miR-375/matrix metalloproteinase-16 (MMP-16) axis.¹⁴⁴

Circ_0002594 and circ_CSNK1E are upregulated in PDGF-stimulated ASMCs, and circ_0000029 exhibits

decreased expression.^{147–149} Both circ_0002594 and circ_CSNK1E are significantly upregulated in samples collected from asthma patients.^{147,148} Functional research shows that shRNA-induced circ_CSNK1E silencing significantly decreases ASMC proliferation and migration after PDGF treatment.¹⁴⁷ Based on computational research and experimental verification, circ_CSNK1E can regulate vesicle-associated membrane protein 2 through binding to miR-34a-5p, therefore promoting the PDGF-mediated ASMC growth and invasion.¹⁴⁷ Besides, circ_0002594 can promote ASMC growth, invasion, and inflammation after PDGF administration. Moreover, circ_0002594 can sponge miR-139-5p to regulate tripartite motif 8 (TRIM8) expression, finally triggering cellular injury.¹⁴⁸ In some studies, miR-139-5p administration and TRIM8 suppression decrease ASMC growth through suppressing the chromatin remodeling factor BRG1 and inhibiting NF- κ B pathway.¹⁵⁰ Circ_0000029 can modulate ASMC growth and invasion by regulating KCNA1 and miR-576-5p expression.¹⁴⁹ Combined with the above-mentioned results, circRNAs are vital for regulating crucial activities of asthmatic ASMCs by interacting with miRNAs and target genes. Nevertheless, the complete circRNA activity scope and their interplay with additional mechanisms within ASMCs during asthma remain unclear. More investigations are needed to comprehensively investigate the impacts of circRNAs on asthmatic ASMCs.

CircRNAs and airway and bronchial epithelial cells

Airway epithelial cells play a crucial role as the first-line protecting barrier, safeguarding both airway and lungs from antigens and inflammatory stimuli. Airway and bronchial epithelial cell impairments have been identified as a common feature of asthma. Abnormal circRNAs expression can significantly impact the functions of airway and bronchial epithelial cells.

In a comprehensive profiling study, Jia et al.¹⁵¹ utilized microarrays to investigate circRNAs within PM2.5-exposed human bronchial epithelial cells (BEAS-2B), and PM2.5 was the respiratory risk associated with pulmonary disorders like asthma. Circ_406961 is one of the dysregulated circRNAs, exhibiting the notable difference in fold change. Experiments indicate that circ_406961 is dose-dependently downregulated within PM2.5-exposed BEAS-2B cells. Circ_406961 knockdown with siRNA aggravates inflammation and decreases cell viability, while its upregulation exerts the opposite effects. Mechanism research suggests that circ_406961 is vital for regulating inflammation through interaction with ILF2 and activation of STAT3/JNK pathways.

Moreover, circVPS33A is upregulated in plasma samples collected from plasma patients and in BEAS-2B cells stimulated by house dust mites (HDM) protein (Der p1).¹⁵²

Der p1 stimulation reduces cell viability, growth, invasion, migration, and promotes autophagy, inflammation, and apoptosis of BEAS-2B cells. CircVPS33A knockdown with siRNA can mitigate the Der p1-induced cellular injuries. Mechanically, circVPS33A can improve the above cellular injuries through sponging miR-192-5p, thus regulating HMGB1 expression. CircARRDC3 can promote mucus generation and aggravate inflammation of IL-13-treated nasal epithelial cells during allergic rhinitis, serving as the prominent risk factor related to asthma progression.¹⁵³ Its regulation can be achieved via miR-375/KLF4 axis. Collectively, the above results suggest the contribution of dysregulated circRNAs to asthma-related dysfunction in bronchial epithelial cells. Nevertheless, the above results need to be validated by clinical studies and in vivo animal models.

CircRNAs and airway goblet cells

Airway goblet cells are crucial for keeping airway homeostasis by producing mucin.¹⁵⁴ Goblet cells can differentiate from airway epithelial cells called club (Clara) cells upon stimulation with growth factors, genetic factors, environmental insults, and inflammation.^{154,155} The out-of-control proliferation of goblet cells promote mucin generation in the airway.¹⁵⁶ Excess mucin accumulation can be frequently observed in different airway disorders, like asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD).¹⁵⁶ Hyperplasia of goblet cells (the higher goblet cell count) in asthma is an important airway remodeling feature, which is correlated with chronic excessive mucus production and the resulting airway obstruction.¹⁵⁷ CircRNAs can induce hyperplasia of goblet cells. For example, Wang et al.¹⁵⁸ suggested that circZNF652, also called circ_0000782, enhanced goblet cell hyperplasia in the allergic epithelium. CircZNF652 is specifically and significantly expressed within airway epithelium in asthmatic children and OVA-mediated experimental mouse models.¹⁵⁸ CircZNF652 upregulation promotes metaplasia of bronchial goblet cells and result in excess mucus production. CircZNF652 can sponge miR-452-5p and activate JAK2/STAT6 axis to promote goblet cell metaplasia.¹⁵⁸ ESRP1, which is a splicing factor, can facilitate circZNF652 expression, leading to goblet cell metaplasia.¹⁵⁸ The above results indicate that ESRP1/circZNF652/miR-452-5p/JAK2/STAT6 axis is vital for modulating mucus hypersecretion, goblet cell metaplasia, and AHR within the experimental asthmatic mouse models. Therefore, it is the possible strategy to target circZNF652 and activate miR-452-5p to intervene with epithelial remodeling in experimental asthma. However, the precise mechanism related to ESRP1 upregulation in allergic airway epithelium is still unknown. CircZNF652 can regulate RhoA, EIF5, JAK2, and SRSF3. JAK2 is found to be related to goblet cell metaplasia during asthma, while

the effects of additional factors on asthma need to be further explored.

CircRNAs and immune cells

The airways are infiltrated and activated by different immune cells during asthma, including dendritic cells (DCs), innate lymphoid cells (ILCs), T cells (Th1/Th2/Th9/Th17/Th22 cells), neutrophils, eosinophils, mast cells, and B cells.¹⁵⁹ The two major types of asthma are type 2 (dominant type) and non-type 2. Type 2 asthma is generally caused by allergies and nonallergic factors. In contrast, non-type 2 asthma usually results from infections and contaminants. Once ILCs and Th2 cells, particularly ILC2 cells, detect an allergen, they are capable of secreting cytokines including IL-4, IL-5, and IL-13. Subsequently, these cytokines trigger the recruitment of eosinophils, ultimately causing inflammation in the airways.¹⁵⁹ Mast cells can produce histamine, thereby facilitating bronchoconstriction, while neutrophils are associated with severe asthma. To initiate immune responses, DCs present antigens to T cells, whereas macrophages accelerate or suppress inflammation according to their M1 or M2 type. Allergies can be triggered by IgE antibodies produced by B cells. It is possible to experience typical asthma symptoms, like bronchoconstriction or acute hypotension, caused by the above-mentioned immune mechanisms.

Recently, circRNAs have been suggested as important ceRNAs for miRNAs in the function and development of T cells. m_circRasGEF1B, the LPS-mediated circRNA, is an example suggesting that circRNAs are involved in immunoregulation. It can modulate the ICAM-1 mRNA stability to promote immunoregulation in human body.¹⁶⁰ As the cell surface glycoprotein, ICAM1 can be found in certain immune cells and endothelial cells, and it has been identified as the inflammation biomarker. Through the analysis of circRNA expression patterns in diverse cells, different expression patterns are revealed, indicating that they can regulate some cellular processes. For instance, hsa_circ_0012919 downregulation can result in DNA methylation of CD11a and CD70 in CD4 T cells.^{161–164} Hsa_circ_0045272 may negatively regulate IL2 production and T cell apoptosis through interaction with hsa-miR-6127.¹⁵⁸ CircIKZF1, circTNIK, circTXK, and circFBXW7 are circRNAs with specific expression in T cells.¹⁶³

Recently, circRNAs have been increasingly suggested to be associated with the asthma pathophysiology via regulating immune responses.^{165,166} CD4 T cells are substantially demonstrated to drive disease occurrence by modulating IgE generation upon allergic conditions, generating proinflammatory factors, and recruiting and activating inflammatory cells including neutrophils, eosinophils, and macrophages.^{167–176} CD4⁺ T cells can produce cytokines. Specifically, Th1 cells produce IFN- γ , while Th2 cells

secrete IL-4, IL-5, IL-6, IL-9 and IL-13, and Th17 cells can release IL-17A and IL-17F.¹⁷⁷ In asthma, the complicated immune response can be modulated through the complicated cytokine network.^{168,173–175,178} To analyze the effect of circRNAs on CD4 T cells during asthma, Huan et al.¹⁷⁹ examined the circRNAs expression patterns within CD4 T cells collected in five asthma patients and five normal subjects by micro-array analysis. Totally 597 circRNAs were abnormally expressed between asthma patients and normal subjects. Among them, hsa_circ_0005519 was most significantly upregulated, as subsequently verified through qRT-PCR assay in the current cohort samples and in another cohort including 65 asthma individuals and 30 normal controls. Through bioinformatic analysis, literature search and reporter assays, the authors suggested the role of hsa_circ_0005519 in regulating IL13 and IL6 expression, probably by interaction with let-7a-5p. IL-13 and IL-6 are extensively suggested to be significantly related to the asthma pathogenesis.^{167,178,180,181} Hsa_circ_0005519 expression within CD4 T cells is negatively related to let-7a-5p, whereas positively related to IL13 and IL6 mRNA expression, FeNO and peripheral blood eosinophil ratio. As a result, hsa_circ_0005519 is the candidate biomarker for asthma.

In one article, hsa_circ_0002594 was found to be upregulated within CD4⁺ T cells from a present microarray dataset containing five asthma patients and five normal subjects.¹⁷⁹ For validation, another cohort including 83 asthma patients and 54 normal controls was analyzed, revealing that hsa_circ_0002594 expression was significantly upregulated in CD4⁺ T cells from asthma patients.¹⁷⁹ Hsa_circ_0002594 expression in CD4⁺ T cells of asthma patients was positively related to FeNO, but negatively correlated with PD20 (the methacholine dosage necessary for inducing FEV1 decline by 20%). The correlation between hsa_circ_0002594 expression of asthma group and specific clinical factors was analyzed, showing that the hsa_circ_0002594 high-expression group had increased FeNO expression but decreased PD20 expression in relative to hsa_circ_0002594 low-expression group. The high-expression subgroup had more skin prick test (SPT)-positive and Th2-high patients than SPT-negative and non-Th2 inflammation counterparts. Based on the above results, asthma patients who showed hsa_circ_0002594 high-expression exhibited clinical indicators consistent with a Th2-mediated allergic response. Inhaled corticosteroids (ICS) administration significantly reduces hsa_circ_0002594 expression, suggesting that it may be the therapeutic target. Furthermore, hsa_circ_0002594 is sensitive and specific in asthma diagnosis, no matter whether ICS is applied or not. Molecular mechanisms related to hsa_circ_0002594 underlying asthma occurrence were explored by computational research; as a result, possi-

ble target miRNAs were identified, proposing the role of hsa_circ_0002594 in the competitive sequestering of the activities of hsa-miR-503-5p, hsa-let-7e-5p, hsa-miR-587, hsa-miR-16-5p, and hsa-miR-514a-3p. However, this study still has the following limitations: (1) The sample size was small, and thus large-scale and more studies are warranted, (2) experimental verification for miRNA-hsa_circ_0002594 interaction was not available, and (3) the hsa_circ_0002594 level in circulation was not evaluated for its potential as a biomarker.

Mmu_circ_0001359 has been recently found to be down-regulated within lungs in the murine model of OVA-mediated asthma.¹⁸² Delivering adipose-derived stem cells (ADSCs)-derived exosomes after mmu_circ_0001359 modification can alleviate airway remodeling by activating M2-like macrophages via miR-183-5p/FoxO1 pathway.¹⁸²

CircRNAs expression within lungs in mice with HDM-induced experimental asthma was analyzed.¹⁸³ The circRNA-miRNA axis was explored, which identified two circRNAs with upregulated expression, including circ_0000629 and circ_0000455 targeting miR-29b and miR-15a separately. Previous research reported that such miRNAs were inversely related to allergic reactions.^{134,184} By contrast, two circRNAs with downregulated expression, namely, circ_0000723 and circ_0001454, target miR-214 and miR-146b, respectively. MiR-214 and miR-146b show a positive relationship to asthma.^{135,185} Therefore, the aforementioned four circRNAs are candidates deserving subsequent analysis concerning the association with asthma.

3.1.3 | CircRNAs in COPD

CircRNAs have been increasingly suggested to be related to the COPD pathophysiology. To identify circRNAs related to COPD, some profiling research is conducted using NGS technology. For instance, Duan et al.¹⁸⁶ explored the circRNA expression patterns in peripheral blood mononuclear cells (PBMCs) from 21 COPD cases together with 21 normal subjects. The results showed that 2132 DEcircRNAs and 2734 DEMRNAs were obtained from COPD cases. As a result of further investigation, circ_0008672 was related to some pivotal COPD pathways, including the NOD-like receptor pathway, NK cell-driven cytotoxicity, and Th17 cell differentiation. A circRNA-miRNA-mRNA network was established to investigate how circRNAs can act as miRNA sponges in COPD. According to the results, circRNAs modulated mRNAs through sponging at least one miRNA. For example, circ_0008672 interacts with miR-1265 to modulate MAPK1 expression. Activation of MAPK pathway is crucial for the COPD pathophysiological characteristics, like airway mucus hypersecretion, lung

inflammation, T-cell activation, and airway fibrosis.¹⁸⁷ Therefore, the ceRNA network is of great importance for COPD. However, there are some limitations. The results should be validated with a larger COPD cohort, the accurate functions of circRNAs must be experimentally investigated, and the PBMC subsets need to be further assessed.

According to serum samples from 21 smokers and 24 smokers with COPD compared with 17 nonsmokers, Circ-HACE1 is overexpressed in serum samples from both groups.¹⁸⁸ Circ-HACE1 was significantly upregulated in cigarette smoke extract (CSE)-exposed human bronchial epithelial cells (16HBE cells), serving as the *in vitro* COPD model.^{188,189} The siRNA-based targeting of circ-HACE1 expression improved the CSE-mediated injuries to 16HBE cells, which was supported by the enhanced cell viability, decreased oxidative stress, apoptosis, and inflammation. The obtained benefits were attained by the interaction of circ-HACE1 with miR-485-3p to regulate TLR4 expression. TLR4 exerts a vital impact on innate immune activation. Besides, it is tightly associated with inflammatory responses in certain diseases, like COPD. The above results show that circ-HACE1 is the candidate target for enhancing the COPD diagnostic accuracy; moreover, suppressing circ-HACE1 may be beneficial for the treatment of COPD.

Moreover, circ_0040929 expression is significantly upregulated in the serum samples collected from COPD patients and within CSE-exposed 16HBE cells.¹⁹⁰ Silencing circ_0040929 protects CSE-treated 16HBE cells from injuries by regulating miR-515-5p/IGFBP3 pathway. Circ-RBMS1, also called hsa_circ_0002136, is derived from RBMS1 gene and overexpressed within PBMCs in COPD patients.¹⁸⁶ Nevertheless, its functions and associated molecular mechanisms are not explored through circRNA profiling and bioinformatic analysis. Similarly, Qiao et al.¹⁹¹ discovered that circ-RBMS1 was upregulated in COPD patients.¹⁹¹ Circ-RBMS1 was dose-dependently upregulated within CSE-exposed 16HBE cells. Functional analysis indicated that siRNA-mediated circ-RBMS1 suppression attenuated CSE-induced injuries in 16HBE cells. From the mechanism perspective, circ-RBMS1 interacted with miR-197-3p to regulate FBXO11, which belongs to the F-box family of proteins and is involved in substrate degradation, ubiquitination, and genome stability modulation. FBXO11 is previously found to be related to inflammation, apoptosis and airway remodeling resulting from CSE.¹⁹² Nevertheless, the above results were acquired based on *in vitro* analysis. Therefore, larger COPD cohorts and *in vivo* assays need to be performed to verify the above findings.

CircFOXO3 displays upregulation within CSE-exposed mouse alveolar epithelial cells and lungs in mice with CS-induced experimental COPD.¹⁹³ However, lentivirus-

mediated CircFOXO3 knockdown mitigates CS-induced mouse lung inflammation through CircFOXO3/miR-214-3p/NF- κ B pathway, targeting the CS-induced inflammatory responses within mouse lungs. Therefore, targeting circFOXO3 is the new way to prevent CS-mediated inflammation.

Circ-OSBPL2 modulates apoptosis, inflammation and oxidative stress of CSE-exposed HBECs by regulating miR-193a-5p/BRD4 pathway.¹⁹⁴ Circ_0061052 expression increases within CSE-exposed HBECs, which can regulate CS-induced EMT and airway remodeling by sponging miR-515-5p, consequently modulating downstream targets Snail and FoxC1.¹⁹⁵ Circ_0026466 is upregulated within blood from CSE-exposed HBECs and smokers with COPD.¹⁹⁶ Circ_0026466 knockdown alleviates the CSE-mediated suppression of proliferation and viability, promotes apoptosis, inflammation, and oxidative stress of HBECs via circ_0026466/miR-153-3p/TRAF6/NF- κ B pathway.¹⁹⁶ Similarly, circXPO1 expression increases within lungs in mice with CS-induced experimental COPD and CSE-exposed AT2 cells.¹⁹⁷ Inhibiting circXPO1 can inhibit CSE-induced cell aging and inflammatory response. Mechanistic analysis indicates that circXPO1 can sponge miR-23b-3p to regulate TAB3 mRNA expression, thus modulating cell aging and inflammatory response. Therefore, circXPO1 may sponge miR-23b-3p to accelerate COPD pathogenesis, thereby regulating TAB3 expression.

On the contrary, circRNAs knockdown promotes the COPD pathogenesis. For example, circ_0006892 expression decreased in lungs of COPD cases and CSE-exposed BEAS-2B and 16HBE cells based on qRT-PCR results.¹⁹⁸ Circ_0006892 exhibited a positive relationship to FEV1% of COPD patients. To explore the function of circ_0006892, the gain-of-function (GOF) test was performed on CSE-exposed BEAS-2B and 16HBE cells to evaluate cell apoptosis, survival, and apoptosis. The findings indicate that circ_0006892 upregulation based on plasmid transfection decreased the CSE-induced inflammatory response and cell apoptosis, suggesting that circ_0006892 protected against the CSE-induced bronchial epithelial injury. Comparatively, circ_0006892 silencing promoted inflammation and apoptosis of CSE-induced HBECs via miR-24/PHLPP2 axis. Nevertheless, the study only analyzed the *in vitro* effect of circ_0006892. In this regard, the conclusions might not precisely indicate the complicated environment among COPD patients. To comprehensively comprehend the COPD pathogenesis, more research based on preclinical animal models is required.

CircRNAs can regulate pulmonary smooth muscle and endothelial cells in the *in vitro* COPD models. For instance, circANKRD11 is upregulated within lungs in smokers with or without COPD as well as within CSE-exposed human pulmonary microvascular endothelial cells (HPMECs).¹⁹⁹

CircANKRD11 silencing within HPMECs lowers the CSE-induced cell apoptosis, oxidative stress, and inflammatory response by regulating miR-145-5p/BRD4 axis. CircBPTF is upregulated within pulmonary arteries in COPD patients, which facilitates hypoxic pulmonary artery smooth muscle cells (PASMCs) proliferation. The circBPTF/miR-486-5p/CEMIP pathway enhances PASMC proliferation.²⁰⁰ Dysfunction of endothelial cells and PASMCs can be observed in pulmonary arterial hypertension, and these cells make great contributions to lung damage and chronic vascular inflammation in COPD. More investigations need to be performed to explore the effects of circRNAs on the above cells by clinical and in vivo studies. On the whole, circRNAs are dysregulated in COPD cells, which exert important effects on disease occurrence and development. Nonetheless, the above results are mainly obtained based on in vitro assays and cannot comprehensively represent the complicated environment in COPD patients. To further comprehend COPD pathogenesis and explore functions of circRNAs, more investigations are warranted by using preclinical animal models.

3.1.4 | CircRNAs as emerging biomarkers for asthma and COPD

CircRNAs are previously indicated to be stable due to the closed-loop structures, conserved degree among different species, and developmental stage- and tissue-specific expression patterns. Furthermore, circRNAs exhibit high abundance within saliva, blood, urine, and exosomes; as a result, they can be sensitively and specifically detected. Considering the above distinct characteristics, circRNAs may be used to discover biomarkers.

CircRNAs are the candidate biomarkers for COPD and asthma. For example, based on receiver operating characteristic (ROC) curve for circ_0002594 expression within CD4⁺ T cells collected in 83 asthma patients without ICS exposure, the area under the curve (AUC) was extremely high (0.727).²⁰¹ Similarly, the AUC value was 0.767 for evaluating the diagnostic performance of circ_0002594 in 48 asthma cases receiving ICS treatment.²⁰¹ Circ_0002594 expression is positively related to family history, exhaled nitric oxide level, Th2 cytokine expression, and positive SPT results.²⁰¹ CircSORT1 and circSERPINB1 were upregulated within induced sputum from 68 asthma cases in relative to 20 normal controls, suggesting that they were more specific and sensitive in asthma prediction.²⁰² CircSORT1 expression is related to different clinical factors of asthma, like EOS%, FeNO, IFN- γ , IL-17A, and PC20.²⁰² CircSERPINB1 expression is associated with IL-6, IFN- γ ,

IL-17A, FVC%, and FEV1%.²⁰² Furthermore, circ_0005519 expression markedly elevated within CD4⁺ T cells and PBMCs from 30 asthma patients in comparison with 24 normal subjects, and the upregulation was correlated with the exhaled nitric oxide level.¹⁷⁹ In addition, circ_0001859 expression in serum decreased among 38 COPD patients and 24 acute exacerbation of COPD (AE-COPD) patients in relative to 28 normal subjects. The downregulation was highly specific and sensitive in the prediction of COPD and AE-COPD, which was also related to FEV1% predicted. Furthermore, circ_004092 expression increases within blood collected from smokers with or without COPD ($n = 22$ each) compared with nonsmokers ($n = 22$). Collectively, circRNAs may be the candidate biomarkers, which can be used to diagnose and predict the prognosis of asthma and COPD. Nevertheless, large sample cohorts are warranted to confirm whether circRNAs can be the biomarkers for asthma and COPD.

3.1.5 | CircRNAs in acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS), the severe stage or type of acute lung injury (ALI), is a major fatal respiratory disease characterized by respiratory failure and refractory arterial hypoxemia. Despite extensive research efforts, progress in understanding the pathogenesis and developing effective therapies for ARDS/ALI is slow, causing the increased incidence and mortality. miRNAs like miR-155²⁰³ and miR-17²⁰⁴ are previously suggested to be crucial for ALI occurrence and management. CircRNAs can sponge miRNAs, which provide a novel perspective for developing effective therapies against ARDS. Wan et al.²⁰⁵ examined circRNA expression patterns in lung tissues collected from LPS-mediated ARDS rats, and identified 395 upregulated and 562 downregulated circRNAs. Among them, four upregulated circRNAs (mmu_circRNA_19423, mmu_circRNA_30664, rno_circRNA_010489, rno_circRNA_011426) and one downregulated circRNA (rno_circRNA_005564) showed significant changes. Ye et al.²⁰⁶ obtained 10 DEcircRNAs in rat lungs after smoke inhalation-mediated ALI. According to Zhong et al.,²⁰⁷ circFLNA exhibited abnormal upregulation within ARDS, and circFLNA depletion increased CD4⁺CD25⁺Foxp3⁺ Tregs level while reducing the inflammatory response. These changes in circRNAs shed more lights on the biological roles and molecular mechanisms associated with circRNAs in ARDS/ALI. However, further research is warranted to identify their specific roles and mechanisms and to demonstrate these findings in patients with ARDS/ALI.

3.1.6 | CircRNAs in pulmonary hypertension

Pulmonary hypertension (PH) is the pathophysiological and hemodynamic state characterized by the elevation of pulmonary arterial pressure to higher than the specific threshold. Many ncRNAs (miRNAs and lncRNAs) are related to the PH pathogenesis. CircRNAs, belonging to the ncRNA family, are emerging as key diagnostic biomarkers and therapeutic targets for PH. Based on our knowledge, our group is the first to identify dysregulation of circRNAs within lungs from hypoxia-related PH mice through circRNA microarray analysis. Among them, 23 circRNAs showed significant upregulation, while 41 exhibited significant downregulation. Furthermore, we employed circRNA-miRNA-mRNA network analysis, Gene Ontology (GO) as well as Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis for shedding more lights on associated pathways and mechanisms. The findings indicated that dysregulated circRNAs were vital for the hypoxia-related PH pathogenesis, which were the candidate therapeutic targets.²⁰⁸ Miao et al.²⁰⁹ obtained 351 DEcircRNAs (including 122 with upregulation whereas 229 with downregulation) in chronic thromboembolic pulmonary hypertension (CTEPH). Based on their findings, upregulated circRNAs probably affected ribonucleotide biosynthesis to exert their effect on CTEPH, while down-regulated ones might regulate cellular response to stress, gene expression and DNA damage stimulus to exert their impact. Among them, hsa_circ_0002062 sponged hsa-miR-942-5p and was mostly related to cancer-related pathways, while hsa_circ_0022342 sponged hsa-miR-940 and was primary expressed in ErbB signaling pathway. Both of them are essential for CTEPH occurrence, and targeting them is the efficient way to treat CTEPH. Based on the obtained findings, circRNAs are crucial for PH occurrence, while they concentrate on analyzing the dys-regulated circRNAs expression patterns, while there still lacks further functional and mechanistic research.

3.1.7 | CircRNAs in pulmonary tuberculosis

Pulmonary tuberculosis (TB) results from *Mycobacterium* TB, which still seriously threatens public health due to the delayed diagnosis and management. The existing diagnostic approaches of pulmonary TB show unsatisfactory specificity and sensitivity. Therefore, novel biomarkers should be identified to diagnose and treat pulmonary TB early. Zhang et al.²¹⁰ obtained 170 circRNAs with dysregulation in pulmonary TB patients relative to normal controls and established the ceRNA networks. According to the results, circRNA-related ceRNA-dependent gene regulation was critical for regulating the pulmonary TB

pathogenesis. Based on Huang et al.,²¹¹ hsa_circ_001937 was important for TB diagnosis (AUC = 0.873), which was related to TB severity and could be the TB-specific signature circRNA; besides, it was significantly upregulated among TB patents in comparison with pneumonia, lung cancer and COPD patients. According to Zhuang et al.,²¹² hsa_circ_0005836 and hsa_circ_0009128 showed decreased expression within PBMCs of active pulmonary TB patients in relative to normal subjects. GO and KEGG analysis revealed that the main biological functions of DEcircRNAs were associated with immune system activation, indicating that TB infection was related to immune system activity. Qian et al.²¹³ obtained DEcircRNAs in PBMCs of TB patients and chose seven circRNAs for the construction of the circRNA-based TB index for all patients. TB patients displayed the increased TB index relative to normal controls, with the AUC value being 0.946 for the validation groups. Through KEGG enrichment, multiple pathways associated with bacterial invasion and inflammation were enriched into active TB patients. Yi et al.²¹⁴ analyzed circRNA expression patterns in serum samples collected from active TB cases. According to their results, hsa_circRNA_103571 expression markedly decreased among active TB patients. Based on bioinformatics analysis, hsa_circRNA_103571 was related to regulating T- and B-cell receptor and actin cytoskeleton pathways. Certain circRNAs are previously demonstrated with diagnostic significance for TB infection. Future studies need to concentrate on nontuberculous mycobacteria (NTM) that cause TB-like imaging findings and clinical symptoms, which may usually result in misdiagnosis and mistreatment. Most NTM are highly resistant to anti-TB agents, which imposes significant disease burden on the society. CircRNAs probably serve as novel biomarkers to help physicians differentiate NTM infections from TB.

3.1.8 | CircRNAs in silicosis

Silicosis is a frequently seen, rapid-growing and severe pneumoconiosis type, exhibiting the representative characteristic of excessive pulmonary nodular fibrosis resulting from long-time inhalation of excess free silica dust. Currently, circRNAs related to silicosis are studied extensively, primarily by the Jie Chao's group. CircZC3H4 RNA is found to sponge miR-212, relieving the miR-212-induced ZC3H4 protein suppression. CircZC3H4 RNA and ZC3H4 upregulation after exposure to SiO₂ affects macrophage activation as well as the subsequent influences on fibroblast growth and invasion. ZC3H4 protein upregulation is revealed in tissues of silicosis patients, exhibiting the feasibility of ZC3H4 as the candidate therapeutic target for silicosis.²¹⁵

According to Zhou et al.,²¹⁶ circHEZCD1/HECTD1 pathway was associated with SiO₂-mediated macrophage activation and HECTD1 upregulation among silicosis patients. In the meanwhile, circHEZCD1 downregulation and HECTD1 upregulation after SiO₂ exposure are modulated via ZC3H12A, the new RBP. Following this, Fang et al.²¹⁷ discovered the possible role of circHECTD1 in regulating HECTD1 (the host gene) protein expression, through competing with the corresponding pre-mRNA. The circHECTD1/HECTD1 pathway, which promotes EMT in vitro after SiO₂ exposure, is the candidate mechanism underlying fibrosis and the novel therapeutic target for pulmonary silicosis patients.

3.2 | CircRNAs in endocrine and metabolic diseases

3.2.1 | CircRNA in diabetes

Type 1 diabetes

Type 1 diabetes (T1D), also called insulin-dependent diabetes, is the chronic autoimmune disorder with the representative characteristic of β -cell destruction and dysfunction, absolute insulin deficiency, and increased blood glucose content.²¹⁸ Substantial evidence demonstrates the effects of circRNAs on autoimmune disorders, partially by evaluating autoimmune disorders in T1D research.

There were 61 circRNAs with upregulation while 7 with downregulation detected within plasma from new-onset T1D patients, with four circRNAs (hsa_circRNA_100332, hsa_circRNA_101062, hsa_circRNA_085129, and hsa_circRNA_103845) being demonstrated in succession using quantitative real-time PCR.²¹⁹ There were 93 DEcircular transcripts detected from peripheral blood in T1D patients relative to normal subjects, with 30 being upregulated while 63 being downregulated. Based on GO and KEGG analyses, such circRNAs contributed to T1D occurrence through diverse pathways. Hsa_circ_0072697 was the possible endogenous miRNA sponge to regulate β -cell activity.²²⁰ The above dysregulated circRNAs serve as potential biomarkers for T1D, which should be further validated based on longitudinal studies. CircRNAs are related to the inflammatory response during T1D, which may offer the new therapeutic target for the disease. CircPPM1F is increasingly suggested to be mainly expressed within and promotes M1 macrophage activation through circPPM1F-HuR-PPM1F-NF- κ B pathway. CircPPM1F upregulation may aggravate injuries to pancreatic islet.²²¹ Macrophages, which are the immune response inflammatory mediators, are essential for insulinitis. Besides, they can support autoimmune T cells during T1D through promoting the infiltration of inflammatory cells.²²² As discovered

by Yang et al.,²²³ hsa_circ_0060450 expression increased in T1D patients, and it sponged miR-199a-5p for suppressing macrophage-induced inflammation through JAK-STAT pathway. Moreover, 1922 significantly expressed circRNAs were detected in mouse islet β -cells after induction of different cytokines, including interleukin-1 β (IL-1 β), TNF- α , and INF- γ .²²⁴ To analyze the impacts of circRNAs on T1D, Yi et al. constructed a circRNA-lncRNA-miRNA-mRNA ceRNA network of T1D by computational and bioinformatic analyses.²²⁵ Nonetheless, there is limited research on therapeutic circRNAs for T1D, and a larger sample size is needed for further validation.

Type 2 diabetes

Type 2 diabetes (T2D) has an increasing incidence rate due to the growing living standards and the changed diet structures, bringing significant health burdens on the patients and society.^{226,227} The function of circRNAs in T2D pathogenic mechanisms and development has recently been explored, suggesting that circRNAs may serve as diagnostic biomarkers and therapeutic targets in diabetics.

Serum hsa_circ_0054633 was used to diagnose prediabetes and T2D among 63 prediabetics, 64 T2D patients and 60 normal controls.²²⁸ Serum hsa_circ_0054633 expression among T2D patients was related to low-density lipoprotein, hemoglobin A1c, and fasting blood glucose levels.²²⁹ Hsa_circ_0063425 combined with hsa_circ_0056891 could differentiate T2D patients and those with fasting glucose impairment from normal subjects among 313 subjects, and the AUC values were 0.837 and 0.719, respectively.²³⁰ Hsa_circ_0063425 and hsa_circ_0056891 are found to sponge miR-19a-3p and miR-1-3p, respectively, aiming to exert crucial effects on insulin phosphatidylinositol 3-kinase/protein kinase B pathway.²³⁰ Furthermore, circHIPK3 and CDR1as have increased expression among T2D patients.²³¹ CircHIPK3, also known as hsa_circ_0000284, is a highly abundant circRNA within pancreatic islets and is obtained based on exon 2 in HIPK3 that is conserved between mouse and human cells.²³² CircHIPK3 facilitates insulin resistance and hyperglycemia by increasing FOXO1 expression and sponging miR-192-5p.²³³ CircHIPK3 expression declines within DB/DB islets. CircHIPK3 knockdown promotes β -cell apoptosis while decreasing glucose-stimulated insulin production. CircHIPK3 significantly affects islet cells partially by sponging miR-29-3p, miR-30, miR-124-3p, and miR-338-3p, which is achieved through regulating critical β -cell genes like Slc2a2, Mtpn, and Akt1.²³⁴ The above miRNAs are widely suggested to significantly affect β -cell proliferation, development, function, and survival.^{235–238} CircHIPK3 can differentiate T2D patients from normal subjects, and the specificity and sensitivity are 88.4 and 50.0%, respectively.²³¹ CDR1, first discovered

in brain tissue²³⁹ is widely expressed in pancreatic β -cells. CDR1as is reported to modulate insulin production and transcription in islet cells by inhibiting miR-7 through regulating endogenous target genes Pax6 and Myrip.²⁴⁰ CDR1as expression is downregulated within OB/OB and DB/DB mice, conforming to its effect on diabetes occurrence. Furthermore, CDR1as overexpression increases islet cell insulin production and insulin level,²⁴⁰ while CDR1as knockdown has opposite effects and reduces the prolactin-mediated MIN6B cell proliferation in isolated rat islets.²³⁴ CDR1as is shown to differentiate prediabetics from normal controls (AUC = 0.605).²³¹

Circ-Tulp4 is the candidate treatment against T2D.²⁴¹ Based on in vitro experimental results, circTulp4 modulated MIN6 cell proliferation. Its overexpression upregulated SOAT1, which then increased cyclin D1 expression, finally promoting cell cycle progression while alleviating β -cell dysfunction by inhibiting miR-7222-3p.²⁴¹ CircGlis3, the exocircRNA obtained in β -cells, exhibits higher expression within serum samples collected from T2D patients and diabetic mice. It is translocated in islet endothelial cells and serves as the therapeutic target.²⁴² CircGlis3 is related to lipotoxicity-mediated β -cell disease and diabetes through inhibiting cell growth and insulin production. From the mechanism perspective, circGlis3 can decrease islet endothelial cell invasion and viability and is transported to target cells by exosomes. Intronic circRNAs produced by insulin genes exert a vital impact on T2D occurrence. For instance, circular intronic-Ins2 (ci-Ins2) is found to modulate β -cell activity.²⁴³ CircRNA containing the lariat sequence of intron 2 in insulin gene is reported to modulate insulin production in T2D patients and diabetes rodent models, which may clarify the impairment of secretion ability.²⁴⁴ CircANKRD36 is also associated with chronic inflammatory factors in T2D. According to subsequent functional analysis, circANKRD36 expression was positively correlated with IL-6 and blood glucose levels.²⁴⁵ Furthermore, dysregulated circRNAs is correlated with pancreatic β -cell autophagy in T2D rats, which may result from rno_circRNA_008565 after interacting with miRNAs.²⁴⁶ Collectively, circRNAs are potentially related to inflammatory response, insulin resistance, and β -cell failure within T2D, and may be the candidate therapeutic target for T2D.

Gestational diabetes mellitus

CircRNAs are crucial for the prediction of several adverse reactions among gestational diabetes mellitus (GDM) patients. CircVEGFC, the new regulatory factor for glucose metabolism, has elevated expression among GDM pregnant women. Its upregulation is related to hypertension and fetal malformations.²⁴⁷ Pregnant women with circACTR2 upregulation may experience GDM. Accord-

ing to Zhu et al.²⁴⁸ aberrant circACTR2 expression was related to premature delivery, fetal malformations, miscarriage and intrauterine infection. Therefore, circRNAs are the candidate biomarkers that can be used for predicting the complication risk of GDM patients. However, their clinical application and the associated mechanisms should be further explored.

GDM is the frequently seen pregnancy complication, which has seriously threatened the maternal and fetal health. CircRNAs are found to be of therapeutic significance. For example, placental villous circRNAs are explored for their expression patterns in GDM women, suggesting that the dysregulated circRNAs are probably associated with GDM.^{249,250} Chen et al.²⁵¹ discovered the high circ_0008285 expression among GDM patients, and circ_0008285 depletion inhibited cell growth, migration, and invasion. Hsa_circ_0005243 is related to suppressing cell growth and invasion and promoting IL-6 and TNF- α expression within GDM via β -catenin/NF- κ B pathway.²⁵² CircPNPT1 expression increases within placental tissues in GDM patients and high glucose (HG)-stimulated trophoblast cells.²⁵³ At the mechanism level, circPNPT1 sponges miR-889-3p and activates p21-activated kinase 1 to modulate trophoblast cell dysfunction. CircPNPT1 is packaged in exosomes and subsequently delivered to additional cells.²⁵³

Effects of circRNAs on diabetic complications

Diabetes complications can result from persistent hyperglycemia, including diabetic retinopathy (DR), diabetic nephropathy (DN), diabetic neuropathy (DNP), diabetic cardiomyopathy (DCM), and HG-mediated endothelial dysfunction. The complications have seriously threatened human life. CircRNAs are widely suggested to play a key role in the occurrence of diabetic complications. Figure 4 displays circRNAs that are verified to be related to diabetes-related disorders.

CircRNAs in DR

DR can be classified as proliferative or nonproliferative DR based on its severity.²⁵⁴ DR, the frequent diabetes-related microvascular complication, is the major factor inducing blindness among working-aged individuals.²⁵⁵ It is correlated with alterations of endothelial cells and pericytes and shows the typical features of vascular leakage and capillary occlusion.²⁵⁵ CircRNA dysregulation is linked with DR progression; therefore, they may be the key biomarkers and reasonable therapeutic targets.

With regard to proliferative DR, circRNAs are the diagnostic biomarkers. According to Zhang et al.,²⁵⁶ the blood hsa_circ_0001953 expression increased in proliferative DR individuals in relative to nonproliferative DR counterparts and normal subjects. Nevertheless, this should be

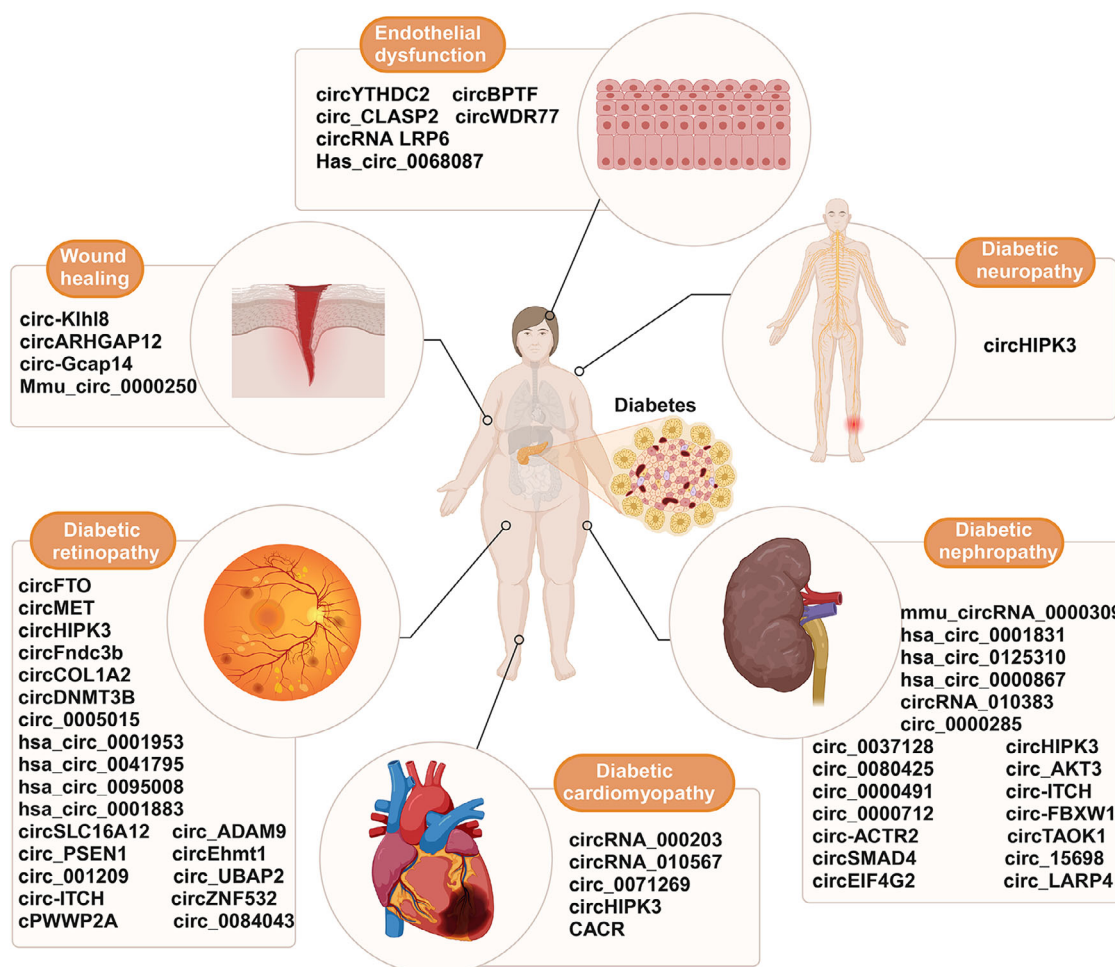


FIGURE 4 The role of circRNAs in diabetic complications. This figure summarizes the involvement of circRNAs in various diabetic complications, including diabetic retinopathy (DR), diabetic nephropathy (DN), diabetic neuropathy (DNP), diabetic cardiomyopathy (DCM), as well as high glucose-related endothelial dysfunction and impaired wound healing.

verified with a larger population. Totally 529 dysregulated circRNAs were detected from two diabetic human retinas. Among them, hsa_circ_0005015 had increased expression within plasma, fibrovascular membrane, and vitreous samples in DR individuals. It promoted retinal endothelial angiogenesis through modulating endothelial cell growth, tube formation, and migration. Hsa_circ_0005015 was the candidate diagnostic biomarker for DR. Subsequent functional experimental analysis showed that hsa_circ_0005015 sponged miR-519d-3p to inhibit miR-519d-3p activity, thus upregulating XIAP, MMP-2, and STAT3.²⁵⁷ Hsa_circ_0001883 and hsa_circ_0095008 have been recently identified as early diagnostic biomarkers for DR patients, and the AUCs for diagnosis are 0.607 and 0.671, respectively.²⁵⁸

Circhipk3 is upregulated in retinal endothelial cells and diabetic retinas, which blocks mir-30a-3p to increase the expression of vascular endothelial growth factor-C (VEGF-C), WNT2 and FZD4, resulting in vascular dysfunction and endothelial proliferation.²⁵⁹ circfto, circdnmt3b, circ-

colla2, circ_001209, circslc16a12, circ-UBAP2, and exosomal circfndc3 can modulate the diabetic retinal vascular function.^{260–264} They are the candidate targets for controlling DR. CircDNMT3B knockdown aggravated visual injury, while its upregulation alleviated retinal vascular dysfunction. By contrast, upregulation of circ_001209 sponges miR-15b-5p to exacerbate retinal injury of diabetic rats.^{265,266} CircRNAs affect the pericyte-endothelial cell crosstalk to modulate DR.^{267,268} cPWWP2A, the new DR-related circRNA, is the ceRNA interacting with miR-579 for promoting retinal vascular dysfunction by upregulating angiopoietin 1, SIRT1, and occludin.²⁶⁷ Interestingly, cPWWP2A is expressed on pericytes rather than on endothelial cells, while it has indirect regulation on endothelial cell biology via exosomes. Pericytes-derived exosomal circEhmt1 is transported into endothelial cells, where it prevents from HG-induced injury.²⁶⁸ CircRNAs are essential for human retinal pigment epithelial (ARPE-19) cells. CircRNA_0084043 and hsa_circ_0041795 are significantly upregulated within HG-mediated ARPE-19

cells, which can decrease their growth and survival. At the mechanism level, hsa_circ_0041795 sponges miR-646 to facilitate HG-induced apoptosis in ARPE-19 cells by activating VEGFC miR-646.²⁶⁹ CircRNA_0084043 deficiency sponges miR-140-3p and induces TGFA to significantly increase HG-exposed ARPE-19 cell apoptosis. CircRNA_0084043 deficiency efficiently suppresses HG-induced inflammation by suppressing the inflammatory factors TNF- α , Cox-2, and IL-6 within ARPE-19 cells.²⁷⁰ Circ-PSEN1 and circ-ADAM9 are upregulated in DR. Circ-ADAM9 promotes injuries to ARPE-19 cells, while circ-PSEN1 knockdown alleviates ferroptosis.^{271,272} Circ-ZNF532 modulates pericyte biology through sponging miR-29a-3p, thereby upregulating NG2, CDK2, and LOXL2 expression. Besides, it regulates pyroptosis and apoptosis of ARPE-19 cells to facilitate inflammation and angiogenesis in DR.^{273–275} Circ-ITCH is related to the DR pathology and physiology in rat retinal pigment epithelial cells.²⁷⁶ Recent research has shown that silencing circMET can reduce retinal angiogenesis.²⁷⁷ CircRNAs are involved in DR progression and may be used for the treatment of the disease.

CircRNAs in DN

DN is a major factor inducing mortality among diabetics.²⁷⁸ Its pathological features include progressive ECM deposition, basement membrane thickening, persistent mesangial cells (MCs) proliferation, and renal fibrosis.²⁷⁹ MC and ECM dysfunction play a vital role and serve as early warning signals for DN pathogenesis. It is of great importance to unravel molecular mechanism underlying DN and identify candidate therapeutic targets, aiming to improve patient survival.

Currently, circRNAs are identified as biomarkers for DN. Hsa_circ_0000867 and hsa_circ_0001831 show increased expression within peripheral blood in early type 2 DN cases.²⁸⁰ Hsa_circ_0001831 can be used to diagnose early type 2 DN, and the sensitivity, specificity, and AUC values are 0.85, 0.85, and 0.95, respectively.²⁸⁰ Hsa_circRNA_102682 is identified to independently predict the risk of DR in one article involving 73 patients), with the AUC for prediction being 0.97.²⁸¹

CircRNAs are widely used to treat DN, including circEIF4G2, circTAOK1, circACTR2, and hsa_circ_0125310.^{282–285} CircFBXW12 has elevated expression within the serum of DN cases and HG-induced human MCs. Based on in vitro functional experimental results, circFBXW12 knockdown inhibited human MC proliferation and decreased ECM generation and oxidative stress via miR-31-5p/LIN28B pathway.²⁸⁶ CircSMAD4 can mitigate ECM accumulation, while circRNA_15698 can promote ECM accumulation.^{287,288} Liu et al.²⁸⁹ suggested that circ_0080425 expression was related to DN

development, which also positively affected MCs fibrosis and growth via the miR-24-3p/FGF11 axis. Circ_0000712 enhances the HG-induced apoptosis, fibrosis, oxidative stress and inflammation in DN through regulating SOX6 and miR-879-5p expression.²⁹⁰ Similarly, circ_0000491 sponges miR-455-3p to regulate Hmgb1 expression, therefore promoting HG-mediated apoptosis, fibrosis, oxidative stress and inflammation in DN.²⁹¹ In vivo, circRNA_010383 upregulation suppresses miR-135a expression, increases transient receptor potential cation channel, subfamily C, and member 1 expression, and suppresses kidney fibrosis and proteinuria of DN mice.²⁹² Circ_0000285 and circ_0037128 are upregulated within the DN mouse models. Circ_0000285 sponges miR-654-3p to activate MAPK6 expression and induce podocyte injury.²⁹³ Circ_0037128 has been recently suggested to modulate DN occurrence by miR-17-3p/AKT3 pathway.²⁹⁴ Circ_0037128 is reported to suppress HK-2 cell growth and enhance their fibrosis and inflammation by miR-497-5p/NFAT5 pathway. By contrast, circAKT3, circLARP4, circITCH, and mmu_circRNA_0000309 expression decreases within DN rats and mice, as well as in DN cell models and tissues.^{224,295–297} Upregulation of circAKT3 sponges miR-296-3p to suppress the fibrosis-associated protein production, therefore modulating E-cadherin, and it may be the significant therapeutic target for patients with DN.²⁹⁵ CircHIPK3 can modulate insulin production and islet proliferation in order to facilitate insulin resistance. In two articles regarding DN, circHIPK3 significantly influenced rat MCs and human renal tubular epithelial HK-2 cells. From the mechanism perspective, circHIPK3 expression significantly decreased within HG-treated HK-2 cells. CircHIPK3 overexpression reduced the accumulation of miR-326 and miR-487a-3p, thereby upregulating SIRT1 while reducing HG-mediated suppression on HK-2 proliferation.²⁹⁸ Furthermore, circHIPK3 expression was found to be upregulated within rat MCs. CircHIPK3 knockdown suppressed cell growth and inhibited the mRNA abundance of PCNA, cyclin D1, TGF- β 1, FN, and Col. I within MCs.²⁹⁹ However, more investigations are warranted to demonstrate the effect of circHIPK3 on DN.

CircRNAs in DNP

DNP, a common diabetic complication, can substantially decline the life quality of diabetic patients. DNP involves the sensory functional loss, which initiates at the distal lower extremities and is featured by stimulus-evoked and spontaneous pain, along with many illnesses.³⁰⁰ Nonetheless, the DNP etiology is still unknown. CircRNAs are found to regulate DNP progression.

NcRNAs, including miRNAs, circRNAs, and long ncRNAs, were analyzed for their expression in streptozotocin-caused DNP mice. There were totally 148 miRNAs, 135

circRNAs, 30 mRNAs, and nine long ncRNAs with significant dysregulation among DNP mice. They were enriched in Rap1, MAPK, protein digestion, and absorption pathways, and human T-cell lymphotropic virus-I infection pathways.³⁰¹ In addition, 133 mRNAs and 15 circRNAs with dysregulated expression were identified within dorsal root ganglia in diabetic and wild-type mice through chip scanning and high-throughput RNA sequencing. Meanwhile, there were 14 mRNAs and seven circRNAs closely associated with diabetic peripheral neuropathy.³⁰² They are the candidate diagnostic and prognostic biomarkers for DNP.

CircHIPK3 is abundantly expressed in DNP rats and patients. CircHIPK3 overexpression is positively related to neuropathic pain among T2D patients. CircHIPK3 knockdown mitigates neuropathic pain of diabetic rats, which may be probably associated with the reduced neuroinflammation. Mechanistically, circHIPK3 interacts with miR-124 to downregulate miR-124. The study provides the first evidence supporting the use of intrathecal circHIPK3 shRNA in the treatment of rat DNP.³⁰³

circRNAs in DCM

DCM is a main factor inducing morbidity and mortality among diabetics and brings significant burdens on the economy and society globally.^{304,305} DCM exhibits the typical features of cardiomyocyte apoptosis, hypertrophy, myocardial interstitial fibrosis, as well as subsequent HF without dyslipidemia, hypertension and coronary artery disease (CAD).^{304,306}

CircRNAs are substantially related to DCM development. According to Zhou et al., circRNA_010567 was significantly upregulated within Ang-II-induced cardiac fibroblasts (CFs) and the myocardium of diabetic mice. It modulated fibrosis-associated protein expression within CFs, including Col I, α -SMA, and Col III by miR-141/TGF- β 1 pathway.³⁰⁷ CircRNA_000203 expression significantly increased within CFs and DCM mouse myocardium. Functional experimental analysis showed that circRNA_000203 upregulation inhibited miR-26b-5p and activates CTGF and Col1a2, finally upregulating α -SMA and Col3a1 within CFs.³⁰⁸ Subsequently, CircHIPK3 was found to promote myocardial fibrosis while reducing cardiac function of DCM mice. CircHIPK3 deficiency suppressed CFs proliferation by the Col3a1 and miR-29b-3p/Coll1a1 regulatory network.³⁰⁹ Therefore, circRNA_010567, circHIPK3, and circRNA_000203 are related to the myocardial fibrosis pathogenesis, providing the therapeutic target and molecular mechanism for DCM.

CircHIPK3 is also discovered with downregulated expression in HG-exposed human cardiomyocytes and in DCM. CircHIPK3 upregulation inhibits the expression of PTEN, the tumor suppressor, and suppresses the

HG-induced apoptosis in human cardiac myocytes.³¹⁰ Circ_0071269 is markedly upregulated in HG-exposed rat cardiomyocytes. Circ_0071269 silencing can sponge miR-145 to enhance cell viability and inhibit inflammatory response, pyroptosis, and cytotoxicity of rat cardiomyocytes in vitro, thereby upregulating GSDMA.³¹¹ Hsa_circ_0076631, called caspase-1-associated circRNA (CACR) as well, has elevated expression in HG-exposed cardiomyocytes and patients with diabetes. CACR knockdown activates caspase-1 by targeting miR-214-3p within cardiomyocytes. On the contrary, miR-214-3p deficiency partly reverses the benefits of CACR knockdown for the pyroptosis of cardiomyocytes. Consequently, CACR is the candidate new therapeutic target for DCM through regulating CACR/miR-214-3p/caspase-1 pathway.³¹²

CircRNAs in hyperglycemia-associated wound healing and endothelial dysfunction

Endothelial cells constitute the inner vascular lining, which are the anticoagulant barrier between blood and vessel wall.³¹³ These unique multifunctional cells regulate vasomotor tone, metabolic homeostasis, vascular smooth muscle cell (VSMC) growth, and immune/inflammatory responses.³¹⁴ Hyperglycemia has been previously suggested to induce endothelial cell dysfunction among diabetics.^{315,316} Hyperglycemia is widely suggested to change circRNA expression, while circRNAs are related to different hyperglycemia-mediated endothelial dysfunction processes during diabetes.³¹⁷

Human umbilical vein endothelial cells (HUVECs) can be easily obtained and extensively applied for in vitro research on endothelial cells. Based on Cheng et al.,³¹⁸ hsa_circ_0068087 promoted the inflammation and dysfunction of endothelial cells via miR-197/TLR4/NF- κ B/NLR family pyrin domain containing 3 (NLRP3) pathway. CircBPTF is under close regulation in hyperglycemia-mediated HUVECs. CircBPTF deficiency targets miR-384 and downregulates LIN28B to suppress oxidative stress and inflammatory injuries.³¹⁹ Comparatively, circ_CLASP2 expression declines in hyperglycemia-mediated HUVECs. Circ_CLASP2 regulates the miR-140-5p/FBXW7 pathway to prevent hyperglycemia-induced dysfunction of HUVECs.³²⁰

Based on significant evidence, circRNAs like circWDR77, circLRP6, and circYTHDC2 show upregulation within hyperglycemia-exposed VSMCs.^{321–323} The above circRNAs enhance VSMCs growth and invasion via diverse mechanisms. Suppressing circWDR77 inhibits VSMC growth and invasion via miR-124/fibroblast growth factor 2 pathway.³²¹ CircYTHDC2 is found to modulate VSMC dysfunction through YTHDC2-induced m6A modification and regulate ten-eleven translocation 2 expression.³²³ CircLRP6, which sponges miR-545-3p, contributes to the

growth and invasion of hyperglycemia-exposed VSMCs by downregulating HMGA1.³²²

Various circRNAs are related to hyperglycemia-mediated wound healing. Circ-Klhl8 expression is enhanced in endothelial progenitor cells under hypoxic pretreatment conditions, whereas circ-Gcap14 expression is enhanced in ADSCs.^{324,325} Upregulation of circ-Gcap14 enhances angiopoiesis and accelerates hypoxic ADSC wound closure in diabetics.³²⁴ Based on Shang et al.,³²⁵ circ-Klhl8 promoted autophagy, suppressed hyperglycemia-mediated endothelial cell injury, and enhanced diabetic wound closure via the miR-212-3p/SIRT5 pathway. Recently, exosomal circARHGAP12 and mmu_circ_0000250 are indicated to promote diabetic wound closure by regulating autophagy.^{326,327} From the mechanism perspective, circARHGAP12 can sponge miR-301b-3p to enhance diabetic wound healing, thereby regulating target genes ATG16L1 and ULK2 expression.³²⁷ CircARHGAP12 is the candidate novel therapeutic target for diabetic wound closure.

3.2.2 | CircRNAs in adipocyte metabolism

Aberrant adipocyte metabolism

Adipocyte metabolism refers to a process to digest, absorb, synthesize and decompose body adipose tissues under the action of different enzymes. Aberrant adipocyte metabolism usually results in further disorders, including metabolic syndrome, hyperlipidemia, AS, and non-alcoholic fatty liver disease (NAFLD).^{328–330} Adipocyte metabolism is a complicated physiological process that involves a variety of regulatory factors and genes. It becomes crucial to maintain the adipocyte metabolic homeostasis to prevent and treat adipogenesis-associated diseases. CircRNAs display specific expression profiles in diverse tissues, cells, and developmental stages, impacting the metabolic processes in vivo.³³¹ CircRNAs are increasingly suggested to be associated with adipocyte metabolism and the associated disorders (Table 2).

CircRNAs modulates adipocyte metabolism within adipose tissue

CircRNAs can impact adipose function in numerous species, including mice, humans, cattle and pigs. As reported by Zhu et al.,³³² hsa_circH19 exhibited upregulation within the blood in patients experiencing metabolic syndrome. Hsa_circH19 silencing enhanced adipose stem cell differentiation via PTBP1. By conducting sequencing on human subcutaneous and visceral adipose tissues, Arcinas et al.³³³ identified circTshz2-1 and circArhgap5-2 as the essential regulatory factors for adipogenesis in vitro. Based on the obtained results, circRNAs expression exerts

a vital role in keeping adipocyte metabolism. CircSAMD4A also sponges miR-138-5p and modulates EZH2 expression in human obese disorders to control the adipogenesis of obese people.³³⁴ CircARF3 can sponge miR-103 to inhibit miR-103 activity and upregulate TRAF3, miR-103's downstream target. Then, it alleviates the high-fat-diet-induced inflammation in mouse adipose tissue.³⁴⁶

CircRNAs can sponge miRNA within adipose tissue and directly bind to RBPs, thus participating in expression. Circ_0075932 expression exerts a vital role in human normal adipose tissue. Exosomes derived from circ_0075932 overexpression adipose cells significantly enhance cell apoptosis and inflammation. circ_0075932 accelerates cell apoptosis and inflammation through direct binding to RBP PUM2 and enhancing PUM2-induced AuroraA/NF- κ B pathway activation.³³⁵

Mesenchymal stem cells (MSCs) are stem cells with high plasticity, which include bone marrow stem cells (BMSCs) and adipose-derived mesenchymal stem cells (ADSCs). They are capable of self-renewal and differentiation into bone cells, adipose cells and chondrocytes.³⁴⁷ As recently discovered, many circRNAs are related to MSCs adipogenesis.^{336,337,348} For instance, circFOXPI sponges miR-17-3p/miR-127-5p and shows indirect regulation of EGFR and noncanonical Wnt pathways, thus maintaining the MSC stemness.³⁴⁹ CircRNA CDR1as silencing can promote osteogenic differentiation of BMSCs and suppress their adipogenic differentiation, whereas CDR1as overexpression has opposite effects. Mechanistically, CDR1as competitively binds miR-7-5p to WNT5B for enhancing adipogenic differentiation.³³⁷ CircRNA-vgll3, through the direct sequestering of cytoplasmic miR-326-5p and inhibition of miR-326-5p activity, promotes osteogenic differentiation of ADSCs.³³⁶ miR-338-3p can upregulate circRNA_013422 and circRNA_22566 in osteogenic differentiation of mouse ADSCs.³³⁸ miR-338-3p targets Fgfr2 and Runx2 to modulate osteogenic differentiation of mouse bone marrow stromal stem cells.³³⁹ CircRNA_23525 targets miR-30a-3p to modulate Runx2 expression, which has been detected as the active regulatory factor for the osteogenic differentiation of ADSCs.³⁴⁰

CircRNAs and liver lipid metabolism

The liver exerts an essential effect on various metabolic processes, including lipid digestion, absorption, production, transportation, and decomposition. Drink abuse, obesity, and diabetes can induce the liver lipid metabolic disturbance. Excess liver lipid accumulation produces massive reactive oxygen species, which causes mitochondrial dysfunction and endoplasmic reticulum stress within hepatocytes, ultimately inducing NAFLD.^{350–352} Numerous circRNAs are suggested to regulate lipid metabolism and influence lipid disorder occurrence.^{345,353}

TABLE 2 Functional circRNAs involved in adipocyte metabolism.

CircRNA	Mechanism/ partner	Role in fat metabolism	Species	References
hsa_circH19	PTBP1	Promotes hADCs adipogenic differentiation	Human	332
circSAMD4A	miR-138-5p/EZH2	Promotes preadipocyte differentiation	Human	333
circARF3	miR-103/TRAF3	Alleviates mitophagy-mediated inflammation	Mouse	334
circ_0075932	PUM2	Promoting effect on inflammation and apoptosis in dermal keratinocytes	Human	335
circRNA-vgl3	miR-326-5p	Promotes osteogenic differentiation of adipose-derived mesenchymal stem cells	Human	336
circRNA CDR1as	miR-7-5p/WNT5B	Promotes adipogenic and suppresses osteogenic differentiation of BMSCs	Human	337
circRNA_013422/ circRNA_22566	miR-338-3p	Regulates osteogenic differentiation of bone marrow stromal stem cells	Mouse	338,339
circRNA-23525	miR-30a-3p	Regulates osteogenic differentiation of adipose-derived mesenchymal stem cells	Mouse	340
circRNA_0000660	miR-693/Igfbp1	Reduces liver lipid accumulation	Mouse	341
circHIPK3	miR-192-5p	Enhances fat deposition and triglyceride content in HepG2 cells	Human	233
circRNA_0046366	miR-34a/PPAR α	Hinders lipid metabolism and cause liver steatosis	Human	342
circRNA_0046367	miR-34a/PPAR α	Alleviates hepatic steatosis	Human	343
circRNA_021412	miR-1972/LPIN1	Contributes to the hepatic steatosis via disrupting the balance of lipogenesis and catalytic separation	Human	344
circSCD1	JAK2/STAT5	Promotes the occurrence of fatty liver disease	Mouse	345

Abbreviations: BMSC, bone marrow mesenchymal stem cell; EZH2, enhancer of zeste homolog 2; hADC, human adipose-derived stem cell; HepG2, hepatocellular carcinoma cell line 2; Igfbp1, insulin-like growth factor binding protein 1; JAK2, Janus kinase 2; PPAR α , peroxisome proliferator-activated receptor alpha; PTBP1, polypyrimidine tract-binding protein 1; PUM2, pumilio RNA binding family member 2; STAT5, signal transducer and activator of transcription 5; TRAF3, TNF receptor-associated factor 3; WNT5B, wingless-type MMTV integration site family, member 5B.

A high-fat diet in the mother can change liver miRNAs expression in her offspring and impair the metabolic health.³⁵⁴ Current research has clarified a novel mechanism underlying the role of maternal obesity in liver lipid metabolism of offspring. Through liver RNA sequencing on offspring of high-fat-diet-fed C57BL/6J mice, Chen et al.³⁴¹ detected 231 DEcircRNAs, including 121 with upregulation whereas 110 with downregulation. circRNA_0000660 expression is significantly related to Igfbp1 expression, while circRNA_0000660 silencing decreases liver lipid accumulation. Maternal obesity induces metabolic disorders in offspring by changing liver circRNA expression. CircHIPK3 modulates lipid metabolism within hepatocytes. It promotes triglyceride level and adipose deposition within HepG2 cells, and induces diabetes-associated metabolic diseases like insulin resistance and hyperglycemia by decreasing miR-192-5p and increasing its downstream TF FOXO1.²³³

CircRNAs are widely suggested with vital effects on regulating hepatic steatosis^{355,356} (Figure 5). miR-34a can bind to PPAR α in rodents, which suppresses lipid metabolism and enhances hepatic steatosis, while circRNA_0046366 and circRNA_0046367 compete against

PPAR α for binding to miR-34a. These circRNAs act as endogenous regulators of miR-34a, reducing hepatic steatosis by suppressing the interaction of miR-34a with MRE within PPAR α mRNA. Aberrant circRNA_0046366 and circRNA_0046367/miR-34a/PPAR α signaling is the potential novel target for treating hepatic steatosis.^{342,343} In high-fat-diet-mediated hepatic steatosis, circRNA_021412 expression significantly decreases.³⁴⁴ circRNA_021412 downregulation suppresses the competitive inhibition on miR-1972, therefore repressing Lpin1, the target gene of miR-1972. Lpin1 downregulation can down-regulate long-chain acyl CoA synthase, causing hepatic steatosis.

NAFLD is the condition of excess fat accumulation within hepatocytes not associated with alcohol abuse. Many NAFLD patients experience nonalcoholic steatohepatitis (NASH).³⁵⁷ Aberrant circSCD1 expression influences hepatocyte lipidation and enhances fatty liver disease via JAK2/STAT5 pathway.³⁴⁵ Jin et al.³⁵³ established four circRNA-miRNA-mRNA pathways using the NASH mouse model. Their results showed that circRNA expression patterns might be employed to diagnose NASH.

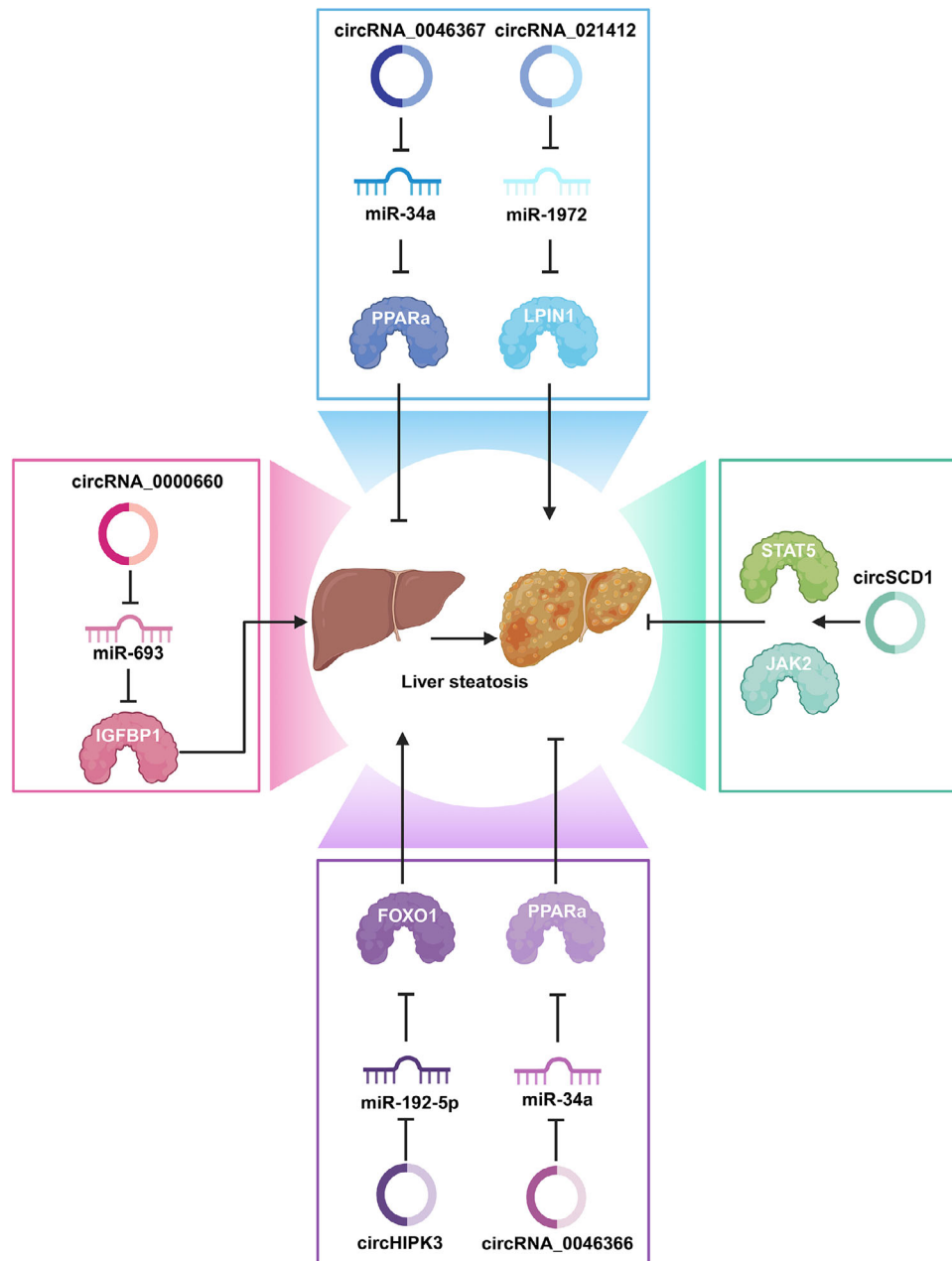


FIGURE 5 CircRNAs in the regulation of hepatic steatosis. This figure highlights the roles of circRNAs in hepatic steatosis. CircRNA_0046366 and circRNA_0046367 reduce hepatic steatosis by competing with PPAR α for miR-34a binding. In NAFLD, abnormal circSCD1 expression promotes fatty liver disease through the JAK2/STAT5 pathway.

3.3 | CircRNAs in CVD

CVD is a group of disorders that affect the heart and cardiovascular system,³⁵⁸ including AS, angina, myocardial infarction (MI), stroke,³⁵⁹ HF, heart valve disease, and cardiomyopathy.³⁶⁰ CVDs are among the leading causes of disability and death worldwide.^{361,362} They can be caused by various risk factors, including diabetes, smoking, advanced age, dyslipidemia, and hypertension.³⁶³ In the field of CVD research and treatment, exosomes play a crucial role, especially as biomarkers of disease progres-

sion and treatment response, reflecting various cardiovascular conditions such as coronary heart disease (CHD), AS, acute myocardial infarction (AMI), and HF.^{364–367} Exosomes, as mediators of cell-to-cell communication, have emerged as important regulators of angiogenesis and cardiac repair.^{368,369} Additionally, exosome-derived circRNAs play a significant role in the pathophysiology of the cardiovascular system by adsorbing miRNAs and regulating protein production, thereby participating in the progression of CVDs. These findings provide new insights into the complex mechanisms of CVDs and offer an important

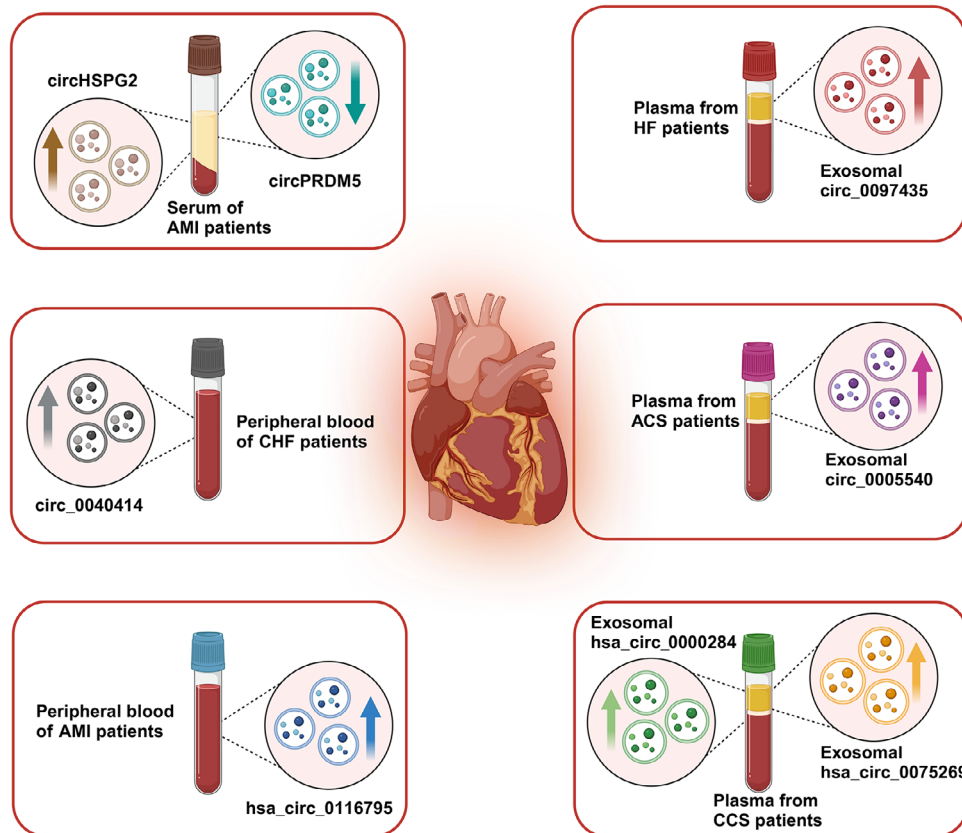


FIGURE 6 CircRNAs in cardiovascular disease. This figure showcases the diverse applications of circRNAs in blood samples from patients with various cardiac conditions. The top left displays plasma containing circHSPG2, associated with AMI patients. Adjacent is plasma from AMI patients featuring circPRDM5, emphasizing its potential role. The top right depicts exosomal circ_0097435 extracted from plasma of HF patients. Moving downward, the middle right panel presents plasma from ACS patients, containing exosomal circ_0005540. The middle left showcases plasma from CHF patients with circ_0040414. The bottom left highlights peripheral blood of AMI patients with hsa_circ_0116795, while the bottom right displays plasma from CCS patients, featuring exosomal hsa_circ_0000284 and circ_0075269. These findings underscore the significance of circRNAs in diagnosing and understanding the pathogenesis of cardiac diseases. (CircRNAs, circulating microRNAs; AMI: acute myocardial infarction; HF: hemodialysis; ACS, acute coronary syndrome; CHF, chronic heart failure; CCS, coronary chronic stable).

theoretical basis for developing new diagnostic tools and therapeutics (Figure 6).

3.3.1 | CircRNAs in CHD

CHD is the most common heart disease worldwide. According to the World Health Organization, approximately 7 million people die from CHD every year.³⁷⁰ AS is a chronic inflammatory disease and the main pathological basis of CHD. The accumulation of lipid, calcium, and fibrous tissue in the inner wall of the artery increases the thickness and decreases the elasticity, leading to hardening, narrowing, and potential occlusion of the blood vessels.³⁷¹ AS mainly occurs in large and medium-sized arteries, such as the coronary artery, carotid artery, abdominal aorta, and femoral artery.³⁷² It is also the root cause of stroke and MI.³⁷³ Many stud-

ies have shown that exosome-derived circRNA is often regarded as a reliable biomarker reflecting the disease status of CHD due to its stability in body fluids and long half-life. Vilades et al.³⁷⁴ found that the level of hsa_circ_0001445 was closely related to the degree of coronary AS in CHD patients and could improve the accuracy of cardiovascular risk assessment models. The Wang's team found that hsa_circ_0001879 and hsa_circ_0004104 were significantly upregulated in CHD patients, providing a new avenue for early diagnosis of the disease.³⁷⁵ The study by Wu et al.³⁷⁶ further revealed 355 DEcircRNAs in CHD patients, especially hsa_circ_0005540, which was significantly associated with CHD ($p < 0.0001$) and showed high discrimination power in ROC analysis (AUC = 0.853). Miao et al.³⁷⁷ also pointed out that circ-YOD1, hsa-miR-21-3p, and hsa-miR-296-3p have important diagnostic value in CHD, with circ-YOD1 showing high prognostic value. The study by Xiong et al.³⁷⁸ found that the expression level of

CircNPHP4 derived from monocyte exosomes was significantly increased in CHD patients. This circRNA showed a high degree of discrimination and could effectively distinguish CHD patients from nonpatients.³⁷⁸ Liu et al.³⁷⁹ confirmed that circRNAs carried by plasma exosomes showed significant differential expression in chronic coronary syndrome (CCS), with *exo-hsa_circ_0075269* and *exo-hsa_circ_0000284* being significantly upregulated in CCS patients.³⁷⁹ Additionally, Liu et al. found that exosome-derived *circ_0026218* was involved in the development of AS by affecting miR-188-3p and regulating the TLR4/NF- κ B pathway.³⁸⁰ Taken together, these studies demonstrate the great potential of circRNAs in the diagnosis of CHD, providing new molecular markers for early diagnosis and possible new targets for the treatment and prognosis of the disease.

3.3.2 | CircRNAs in acute coronary syndrome

Acute coronary syndrome (ACS) is a sudden occurrence of CAD, mainly consisting of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina.³⁸¹ ACS is usually caused by plaque rupture in AS and subsequent thrombus formation.³⁸² Studies have shown that circRNA plays a regulatory role in MI models.

Role as biomarkers

Huang et al.³⁸³ found that *hsa_circ_0116795* was significantly upregulated in the peripheral blood of AMI patients, and its expression increased in cardiomyocytes under hypoxic conditions, suggesting it may be used as a biomarker for early diagnosis of AMI. Liu et al.'s study³⁸⁴ indicated that the expression of *circPRDM5* in the serum of AMI patients was significantly reduced. The sensitivity of AMI diagnosis could be significantly improved when *circPRDM5* was combined with cardiac troponin T and creatine kinase-MB.³⁸⁴ Tian et al.,³⁸⁵ while exploring biomarkers of sudden cardiac death (SCD) caused by acute ischemic heart disease (IHD), found time-dependent expression patterns of *circSLC8A1* and *circNFIX* in animal and cellular models that matched findings from autopsy cases. This suggests their potential value in distinguishing IHD-related SCD. In particular, the high sensitivity and specificity of *circSLC8A1*, as well as its positive correlation with creatine kinase-MB in pericardial fluid, and downregulated *circNFIX* levels may reflect ischemic myocardial injury, which is negatively correlated with the degree of coronary artery stenosis.³⁸⁵ The study by Tong et al.³⁸⁶ analyzed microarray data of exocircRNA and mRNA in AMI from CHD patients. The constructed ceRNA network analysis revealed specific circRNAs (such as *circRNA0001785*,

circRNA0000973, *circRNA0001741*, and *circRNA0003922*) as promising candidates for effective prediction of CHD.³⁸⁶

CircRNA promotes the progress of ACS

MI and I/R injury are the most common and fatal manifestations of ACS. Increasing evidence shows that circRNAs play an important role in the occurrence and development of ACS.

First, circRNAs affect cardiac fibrosis after MI by regulating the proliferation and migration of CFs. Pang et al.³⁸⁷ showed that *circHelz* can bind to Yes-associated protein (YAP) and promote its localization to the nucleus, thereby promoting cell proliferation and growth. Reducing *circHelz* expression alleviates cardiac fibrosis and the activation of CFs.³⁸⁷ Wang et al.³⁸⁸ pointed out that exosome *circUbe3a* released by M2-type macrophages promotes the proliferation and migration of CFs by adsorbing miR-138-5p and inhibiting the translation of Rho family GTPase 3 (*RhoC*). Deng et al.³⁸⁹ revealed that *circ-HIPK3* interacts with miR-17-3p and adenylate cyclase type 6 (*ADCY6*) to regulate calcium ion concentration in cardiomyocytes and affect cardiac function. Reducing its level can reduce cardiac fibrosis and maintain cardiac function after MI.³⁸⁹ These studies suggest that regulating the expression of specific circRNAs may effectively reduce cardiac fibrosis after MI, providing a new strategy for the treatment of CVDs.

Second, circRNAs affect MI and I/R injury by regulating inflammatory responses and immunomodulatory processes. For example, Huang et al. found that *circ_SMG6* binds to miR-138-5p, upregulates early growth response 1 (*EGR1*) expression, promotes neutrophil recruitment, and exacerbates myocardial injury.³⁹⁰ Additionally, Zhu et al.³⁹¹ showed that the expression of *circITGB1* was increased in the plasma of AMI patients, which increased the expression of NFAT activating molecule 1 (*NFAM1*) by competitively binding to miR-342-3p and affected the maturation of DCs, highlighting the role of circRNA in inflammatory response and immune regulation. Ye et al.³⁹² pointed out that the serum concentrations of IL-1 β and IL-18 were increased, *circ-NNT* and ubiquitin specific peptidase 46 (*USP46*) were upregulated, while miR-33a-5p was downregulated in MI patients. By regulating *USP46*, *circ-NNT* promoted pyroptosis in myocardial I/R injury.³⁹²

Notably, circRNAs also act by affecting specific signaling pathways. Zhang et al.³⁹³ found that *circ_0030235* activated the PI3K/AKT and MEK/ERK signaling pathways by regulating miR-526b to promote injury in MI models using an oxygen glucose deprivation/reperfusion (OGD/R) model. Zhu et al.³⁹⁴ found that *circMAT2B* increased OGD-induced cell damage and inflammatory damage by positively regulating miR-133 and activating the PI3K/AKT and Raf/MEK/ERK signaling pathways in MI. Li et al.³⁹⁵ found that inhibition of *circARPA1* could effectively reduce

myocardial cell fibrosis and apoptosis, emphasizing the importance of the Wnt/ β -catenin signaling pathway in this process.

In addition, numerous studies have revealed that circRNAs aggravate myocardial injury. For example, circROBO2 can act as a sponge for miR-1184, promoting cardiomyocyte apoptosis by upregulating the expression of TNF receptor associated death domain.³⁹⁶ Circ_0049271 aggravated myocardial cell damage through the miR-17-3p/FZD4 signaling axis in hypoxia-reoxygenation induced myocardial cell damage.³⁹⁷ The expression of circHSPG2 and MAPK kinase kinase 2 (MAP3K2) is increased in the serum of AMI patients, while the expression of miR-1184 is decreased. Downregulation of circHSPG2 can reduce myocardial cell injury.³⁹⁸ Circ_0023461 is upregulated under hypoxic conditions and upregulates the expression of phosphodiesterase 4D (PDE4D) by acting on miR-370-3p, thereby regulating the viability and glycolytic ability of AC16 cardiomyocytes.³⁹⁹ CircRbms1 promotes myocardial cell injury by regulating the miR-742-3p/forkhead box O1 (FOXO1) axis in the progression of MI.⁴⁰⁰ Circ_0124644 increases myocardial cell injury in AMI by targeting miR-590-3p and affecting the expression of SRY-box TF 4.⁴⁰¹ Circ_0007059 is upregulated during MI and promotes inflammation and cardiomyocyte apoptosis by acting as a sponge for miR-378 and miR-383.⁴⁰² Under hypoxia/reoxygenation (H/R) conditions, the expression of circ-CBFB in cardiomyocytes increases, promoting apoptosis by adsorbing miR-495-3p, revealing the role of circ-CBFB in H/R injury.⁴⁰³

In summary, circRNAs play a key role in cardiac fibrosis, myocardial apoptosis, inflammatory response, and myocardial I/R injury after MI by regulating the proliferation, migration, myocardial apoptosis, inflammatory response, and immunomodulatory processes of CFs, as well as specific signaling pathways. These studies not only deepen our understanding of the pathogenesis of CVDs but also provide important clues for the development of new therapeutic strategies.

CircRNA inhibits the progress of ACS

By acting as a “molecular sponge” for miRNA, circRNAs can affect the activity of miRNA and regulate the expression of downstream target genes. This mechanism also plays a key inhibitory role in the occurrence and development of ACS.

CircRNAs play an important role in alleviating myocardial hypoxia. For example, Zhao et al.⁴⁰⁴ revealed the protective effect of circHSPG2 on cardiomyocytes under hypoxic conditions. By acting as a molecular sponge for miR-25-3p, circHSPG2 positively regulates the miR-25-3p/proapoptotic WT1 regulator axis and protects cardiomyocytes from hypoxia-induced damage.⁴⁰⁴ Similarly,

Zhou et al.⁴⁰⁵ found that circ_0001747 in ADSC exosomes alleviated I/R injury in cardiomyocytes by targeting miR-199b-3p. Gao et al.⁴⁰⁶ found that H/R-induced cardiomyocyte death could be alleviated by enhancing the expression of mmu_circ_000338 in H/R-treated and I/R-injured mouse hearts. By directly binding to histone deacetylase 7 (HDAC7) and interfering with its entry into the nucleus, mmu_circ_000338 alleviated the inhibition of HDAC7 on forkhead box protein A2 (FOXA2) transcription, thereby upregulating FOXA2 and inhibiting receptor-interacting protein kinase 3-dependent necrosis.⁴⁰⁶ Zhao et al.⁴⁰⁷ investigated hypoxic conditions in vitro and found that circRNA_010567 enhanced mitochondrial activity by adsorbing miR-141 and increasing death-associated protein kinase 1 expression, thus playing a protective role in hypoxia-induced myocardial cell damage. Liu et al.⁴⁰⁸ revealed the protective role of circ_0002612 in I/R injury. Circ_0002612 releases the expression of its target peroxisome proliferator-activated receptor gamma coactivator 1 alpha (Ppargc1a) by competitively binding to miR-30a-5p, thereby inhibiting the expression of NLRP3 and contributing to the survival of cardiomyocytes and reducing apoptosis.⁴⁰⁸

In addition, circRNAs are also involved in the process of cardiac repair and remodeling. These studies reveal the important role of circRNA in the pathological process of the heart and provide a new target for the treatment of heart diseases. For example, Wang et al.⁴⁰⁹ found that circHIPK3 could promote cardiac endothelial cell cycle progression and proliferation by reducing miR-29a activity and increasing vascular endothelial growth factor A (VEGFA) expression, thus alleviating damage after MI. Garikipati et al.⁴¹⁰ showed that overexpression of circFndc3b, which was downregulated after MI, promoted angiogenesis, reduced cardiomyocyte apoptosis, and improved cardiac function. Ju et al.⁴¹¹ found that overexpression of circRNA FEACR could inhibit MI and improve cardiac function by directly binding to nicotinamide phosphoribosyltransferase (NAMPT), improving NAMPT protein stability, enhancing SIRT1 expression, and promoting forkhead box protein O1 (FOXO1) transcriptional activity, thereby upregulating the transcription of the ferroptosis inhibitor Fth1. Li et al.⁴¹² revealed that regulating the circCELF1/miR-636/Dickkopf WNT signaling pathway inhibitor 2 (DKK2) pathway can reduce myocardial fibrosis and improve cardiac function. Zhu et al.⁴¹³ showed that circNFIB expression was reduced after MI, and its overexpression could reduce the proliferation of CFs by adsorbing miR-433. Zhou et al.⁴¹⁴ found that circRNA ACR activated (Pink1) expression and reduced myocardial infarct size by blocking DNA methyltransferase 3B (DNMT3B)-mediated DNA methylation of the Pink1 promoter. Sun et al.⁴¹⁵ explored the role of

circFoxo3 in MI and found that overexpression of circFoxo3 improved cardiac dysfunction caused by MI. Wang et al.⁴¹⁶ focused on the role of mitochondrial fission and apoptosis-related circRNA (MFACR) in cardiac cell death and pointed out that MFACR prevented mitochondrial protein 18 kDa (MTP18) translation by inhibiting miR-652-3p and reducing cardiac cell death. Zhao et al.⁴¹⁷ found that circMACF1 could act as a “sponge” of miR-500b-5p to upregulate the expression of EMP1 and slow down the progression of AMI. Notably, Wei et al.⁴¹⁸ found that circWhsc1 in EVs produced by endothelial cells under hypoxic conditions promoted cardiomyocyte proliferation and cardiac regeneration. This process enhances tripartite motif containing 59 (TRIM59) phosphorylation, thereby increasing TRIM59 binding to signal transducer and activator of transcription 3 (STAT3) and promoting STAT3 phosphorylation, which ultimately leads to cardiomyocyte proliferation, potentially providing a therapeutic target for cardiac repair after MI.⁴¹⁸ Yu et al.⁴¹⁹ showed that circCEBPZOS levels were reduced in the serum of patients with poor cardiac remodeling. Overexpression of circCEBPZOS can improve cardiac function by regulating the miR-1178-3p/phosphoinositide-dependent kinase-1 (PDK1) axis, thereby reducing adverse remodeling and promoting angiogenesis after MI.

In terms of enhancing the antioxidant capacity of cardiomyocytes, studies have shown that circRNAs are involved in regulation through different mechanisms. For example, Fan et al.⁴²⁰ found that H₂O₂-induced cardiomyocyte injury could be alleviated by increasing circ_HIPK3 expression. The mechanism is that circ_HIPK3 upregulates the expression of its target IRS1 by adsorbing miR-33a-5p, thereby improving cell survival.⁴²⁰ Chen et al.⁴²¹ found that elevated circ-SWT1 expression attenuated H₂O₂-induced cardiomyocyte injury in an AMI model. Circ-SWT1 interacts with miR-192-5p to reduce the inhibition of SOD2 by miR-192-5p, thereby enhancing the antioxidant capacity of cells.⁴²¹

These research results demonstrate the multifaceted role of circRNAs in MI and its subsequent cardiac pathological processes, involving not only the protection and repair of cardiomyocytes but also the regulation of cardiomyocyte death. These findings advance our understanding of the molecular mechanisms of CVDs and provide possibilities for developing new therapeutic strategies.

3.3.3 | CircRNAs in HF

CircRNAs have potential as markers in the diagnosis of chronic heart failure (CHF). Feng et al.⁴²² found that circ_0040414 was significantly upregulated in CHF

patients and inhibited AKT signaling pathway activity by promoting apoptosis and inflammatory response, suggesting its possibility as a biomarker of CHF. Sun et al.,⁴²³ through the analysis of circRNA in the plasma of HF patients, specifically pointed out that hsa_circ_0062960 was highly correlated with the serum level of B-type natriuretic peptide, which had high diagnostic value. Therefore, circRNAs have great potential as diagnostic markers of HF and can provide a new direction for the early diagnosis and treatment of HF.

In recent years, remarkable progress has been made in understanding the molecular mechanisms of HF, especially in the mechanism of circRNA action. Han et al.⁴²⁴ identified 56 DEcircRNAs in the peripheral blood samples of HF patients and healthy volunteers through next-generation sequencing technology, highlighting the possible important role of hsa_circ_0097435 in HF, which may participate in the regulation of myocardial cell damage by absorbing multiple miRNAs. Guo et al.⁴²⁵ pointed out that circ_0036176 reduced the proliferation of CFs by inhibiting the CDK/retinoblastoma protein (Rb) pathway by encoding the Myo9a-208 protein, and the intervention of miR-218-5p could relieve its inhibitory effect on the proliferation of CFs. Zhu et al.,⁴²⁶ by studying the role of circRNA in hypertrophic preconditioning (EHP), identified a novel circRNA, c-Ddx, which was involved in the antihypertrophic memory of EHP by binding to and activating eukaryotic elongation factor 2. Wang et al.⁴²⁷ found that increased expression of circSnap47 in the HF condition resulted in decreased cardiomyocyte viability and increased apoptosis. By silencing circSnap47 and regulating its downstream target gene miR-223-3p and the MAPK pathway signaling pathway, the survival rate of cardiomyocytes can be improved, and cell apoptosis can be reduced, thus inhibiting the progression of HF.⁴²⁷ These studies not only reveal the potential role of circRNA in HF and cardiac hypertrophy but also provide important clues for developing new therapeutic strategies.

In addition, circRNAs also have a protective effect on HF. Yan et al.⁴²⁸ found that the endogenous proliferation ability of cardiomyocytes was activated after surgical ventricular reconstruction (SVR), and circRNAs played an important role in this process. By performing SVR surgery on mice with MI, they found that the upregulation of circMap4k2 expression was correlated with cardiomyocyte proliferation. Overexpression of circMap4k2 significantly promoted the proliferation of cardiomyocytes, while silencing circMap4k2 inhibited the proliferation. Further studies found that circMap4k2 affects antizyme inhibitor 1 (Azin1), a key factor in cardiomyocyte proliferation, by binding to miR-106a-3p, thereby reducing cardiac remodeling after SVR.⁴²⁸ Hu et al.⁴²⁹ then explored the core circRNA signaling pathways related to HF from the global

triple network of miRNA, circRNA, and mRNA. They found that the downregulation of circRNA CHRC was associated with cardiac hypertrophy, and it affected the progression of cardiac hypertrophy and HF by interacting with miR-431-5p to regulate the key TF Krüppel-like factor 15 (KLF15). This finding provides a new target for the treatment of HF.⁴²⁹ Li et al.⁴³⁰ showed that statins could upregulate the expression of circRNA-RBCK1 and promote its interaction with miR-133a, which involves the direct interaction between TF activator protein 2 alpha and ring-B-box-coiled-coil protein interacting with protein kinase C-1 (RBCK1). Through this signaling pathway, statins can improve cardiac diastolic function in patients with HF.⁴³⁰ Wang et al.⁴³¹ investigated the role of a specific circRNA HRCR in cardiac hypertrophy and HF and found that HRCR could act as a sponge for miR-223 and prevent the development of cardiac hypertrophy. They further found that the overexpression of miR-223 led to cardiac hypertrophy, and HRCR increased the expression of the antiapoptotic protein ARC, an inhibitor of apoptosis, by sequestering miR-223, thereby reducing the cardiac hypertrophy response.⁴³¹ Zuo et al.⁴³² investigated the role of endothelial progenitor cell-derived exosomal circ_0018553 during cardiac hypertrophy and found that this circRNA plays an important role in Ang II-induced cardiac hypertrophy. Circ_0018553 affects the expression of sirtuin 2 (SIRT2) by acting as a sponge for miR-4731, thereby inhibiting the process of myocardial hypertrophy.⁴³²

Taken together, these studies reveal the complex regulatory roles of circRNA in the process of HF pathology. Through different mechanisms, including directly affecting cardiomyocyte proliferation, regulating the activity of specific miRNAs, participating in signaling pathways, and interacting with drugs, circRNAs play key regulatory roles in HF.

3.3.4 | CircRNAs in other CVDs

In other CVDs, circRNAs also play an important role. Zhu et al.⁴³³ identified a large number of DEcircRNAs in patients with valvular heart disease accompanied by atrial fibrillation (AF), suggesting that cAMP and Wnt signaling pathways may play a key role in the pathological process. These pathways, regulated by DEcircRNAs, may alter the electrophysiological properties and systolic function of the heart by affecting gene expression and protein synthesis in cardiomyocytes.⁴³³ Wu et al.'s⁴³⁴ study further explored the specific role of circRNA in AF and found that mmu_circ_0005019 regulated the expression of potassium channel SK3 (KCNN3) by acting as a sponge for miR-499-5p, thereby affecting the expression of key ion channel proteins in cardiac electrophysiology. Additionally, Li

et al.⁴³⁵ showed that circRNA secreted by MSC-derived exosomes can reduce oxidative stress in cardiomyocytes and improve cell survival rates in myocardial injury caused by sepsis by regulating the miR-497-5p/MG53 axis, demonstrating potential therapeutic value. These studies not only reveal the complex regulatory network of circRNA in CVDs but also provide important clues for developing new therapeutic strategies.

3.4 | CircRNAs in kidney disease

Kidney disease is a global public health problem affecting hundreds of millions of people worldwide.^{436,437} It includes various types such as chronic kidney disease (CKD), acute kidney injury (AKI), and nephritis. CKD is of particular interest due to its high incidence and close association with other major health problems like CVD and diabetes.⁴³⁸ Recently, an increasing number of studies have focused on the effects of exosome-derived circRNAs on AKI, DN, nephrotic syndrome, and renal cancer. These circRNAs have the potential to become new diagnostic markers and therapeutic targets, bringing new hope for the diagnosis and treatment of kidney diseases.

3.4.1 | Acute kidney injury

CircRNAs play an important regulatory role in the progression of AKI. The study by Kuang et al.⁴³⁹ revealed that circ_0001818 exacerbates sepsis-induced AKI by adsorbing miR-136-5p, thereby increasing the expression of thioredoxin interacting protein and aggravating cell death and inflammation. Li et al.⁴⁴⁰ found that circ-FANCA also plays a key role in sepsis-induced AKI by influencing the interaction between miR-93-5p and oxidative stress responsive 1 to regulate cell survival and apoptosis. Additionally, using the exosome inhibitor GW4869, the level of circ-FANCA released by exosomes under septic conditions can be reduced, thereby decreasing cell damage.⁴⁴⁰ Kölling et al.⁴⁴¹ investigated the role of circRNAs in acute renal rejection and found that the concentrations of hsa_circ_0001334 and hsa_circ_0071475 were significantly increased in the urine of patients with acute renal rejection. The abnormal expression of these circRNAs not only plays an important role in diagnosis but can also serve as an indicator of treatment response. Moreover, there was a correlation between hsa_circ_0001334 and a decrease in glomerular filtration rate 1 year after transplantation, suggesting it may be associated with the deterioration of renal function after acute rejection.⁴⁴¹ Yang et al.⁴⁴² investigated the protective effect of human urine-derived stem cell-derived exosomes (USC-Exos) in AKI.

USC-Exos affected the interaction between miR-138-5p and FOXO3a by increasing the expression of circDENND4C. Through this mechanism, USC-Exos promote cell proliferation and inhibit the activation of NLRP3, which helps reduce pyroptosis and inflammation, ultimately alleviating AKI.⁴⁴²

Taken together, these studies highlight the different roles of circRNAs in the development and progression of AKI, and further research will help to understand the mechanisms of AKI and identify appropriate therapeutic targets.

3.4.2 | Nephrotic syndrome

Nephrotic syndrome refers to a group of clinical symptoms and signs caused by abnormal glomerular permeability, including massive proteinuria, hypoproteinemia, hyperlipidemia, and edema.^{443,444} Primary nephrotic syndrome, which is not caused by external diseases, results from conditions that directly affect the kidneys. Common forms of primary nephrotic syndrome include minimal change disease, membranous nephropathy (MN), and focal segmental glomerulosclerosis (FSGS).⁴⁴⁵ In contrast, secondary nephrotic syndrome arises from systemic diseases or other conditions that damage the kidneys, such as lupus nephritis (LN).⁴⁴⁶ Recently, the unique function of circRNA in nephrotic syndrome has garnered significant attention. The differential expression and regulatory mechanisms of circRNA in pathological states, including MN and FSGS, highlight its crucial role in the development and progression of nephrotic syndrome.

3.4.3 | Lupus nephritis

LN is a severe complication of systemic lupus erythematosus (SLE) that affects the kidneys. SLE is an autoimmune disease where the body's immune system mistakenly attacks and destroys healthy tissues, leading to inflammation and kidney problems.⁴⁴⁷ SLE is more common in women, particularly those of reproductive age, and is also more prevalent in certain racial and ethnic groups, such as African Americans, Asians, and Hispanics.^{448,449} Approximately 40–70% of patients with SLE develop LN.⁴⁵⁰ Recent studies have highlighted the complex role of circRNA in the pathological mechanisms of LN, revealing both its promotive and inhibitory effects on disease progression. For instance, Miao et al.⁴⁵¹ discovered that circRTN4 is upregulated in MCs in LN and transferred from monocytes to MCs via exosomes. CircRTN4 interacts with miR-513a-5p, enhancing fibronectin expression, promoting cell proliferation, and ECM deposition, thereby exacerbating

kidney injury. This suggests that circRTN4 upregulation contributes to the pathological process of LN.⁴⁵¹ Ouyang et al.⁴⁵² found significantly higher levels of circRNA_002453 in the plasma of LN patients compared with a control group. The expression level of circRNA_002453 was positively correlated with disease severity indicators, indicating its potential as a biomarker for LN diagnosis.⁴⁵² However, some studies have shown the opposite. Zhang et al.⁴⁵³ showed that the expression of hsa_circ_0123190 is decreased in LN patients, leading to increased activity of its adsorbed hsa-miR-483-3p. This interaction affects the expression of the apelin receptor (APLNR) gene, which is related to renal fibrosis, highlighting the critical role of hsa_circ_0123190 in inhibiting LN pathogenesis.⁴⁵³ Additionally, Luan et al.⁴⁵⁴ reported that circMTND5, located in the mitochondrial genome, is significantly downregulated in renal biopsy samples of LN. This downregulation is associated with mitochondrial dysfunction, decreased mitochondrial gene expression, and increased profibrotic gene expression, promoting renal fibrosis. CircMTND5 mitigates mitochondrial damage and renal fibrosis by adsorbing miR6812, suggesting that its downregulation adversely affects LN, while increased expression may provide renal protection.⁴⁵⁴

These studies collectively demonstrate the complex role of circRNAs in LN, showing that specific circRNA-miRNA interactions can either promote or inhibit disease progression. This provides crucial molecular targets for developing new therapeutic strategies.

3.4.4 | Others

First, the study by Li et al.⁴⁵⁵ revealed that the expression of numerous circRNAs is altered in patients with idiopathic membranous nephropathy (IMN). Notably, the significant upregulation of hsa_circ_0001250 is closely related to the high levels of proteinuria characteristic of IMN. This finding suggests that hsa_circ_0001250 is involved in the pathological process of IMN by targeting hsa-miR-639 and hsa-miR-4449, thereby regulating the expression of specific genes. This provides new insights for the development of noninvasive diagnostic methods.⁴⁵⁵ Second, the work of Sun et al.⁴⁵⁶ found that circ_0000524 affects podocyte apoptosis through its interaction with miR-500a-5p and CXC motif chemokine ligand 16 (CXCL16), which is key to the pathogenesis of MN. This study not only reveals the importance of podocyte apoptosis in MN but also suggests a new treatment strategy by interfering with the circ_0000524/miR-500a-5p/CXCL16 signaling pathway.⁴⁵⁶ Additionally, Qiu et al.⁴⁵⁷ showed that circ_CDYL expression is significantly increased in MN and affects podocyte apoptosis by regulating the expression of miR-149-5p and

TNF superfamily member 11. This finding highlights the critical role of podocytes in renal filtration function and suggests that circ_CDYL may become a new target for treating MN.⁴⁵⁷ Finally, the study by Cui et al.⁴⁵⁸ focused on FSGS and found that circZNF609 is upregulated during disease development. It affects podocyte injury and renal fibrosis by regulating the expression of miR-615-5p. This study illuminates the molecular mechanisms of FSGS and provides directions for developing new treatment strategies.⁴⁵⁸

CircRNAs play diverse and complex roles in nephrotic syndrome. By interacting with miRNAs, circRNAs can affect key pathological processes such as podocyte apoptosis and proteinuria, thus playing a central role in the occurrence and development of nephrotic syndrome.

3.5 | CircRNAs in musculoskeletal and connective tissue diseases

3.5.1 | CircRNAs in RA

Inflammatory RA causes joint deformities and complete impairment of joint function. There are abnormalities in mast cells, B cells, macrophages, DCs, plasma cells, and T cells involved in RA pathogenesis, as well as the functional behavior of fibroblast-like synoviocytes (FLSs).⁴⁵⁹

CircRNAs and their sponge effect on miRNAs contribute to the pathogenesis of RA by regulating target genes. Many circRNAs, such as circRNA_092516, circRNA_003524, circRNA_103047, and circRNA_101873, are documented to be aberrantly expressed in RA.⁴⁶⁰ CircRNAs in exosomes and RNA methylation are closely related to RA pathogenesis.⁴⁶¹ Additionally, circulating RNAs play a role in RA's pathological mechanisms in PBMCs and macrophages. Ouyang et al.⁴⁶² identified and validated five circRNAs (092516, 003524, 103047, 104871, 101873) significantly elevated in PBMCs of RA patients. The circ_0008360 gene has emerged as a pivotal regulator of inflammation, with its dysregulation considered highly significant in RA.⁴⁶³ Geng and colleagues⁴⁶⁴ investigated the functional consequences of circ_0088036 in the advancement of RA and revealed the mechanisms behind it. Circ_0088036 contributes to the activity of RA induced by TNF- α , partly through the miR-326/FZD4 signaling pathway.⁴⁶⁴ Additionally, circ_0088036 promotes synovial pathogenesis through the circ_0088036/miR-140-3p/SIRT1 axis in RA.⁴⁶⁵ Circ_0000479 facilitates RA development by interacting with miR-766, leading to increased FKBP5 expression.⁴⁶⁶ Yang et al.⁴⁶⁷ discovered that circRNA_17725 promotes M2 polarization of macrophages to alleviate arthritis symptoms. Wang et al.⁴⁶⁸ demonstrated

that blocking the circPTN/miR-145-5p/FZD4 signaling axis could effectively inhibit RA pathology.

CircRNAs affect the proliferation, migration, and inflammatory reactions of RA-FLSs. These interactions form circRNA-miRNA axes that participate in various biological activities within RA-FLSs. FLSs are mesenchymal-origin cells crucial for the synovium's physiological functions, contributing to synthesizing specific constituents in synovial fluid and articular cartilage. Recent investigations have revealed that circRNAs contribute to various FLS activities, including metastasis, proliferation, and cytokine production.⁴⁶⁹ Circ_0001947 is involved in RA pathogenesis by enhancing STAT3 expression through sequestering miR-671-5p.⁴⁷⁰ Circ_0002984 regulates RA-FLS activity by interacting with miR-543, leading to upregulated PCSK6 expression.⁴⁷¹ CircAFF2 promotes RA initiation and advancement by modulating the miR-650/CNP axis, enhancing proliferation, inflammatory response, migration, and invasion of RA-FLSs.⁴⁷² CircMAPK9 affects RA-FLS activity by modulating the miR-140-3p/PPM1A axis.⁴⁷³ CircSirt1's protective mechanism on FLS involves impeding cell proliferation, fostering apoptosis, and facilitating the miR-132-mediated Sirt1 pathway, thus reducing inflammation.⁴⁷⁴ Inhibition of circ_0004712 suppresses aggressive phenotypic changes in RA-FLSs by modulating the miR-633/TRAF6 axis and NF- κ B signaling.⁴⁷⁵ Circ_0025908 silencing alleviates dysfunctions in RA-FLSs by targeting the miR-650/SCUBE2 axis.⁴⁷⁶ Circ_0007707 modulates inflammatory response and cell apoptosis in RA-FLSs via the miR-27b-3p/PDE3B axis, highlighting its potential as a therapeutic target for RA.⁴⁷⁷ Circ_0088194 affects RA-FLSs through the miR-30a-3p/ADAM10 axis, promoting inflammation, migration, proliferation, and inhibiting apoptosis.⁴⁷⁸ Silencing circ-PTTG1IP represses cell proliferation, migration, and inflammatory response in RA-FLSs by modulating the miR-671-5p/TLR4 axis.⁴⁷⁹ Inhibiting circCDKN2B-AS_006 mitigates arthritis severity by suppressing tumor-like growth and metastasis in RA-FLSs.⁴⁸⁰

CircRNAs are critical for RA progression, as they are released by FLSs in RA (RA-FLSs-Exos). The proliferation and migration of RA-FLSs-derived exosomes overexpressing circFTO is inhibited, which promotes the modification of chondrocytes by m6A, ultimately resulting in RA by upregulating the sex-determining region Y-related high-mobility group box 9 (SOX9).⁴⁸¹ A microarray analysis of RA revealed a distinct profile of circRNA expression.⁴⁶⁰ The overexpression of CircEDIL3 leads to an upregulation of PIAS3 protein expression, which in turn inactivates STAT3, thereby alleviating the progression of RA. Moreover, CircEDIL3 originating from SMCs-Exos effectively suppresses inflammation-induced angiogenesis and

promotes pannus progression, both in vitro and in vivo, via the miR-485-3p/PIAS3/STAT3/VEGF functional module, ultimately ameliorating RA.⁴⁸² CircFBXW7, delivered by exosomes from MSCs to RA-FLSs, suppresses cell proliferation, migration, invasion, and inflammatory cytokines like TNF- α , IL-1, IL-6, and IL-8 via the circFBXW7/miR-216a-3p/HDAC4 axis.⁴⁸³

CircRNA expression levels are tissue- and stage-specific, with many circRNAs found in human peripheral blood, suggesting their potential as biomarkers for RA screening, diagnosis, characterization, and monitoring. Investigating novel diagnostic and therapeutic strategies targeting circRNAs is promising. Due to their unique expression characteristics and pivotal role in RA, circRNAs hold promise as diagnostic biomarkers and therapeutic targets.⁴⁶⁰

3.5.2 | CircRNAs in osteoarthritis

It is also known as degenerative arthritis, senile arthritis, and hypertrophic arthritis.⁴⁸⁴ A key feature of osteoarthritis (OA) is abnormal chondrocytes, which cause joint pain, tenderness, stiffness, joint swelling, movement limitations, and joint deformity.⁴⁸⁵ A number of mechanisms are involved in OA, including inflammation, proliferation, apoptosis, autophagy, differentiation, oxidative stress, and mechanical stress (Figure 7). CircRNAs play a key role in OA pathogenesis by acting as intracellular miRNA sponges in chondrocytes, endplate chondrocytes, MSCs, synovio-cytes, and macrophages.⁴⁸⁶ In addition, some circRNAs are involved in OA through other mechanisms, including RBP, m6A, or intercellular exosomal mechanisms, including ECM metabolic imbalance, local tissue inflammation, and multidirectional cell differentiation.⁴⁸⁶

Many circRNAs are disorderedly expressed in OA synovial tissues and immune cells, contributing to abnormal chondrocyte proliferation, synovial inflammation, cartilage erosion, bone damage, and abnormal immune responses. A study by Lin et al.⁴⁸⁷ found that circPhf21a was upregulated in an OA mouse model, affecting OA chondrocyte proliferation through its target VEGFA. CircumPhc3 was downregulated in OA and regulated FoxO1 through miR-9-3p, affecting chondrocyte metabolism.⁴⁸⁸ Further, circHGF competes with miR-25-3p to regulate its expression, affecting the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs).⁴⁸⁹ Further research indicates that miR-9-5p/KLF5 targets circStrn3 and regulates cartilage matrix metabolism and subchondral bone remodeling in OA.⁴⁹⁰ The findings suggest that circ_0008365 might be a potential therapeutic target or diagnostic biomarker for OA, as it acts as a sponge for miR-338-3p to regulate SOX9 expression in vitro.⁴⁹¹ In another study, knock-

down of hsa_circ_0134111 alleviated OA symptoms by sponging miRNA-224-5p.⁴⁹² According to experiments, circVMA21 protected injured chondrocytes via miR-495-3p/FBXW7 axis through its role in OA rats.⁴⁹³ In OA, circCTNNA1 was downregulated, and its overexpression suppressed synovio-cyte apoptosis by sponging miR-29a.⁴⁹⁴ The overexpression of Hsa_circ_0005567 reduces chondrocyte apoptosis and may inhibit OA progression by promoting the polarization of M2 macrophages through the miR-492/SOCS2 axis.⁴⁹⁵ CircRHOT1 augments the expression of CCND1 in chondrocytes by functioning as a sponge for miR-142-5p. Both the overexpression of CCND1 and the inhibition of miR-142-5p counteract the chondrocyte phenotypes resulting from circRHOT1 depletion, thereby playing a role in chondrocyte autophagy and proliferation during OA.⁴⁹⁶ A circRSU1-miR-93-5p-MAP3K8 axis modulates OA progression via oxidative stress regulation, serving as a possible therapeutic target.⁴⁹⁷

In a comparative analysis of synovial exosomes between OA synovial and control groups, 98 circRNAs were identified to be differentially expressed. Among these, 34 circRNAs were found to be enriched in the PI3K/Akt and autophagy pathways, exhibiting correlations with 7 mRNAs. These circRNAs play crucial roles in the pathological mechanisms underlying OA.⁴⁹⁸ CircRNAs act as miRNA sponges to inhibit mRNA translation responsible for OA development, with miRNA sponges acting as circRNA sponges.⁴⁹⁹ In exosomes originating from chondrocytes treated with IL-1 β , there was an elevation in CircRNA-BRWD1 levels. The miR-1277/TRAF6 axis was modulated by exosomal circ-BRWD1, and the suppression of circ-BRWD1 hindered ECM degradation in chondrocytes stimulated by IL-1 β .⁵⁰⁰ Exosomes expressing CircRNA_0001236 might alleviate cartilage degradation, suppress OA progression, and enhance cartilage repair.⁵⁰¹ Combined with sleep-related circRNA3503, small EVs prevent OA. CircRNA3503-OE-sEVs, by sponging hsa-miR-181c-3p and hsa-let-7b-3p, effectively eased inflammation-triggered apoptosis and restored the balance between ECM synthesis and degradation.⁵⁰² Additionally, these sEVs facilitated chondrocyte renewal, thus helping to counteract the gradual depletion of chondrocytes.⁵⁰²

Cartilage degeneration is the main pathological characteristic of OA. Previous studies have shown that aberrant biological functions of chondrocytes, including ECM formation, apoptosis, inflammation, proliferation, and autophagy, are causally involved in OA pathogenesis. CircRNAs participate in OA pathogenesis in chondrocytes through ECM formation, apoptosis, proliferation, inflammation, and autophagy.⁵⁰³ CircSERPINE2 overexpression could alleviate HCs apoptosis and promote ECM anabolism through the miR-1271-ERG pathway, providing a potential therapeutic strategy for OA progression.⁵⁰⁴

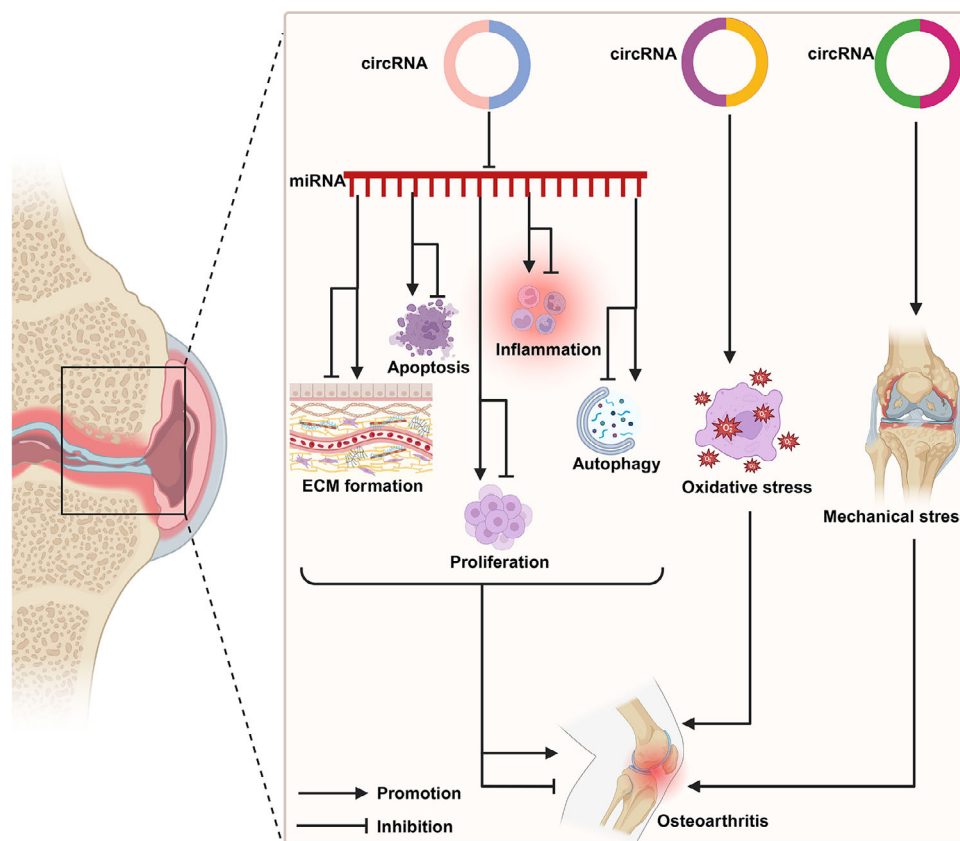


FIGURE 7 CircRNAs in osteoarthritis. This diagram elucidates the intricate interactions among circRNAs, miRNAs, and diverse cellular processes implicated in the pathogenesis of osteoarthritis. The circRNA–miRNA interplay is represented as a pivotal regulatory mechanism, modulating apoptosis, inflammation, autophagy, oxidative stress, mechanical stress, cellular proliferation, and extracellular matrix formation. Collectively, these processes play a crucial role in either facilitating or impeding the progression of osteoarthritis. The figure also highlights the importance of understanding these molecular interactions for potential therapeutic interventions in managing osteoarthritis.

CircPDE4D was significantly downregulated in OA cartilage tissues and during stimulation with inflammatory cytokines. Targeting the circPDE4D–miR-103a-3p–FGF18 axis might provide a promising approach for OA therapy.⁵⁰⁵ Another study revealed an important role of the CircCDK14/miR-125a-5p/Smad2 axis in OA progression, providing a potential molecular therapeutic strategy.⁵⁰⁶ CircCDH13 contributes to OA pathogenesis by functioning as a sponge for miR-296-3p and regulating the miR-296-3p–PTEN pathway. Silencing CircCDH13 could reduce chondrocyte apoptosis, inhibit ECM catabolism, and promote ECM anabolism.⁵⁰⁷ Certain circRNAs or related pathways can be used as diagnostic and prognostic biomarkers for OA treatment, providing potential targets for developing effective interventions.

3.5.3 | CircRNAs in Sjögren's syndrome

Sjögren's syndrome (SS) is a chronic autoimmune disorder of the exocrine glands characterized by lymphocytic infil-

tration in the salivary and lacrimal glands (LGs), resulting in oral and eye dryness.⁵⁰⁸ Extraglandular manifestations such as musculoskeletal pain, fatigue, and systemic features also develop in a significant percentage of patients. This exocrinopathy can occur alone (primary SS, pSS) or secondary to another autoimmune disease such as RA, SLE, and systemic sclerosis (SSc).⁵⁰⁹ Studies have demonstrated significantly different circRNA expression profiles in the minor salivary glands of pSS patients compared with non-pSS individuals by RNA-seq. Researchers identified 13 significantly DEcircRNAs, most of which showed upregulated expression in pSS. circRNA sequencing indicated circ-IQGAP2 (hsa_circ_0129656) and circ-ZC3H6 (hsa_circ_0001062) as noninvasive biomarkers of pSS.⁵¹⁰

3.5.4 | CircRNAs in spondyloarthritis

Ankylosing spondylitis (AS) is a typical inflammatory rheumatic disease characterized by pathological new bone formation, ankylosis, and chronic inflammation in the

spine, with osteoclastogenesis playing a critical role in bone formation.⁵¹¹ Previous research has shown that exosomes from MSCs participate in the modulation of osteoclastogenesis in vitro.⁵¹² Researchers discovered that the circRNA derived from TNFRSF1B, circ-0110634, was significantly upregulated in AS-MSCs and exosomes from AS-MSCs compared with HD-MSCs and HD-MSC exosomes. They found that circ-0110634 plays an inhibitory role in osteoclastogenesis, with AS-MSCs delivering exosomal circ-0110634 to restrain the osteoclastogenesis of PBMCs. This role is similar to that of hsa_circ_0002715 and hsa_circ_0035197 in patients with new-onset RA.⁵¹³ Researchers investigated the circRNA profiles of exosomes via high-throughput RNA sequencing and identified 56 DEcircRNAs in the exosomes of patients with AS compared with healthy controls. These circRNAs were mainly involved in the negative regulation of the TF nuclear factor- κ B and bone remodeling, which are potentially related to AS. The most highly AS-correlated pathways identified were the “Notch signaling pathway” and those primarily involved with “cholinergic synapse.”⁵¹⁴ Another study conducted circRNA and miRNA expression profiling of osteogenically differentiated BMSCs from patients with AS compared with healthy donors using RNA sequencing. The results showed that 418 circRNAs were significantly differentially expressed, with 204 circRNAs upregulated and 214 downregulated. In vitro experiments showed that silencing hsa_circ_0070562 weakened the osteogenesis of AS-BMSCs, indicating that circ_0070562 functions as a pro-osteogenic factor and might serve as a potential biomarker and therapeutic target for AS.⁵¹⁵

3.5.5 | CircRNAs in osteoporosis

Osteoporosis is one of the most common systemic metabolic bone diseases, particularly prevalent in postmenopausal women.⁵¹⁶ It occurs due to excessive bone resorption and impaired bone formation.⁵¹⁷ Accumulating evidence suggests that dysregulated circRNAs are associated with the occurrence and progression of osteoporosis, regulating osteoblast and osteoclast differentiation, and may serve as potential biomarkers for the disease. For example, studies have identified circARSB, circAKT3, circPTEN, and circTRPM7 as being associated with osteogenic differentiation during glucocorticoid-induced osteoporosis (GIOP) through a circRNA-targeted miRNA-mRNA axis, providing insights into the pathophysiological mechanisms of GIOP.⁵¹⁸ A total of 387 circRNAs were found to be differentially expressed in osteoporosis compared with healthy controls, with circDNAH14 (hsa_circ_0016624) preventing osteoporosis by regulating BMP2 via miR-98 sponging.⁵¹⁹ Among women with post-

menopausal osteoporosis (PMO), Liu et al. identified 250 DEcircRNAs, with 64 showing a decreasing expression trend and 186 showing increased expression. Circ_0007059 might play a crucial role in osteoclastogenesis via the miR-378/BMP-2 signaling pathway, suggesting that targeting the circ_0007059/miR-378/BMP2 axis could be a novel therapeutic approach for osteoporosis.⁵²⁰ Qiao et al. found that circRNA_0048211 negatively targets miRNA-93-5p to upregulate BMP2, thus alleviating the progression of PMO.⁵²¹ Furthermore, using postmenopausal mouse models, Wang et al.⁵²² focused on DEcircRNAs in osteoporotic mice. They identified two ceRNA regulatory pathways in this osteoporosis mouse model: novel circRNA 0020/miR-206-3p/Nnmt and circRNA 3832/miR-3473e/Runx3, validated by real-time PCR.⁵²²

Some studies have revealed that hsa_circ_0001275, hsa_circ_0002060, and hsa_circ_0006859 are recognized as potential novel diagnostic biomarkers of osteoporosis.^{523–525} CircFOXPI can promote osteogenic differentiation of ADSCs and bone regeneration via miR-33a-5p.⁵²⁶ Circ_0007059 can inhibit bone marrow stromal cell differentiation into osteoclasts via the mRNA-378/BMP-2 axis.⁵²⁰ By constructing a circRNA-miRNA-TF-mRNA regulatory network using bioinformatics analysis, researchers identified four associated circRNAs in the ceRNA network: hsa_circ_0023417, hsa_circ_0078309, hsa_circ_0063533, and hsa_circ_0036760, suggesting that these circRNAs may be important regulators of osteoporosis development.⁵¹⁶

4 | CircRNAs IN CANCER

In this section, we examine the pivotal role of circRNAs in cancer biology, focusing on their implications in tumorigenesis, tumor progression, and therapeutic resistance. By exploring their interactions within the tumor microenvironment (TME) and their influence on cancer cell behavior, we highlight circRNAs as potential biomarkers for early diagnosis and as targets for innovative therapeutic strategies. This section aims to elucidate the complex landscape of circRNAs in cancer and their promise for advancing cancer diagnostics and treatments.

4.1 | Multiple cancer-circRNA signaling pathways

Carcinogenesis is closely linked to several signaling pathways. The complexity of signals and their functional roles are essential for the emergence and spread of malignancies and other diseases. Various types of human

malignancies have been linked to dysregulated signaling pathways.^{527–530} Additionally, certain signaling pathways trigger epithelial–mesenchymal transition (EMT), a significant accelerator of cancer progression. During this process, considered an inducer of cancer metastasis, epithelial cells lose their polarity and differentiated state, obtaining a mesenchymal-like phenotype. Although the underlying processes remain unclear, it has been discovered that certain circRNAs function as ceRNAs for miRNAs involved in EMT signaling pathways, contributing to tumor growth.⁵³¹ In this study, we explore the roles of signaling pathways in malignant carcinomas, focusing on molecular mechanisms and potential avenues for future intervention.

4.1.1 | The PI3K/AKT/mTOR signaling pathway and circRNAs

Numerous malignancies exhibit highly activated PI3K/AKT/mTOR signaling pathways, facilitated by upstream oncoprotein receptor tyrosine kinases, G-protein-coupled receptors, or RAS oncogenes. Carcinogenesis is associated with dysregulation of the PI3K/AKT/mTOR signaling pathway. Consequently, research has increasingly focused on the associations of circRNAs with the PI3K/AKT signaling pathway.^{532,533} CircRNAs commonly function as ceRNAs for miRNAs in tumor progression. Based on the ceRNA mechanism, downstream pathways are activated or suppressed by sponging miRNAs. For instance, in CRC, circCDYL (116), circ_0001313,⁵³³ hsa_circRNA_002144,⁵³⁴ and circIL4R⁵³⁵ utilize the ceRNA mechanism to regulate the PI3K/AKT signaling pathway, either promoting or inhibiting tumor growth. By acting as a miR-149-5p sponge, circNRIP1 enhances the progression of gastric cancer (GC) via the AKT1/mTOR pathway.⁵³⁶ CircFGFR3 regulates the ERK1/2 and AKT signaling pathways in non-small cell lung cancer (NSCLC) by sponging miR-22-3p.⁵³⁷ Patients with hepatitis B-associated HCC have a poor prognosis due to elevated levels of circRNA-100338, which are linked to the activation of the mTOR signaling pathway in HCC via the circRNA-100338/miR-141-3p/RHEB axis.⁵³⁸ According to Shi et al.⁵³⁹ circ_0014359 sponges miR-153, which regulates the expression of p-AKTser473 and accelerates the progression of gliomas. CircPLEKHM3⁵⁴⁰ and circKDM4B⁵⁴¹ are other miR-sponging circRNAs that, in ovarian cancer (OC) and breast cancer respectively, promote or suppress the AKT signaling pathway.

Furthermore, it has been discovered that circRNAs regulate tumor progression by altering epigenetic processes. Circ-0124554 (circ-LNLM), for instance, inhibits AKT ubiquitination and thus enhances CRC hepatic metastasis.⁵⁴² Additionally, in oral squamous cell carcinoma (OSCC) and thyroid carcinoma respectively,

circ_0067934 and circ_0007059 influence malignant cell behavior through phosphorylating AKT/mTOR.^{543,544} According to a recent report, circ-ANAPC7 regulates the CREB–miR-373–PHLPP2 feed-forward loop through the PHLPP2–AKT–TGF- β signaling axis, preventing pancreatic cancer muscle atrophy and tumor progression.⁵⁴⁵ Interestingly, the PI3K/AKT/mTOR signaling pathway has been shown to influence tumor progression through circRNAs that encode novel proteins. The circ-AKT3 RNA-encoded tumor suppressor protein, for instance, competes with active PDPK1, thus reducing the tumorigenicity of glioblastoma.⁵⁰ This evidence demonstrates that circRNAs play a dual role in protein modification and oncogenic promoter activity.

4.1.2 | The Wnt signaling pathway and circRNAs

Positive associations exist between tumorigenesis and the canonical Wnt signaling pathway. In summary, a destruction complex composed of casein kinase 1, adenomatous polyposis coli (APC), glycogen synthase kinase-3 (GSK-3), β -catenin, and axin first phosphorylates and then ubiquitinates β -catenin inside the cytoplasm. The formation of this complex is inhibited by the presence of Wnt ligands. Consequently, β -catenin, the primary protein, is transported from the extracellular space to the nucleus to activate downstream proteins targeted by Wnt.^{546,547} The sponging of miRNAs activates or represses downstream pathways based on the ceRNA mechanism.^{548,549} CircRNAs within the cytoplasm interact with proteins in the destruction complex, influencing Wnt activation. The Wnt/ β -catenin signaling pathway is negatively regulated by APC, a key protein in the destruction complex. The tumor-suppressive properties of hsa_circ_0009361 were revealed by Geng et al.,⁵⁴⁶ along with its ability to sponge miR-582 and subsequently enhance the expression of APC2, which then influences the Wnt/ β -catenin pathway in CRC. The Wnt signaling pathway is activated or suppressed by Wnt ligands binding to the Wnt antagonist Dickkopf-1 (Dkk1), lipoprotein-related protein (LRP), or Frizzled (FZD) receptors on the cell surface.⁵⁵⁰ Because DKK1 selectively binds to LRP5/6, it inhibits the formation of the Wnt–LRP5/6–FZD complex and suppresses the downstream Wnt pathway. Hsa_circ_0000523, hsa_circ_0000177, and circ_100290 regulate these surface proteins in gliomas and CRCs and are associated with the Wnt pathway.^{551–553}

Several circRNAs interact with the downstream genes of the Wnt pathway when β -catenin enters the nucleus. CircMTCL1 accelerates the development of advanced laryngeal squamous cell carcinoma by inhibiting the degradation of C1QBP ubiquitin and regulating the

accumulation of β -catenin in the nucleus and cytoplasm.⁵⁵⁴ The Wnt signaling pathway is stimulated in endometrial cancer through the hsa_circ_0002577/miR-197/CTNND1 axis, which also affects the expression of c-Myc, cyclin D1, and β -catenin.⁵⁵⁵ In papillary thyroid carcinoma (PTC), Bi et al.⁵⁵⁶ showed that circRNA 102171 interacts with CTNNBIP1 and then inhibits its interaction with the β -catenin/TCF3/TCF4/LEF1 complex, thus stimulating the Wnt/ β -catenin pathway. The Wnt pathway is influenced by several novel proteins encoded by circRNAs.^{547,557–559} The competitive interaction between the AXIN1-295 aa protein, encoded by circAXIN1, and APC has been shown to contribute to the malfunction of the ‘destruction complex’ in GC, highlighting a key aspect of circRNA involvement in cancer pathology.⁵⁵⁷ The novel protein circ β -catenin-370 aa, encoded by circ β -catenin in HCC, stabilizes β -catenin and activates the Wnt pathway.⁵⁴⁷ Additionally, hsa_circ_0007059 appears to inhibit the interaction between β -catenin and Wnt3a, potentially suppressing EMT in lung cancer.⁵⁶⁰ Furthermore, it has been demonstrated that circRNAs function as feedback loops to regulate cancer growth. CircESRP establishes a positive feedback loop that influences cancer progression through EMT.⁵⁶¹ Accordingly, research has demonstrated the crucial role of circRNAs in the circRNA/Wnt/ β -catenin signaling pathway. If these findings are validated, they could lead to the development of innovative cancer treatments.

4.1.3 | The notch and hippo signaling pathways and circRNAs

Neurogenesis, angiogenesis, as well as overall cell survival and growth, are regulated by the Notch signaling pathway. Transmembrane proteins known as Notch receptors (NOTCH1, NOTCH2, NOTCH3, and NOTCH4) bind to specific ligands to trigger a myriad of biochemical reactions.⁵⁶² CircRNAs commonly function as ceRNAs in Notch signaling, sponging up miRNAs to activate pathways by directly stimulating receptors and/or their ligands.^{563–566} Aberrant Notch signaling is often linked to genetic alterations in key components, particularly NOTCH1. According to Xu et al.,⁵⁶³ circNFIX binds to NOTCH1 and sponges miR-34a-5p, activating the Notch pathway in gliomas. By sponging miR-34a and consequently regulating Notch1, circ-ASH2L promotes tumor growth in pancreatic ductal adenocarcinoma (PDAC).⁵⁶⁵ These findings suggest that circRNAs involved in Notch signaling could be utilized to develop novel approaches to inhibit the progression of cancer.

Numerous tumor suppressors and oncogenes are part of the Hippo signaling pathway. The PDZ-binding motif and

YAP become active and accumulate in the nucleus following the inactivation of the Hippo signaling pathway, subsequently enhancing cellular proliferation.^{39,567,568} Multiple studies have demonstrated the involvement of circRNAs in the Hippo signaling pathway, with dominant mechanisms including ceRNA competition,^{569–571} translation of novel proteins,³⁹ feedback loops,⁵⁷² and YAP nuclear accumulation.⁵⁷³ Circ-LECRC, generated from YAP, acts as a “brake signal,” inhibiting the overactivation of carcinogenic YAP signaling in CRC.⁵⁷² Louis and Coulouarn⁵²⁸ discovered that circACTN4 elevates YAP1 levels by acting as a miR-424-5p sponge, thereby recruiting Y-box binding protein 1 (YBX1) to trigger FZD7 transcription and accelerate the progression of intrahepatic cholangiocarcinoma. According to Wu et al.,⁵⁶⁷ circYap binds to Yap mRNA, PABP, and eIF4G to prevent Yap translation initiation in breast cancer cells. The novel peptide circPPP1R12A-73 aa, encoded by circPPP1R12A, accelerates the development of CRC by activating the Hippo-YAP signaling pathway.³⁹ Liu et al.⁵⁶⁹ demonstrated that YAP1 suppresses the transcription of circRNA-000425 in GC, thereby enhancing the oncogenic activity of miR-106 and miR-17. Altogether, these findings suggest that circRNAs influence tumor-related signaling pathways by serving as miRNA sponges or interacting with proteins, thereby affecting the functioning of the Hippo/YAP pathway.

4.1.4 | The p53/Bcl-2 signaling pathway and circRNAs

The apoptotic process and the cell cycle are regulated by the tumor protein 53 (p53) via a myriad of distinct routes. Additionally, through the ceRNA mechanism, circRNAs such as circ-BRIC6, circ-0001785, hsa_circ_006100, hsa_circ_0002874, circPVT1, and circ_0021977 regulate the p53 signaling pathway.^{574–579} The homo-tetrameric TF known as wild-type p53 protein (wt-p53) acts as a tumor suppressor by controlling the transcription of downstream target genes.^{580,581} Mutant p53 (mut-p53) loses its tumor-suppressive functions and gains tumor-promoting activities, known as GOF activities. Elevated levels of mut-p53 proteins are necessary for effective mut-p53 GOF activity in cancer cells. When the ability of remaining wt-p53 to regulate tumor growth is inhibited by the creation of a hetero-tetrameric mut-p53/wt-p53 complex, tumor cells proliferate, survive, migrate, and invade. It has been discovered that mut-p53 and circRNA interact.⁵⁸² For instance, mut-p53 activates circPVT1⁵⁷⁶ and circ-Ccnb1.⁵⁸³ CircPVT1 and mut-p53 expression profiles were found to be upregulated in cancerous tissues compared with normal tissues in a study of 115 patients with head and neck squamous cell carcinoma. The mut-p53/YAP/TEAD complex is

hypothesized to be a mechanism for enhancing circPVT1 transcription.⁵⁷⁶

Wt-p53 promotes circ-Ccnb1 expression in breast cancer cells, but wt-p53 suppression or mut-p53 expression inhibits circ-Ccnb1 expression. Circ-Ccnb1 separates the CyclinB1/Cdk1 mitotic complex, which inhibits carcinogenesis and cellular invasion.⁵⁸³ Mechanistically, it has been proposed that circRNAs and p53 directly bind to prevent the degradation of p53. This interaction could prevent p53 from being ubiquitinated by E3 ubiquitin ligases (such as MDM2) and subsequently degraded.⁵⁸² The p53/MDM2 complex is disrupted when the circRNA CDR1as binds to p53, leading to the stabilization of p53 in glioblastoma.⁵⁸⁰ Conversely, when circ-DNMT1 binds to p53, it induces nuclear translocation of p53 and AUF1, thereby mediating DNMT1 upregulation and inhibiting p53 expression in breast cancer.⁵⁸⁴ Additionally, circRNAs influence Bcl-2, a downstream target of p53, leading to apoptosis in HCC, CRC, and GC cells.^{574,578,585,586} Furthermore, in OSCC and osteosarcoma, circ_0007534, circ_0001785.^{579,587} Moreover, a new regulatory mechanism related to the p53 signaling pathway involves the generation of feedback loops. The FMR1/circCHAF1A/miR-211-5p/HOXC8 feedback loop in glioblastoma regulates the proliferative rate and carcinogenesis through MDM2-dependent p53 signaling.⁵⁸⁸ The most prevalent cause of cancer is p53 inactivation or mutations, yet p53 stability is regulated by the formation of the p53/MDM2 complex. Consequently, p53 has emerged as one of the most promising treatment targets for cancer.

4.1.5 | CircRNAs promote EMT through the TGF- β /Smad signaling pathway

Receptor-regulated Smad (R-Smad), which triggers transcriptional responses by attaching to Smad binding sites in cell nuclei and suppressing the expression of epithelial genes, mediates TGF- β 1 canonical signaling.⁵⁸⁹ EMT, initiated and perpetuated by TGF- β 1, is a crucial phase in cancer metastasis. CircRNAs also play a role in the process by which the TGF- β /Smad pathway regulates the development and metastasis of various malignancies. CircPTK2 was shown by Wang et al.⁵⁹⁰ to be significantly down-regulated in NSCLC cells and to be inversely related to EMT induced by TGF- β . CircANKS1B binds to miR-152-3p and miR-148a-3p in triple-negative breast cancer (TNBC), thereby enhancing the expression of upstream TF1 (USF1), which in turn activates TGF- β 1.⁵⁹¹ Through the ceRNA mechanism, circPTK2 and circANKS1B can either stimulate or inhibit EMT in tumorigenesis. The ceRNA mechanism also applies to the functions of circRIP2⁵⁹² in bladder cancer and circANKS1B⁵⁹³ in OSCC. When CircPTEN1 binds to the MH2 motif of Smad4, it disrupts its inter-

action with Smad2/3, thereby inhibiting the expression of downstream genes involved in EMT induced by TGF- β .⁵⁹⁴ Additionally, circRNAs such as circ-DOCK5⁵⁹⁵ and circUHRF1⁵⁹⁶ have been demonstrated to form feedback loops that modulate the TGF- β /Smad signaling pathway.

Here, we have concentrated on the canonical pathway linked to carcinogenesis and the development of cancer. CircRNAs also interact with other signaling pathways, including the carcinogenic MAPK and JAK/STAT pathways.⁵⁹⁷ Any abnormal interaction between these pathways may lead to cancer progression. Collectively, these data suggest that circRNAs play critical roles in regulating the behavior of cancer cells.

4.2 | CircRNAs and exosomes

4.2.1 | Exosomal biogenesis and activity

The membrane-bound EVs known as exosomes are generated from the late endosomal limiting membrane. These single-membrane, small, secreted organelles range from 40 to 100 nm in diameter.^{598,599} Moreover, they significantly affect various biological activities, including physiological and pathological inter- and intra-cellular communication, as well as the transfer of biomolecules such as enzymes, proteins, RNAs, and lipids in diverse disorders.^{600,601} The endosomal system accounts for the initial step in exosomal biogenesis. Following various maturation processes, invagination of the endosomal membrane leads to the formation of multivesicular bodies (MVBs). In addition to producing intraluminal vesicles, MVBs are also degraded by fusing with lysosomes.⁶⁰² Exosomal biogenesis and production involve multiple mechanisms. The ESCRT-mediated biogenesis of MVBs represents a frequently investigated pathway, dependent on intracellular homeostasis and cell type.⁶⁰³ Exosomes have emerged as potential diagnostic and prognostic biological markers, as well as treatment targets, significantly impacting the TME, tumor migration, invasion, progression, chemoresistance, and targeted drug delivery.^{604–607}

4.2.2 | The properties and biological functions of exosome

Exosomes serve as critical mediators for intercellular communication, particularly in the TME.⁶⁰⁸ An increasing number of studies indicate the presence of abundant binding sites for miRNAs in circRNAs. CircRNAs can stabilize miRNAs, regulate alternative splicing, encode small peptides, and serve as protein “decoys” and miRNA inhibitors (“sponges”) to exert their effects.^{609,610}

ExocircRNAs derived from tumor cells can influence target cells or organs via exosome transportation, potentially promoting or suppressing tumor growth.⁶¹¹

As an increasing number of studies are conducted, researchers are analyzing the relationship between exosomes and circRNAs in tumors, reporting that exocircRNAs are novel biological markers for tumor detection, providing a new direction for tumor diagnosis.^{62,612} According to Dou et al.,²⁸ circRNAs were discovered in tumor-derived exosomes, and their abundances were higher compared with those in mutant KRAS cells, suggesting a potential link between circRNAs and tumorigenesis. This indicates the potential role of exocircRNAs as tumor biomarkers.

According to Shang et al.,⁶¹³ circPACRGL was remarkably upregulated in CRC cells when tumor-derived exosomes were added, indicating its role in inhibiting CRC proliferation and metastasis. The level of exosomal circSHKBP1 was significantly increased in GC serum and tissues, and it was associated with unfavorable prognoses and advanced tumor node metastasis (TNM) stages. Additionally, exosomal circSHKBP1 enhanced GC cell proliferation, motility, invasiveness, and angiogenesis by modulating the miR-582-3p/HUR/VEGF axis and inhibiting the degradation of HSP90.⁶¹⁴

Hsa_circ_0074854 may be transferred by exosomes from NSCLC cells to macrophages, where its expression level was elevated. To inhibit NSCLC invasion and migration, the knockdown of Hsa_circ_0074854 suppresses HuR interaction and macrophage M2 polarization.⁶¹⁴ ExocircRNAs derived from MSCs represent a potential antitumor treatment. By functioning as a sponge for miR-216a-3p and thus releasing HDAC4, exosomal circFBXW7 generated from MSCs inhibits synovial cell proliferation, migration, and invasion, and suppresses the inflammatory response in RA.⁴⁸³

Recent studies have revealed that circRNAs are highly abundant in human platelets compared with other hematopoietic cells and are packaged and released in platelet-derived exosomes and microvesicles.⁶¹⁵ Given that platelets are implicated in tumor migration, inflammation, and hemostasis, research on exocircRNAs may provide a new avenue for disease diagnosis and treatment.⁶¹⁵

4.2.3 | Exosomes contain abundant and stable CircRNA

In an RNA-Seq study of total RNA with depleted ribosomal RNA from MHCC-LM3 liver cancer cells and the exosomes they produce, it was first discovered that exocircRNAs are abundant and stable.²⁶ RNA-Seq analysis revealed that the ratio of circRNA levels to their linear RNA coun-

terparts in exosomes was approximately sixfold higher than in the producer cells. Additionally, circRNA levels remained stable even after being incubated for up to 24 h at ambient temperature.²⁶ According to these findings, exosomes contain an exceptionally high concentration of stable circRNAs.

ExocircRNA exhibits a distinct expression pattern from that of the parent cells,^{26,28} indicating that exosomes actively incorporate circRNAs. Exosome RNA sorting has been shown to involve a variety of methods, including specialized RNA sequences and/or secondary structures associated with RBPs.^{616,617} The precise mechanism by which circRNAs are sorted into exosomes remains undetermined.

CircRNA may be more abundant in exosomes due to its stability. The extended half-life of circRNA, relative to linear RNA, is attributed to its resistance to exonuclease digestion, as it lacks a 5' or 3' end.^{73,105,618} Although the production of nascent circRNA is not highly efficient due to its lengthy half-life, it tends to accumulate in cells with slower division rates, such as neuronal cells.^{119,619,620} Additionally, exosomes can protect their RNA cargo from degradation by RNases.^{621,622} Consequently, circRNA that has been incorporated into exosomes may be highly stable.

The concentration of miRNA in producer cells can influence the amount of circRNA present in exosomes. Among the most extensively studied circRNAs, CDR1-AS has been shown to bind to miR-7 and significantly inhibit miR-7 activity.³³ When miR-7 is produced ectopically, CDR1-AS is significantly reduced in exosomes but slightly increased in cells.²⁶ This evidence suggests that the relative miRNA levels in producer cells are at least partially responsible for regulating the trafficking of circRNAs into exosomes.

4.2.4 | ExocircRNAs' biological functions

CircRNAs may influence the expression of miRNA target genes in recipient cells and maintain the miRNA sponging activities of exosomes. The exosomal form of CDR1-AS is the first circRNA shown to maintain biological activity by sponging miR-7, exosomal CDR1-AS can potentially reverse miR-7-mediated growth inhibition in recipient cells.²⁶ There is increasing evidence that cancer cells, endothelial cells, and adipose cells interact with one another to promote cellular proliferation, invasion, EMT, metastasis, chemoresistance, and cancer cachexia.

Cell proliferation

Several reports indicate that exocircRNAs enhance cellular proliferation. Human hepatic epithelial cells exposed to arsenite release circRNA 100284, which is then conveyed via exosomes to surrounding normal cells. By acting as a miR-271 sponge and upregulating EZH2 expression,

exocircRNA_100284 accelerates the cell cycle and enhances cellular proliferation.⁶²³ A circRNA called exosomal CDR1-AS promotes the onset and progression of HCC. By acting as a sponge for miR-1270 and increasing alpha-fetoprotein expression in HCC cells, the upregulation of CDR1-AS enhances cell proliferation and motility. Exosomes carrying CDR1-AS are then delivered to nearby cells, stimulating their migration and proliferation.⁶²⁴ Circ0000284 is found in plasma exosomes, malignant tissues, and cholangiocarcinoma cell lines. Circ0000284 upregulates LY6E expression and encourages cholangiocarcinoma cell proliferation, migration, and invasion by acting as a sponge for miR-637 in cells. Circ0000284, released into exosomes, is then delivered to surrounding cells, promoting their proliferation and motility.⁶²⁵

ExocircRNAs produced by healthy cells inhibit proliferation in recipient cells, in contrast to those produced by tumors, which increase it. For example, circ0051443, downregulated in HCC patients' plasma exosomes, is released by healthy hepatic cells and transported to adjacent HCC cells, where it increases BAK1 expression and sponges miR331-3p, resulting in cell cycle arrest and apoptosis in tumor cells.⁶²⁶

EMT, invasion, and metastasis

Intercellular communication mediated by exosomes has been shown to facilitate the formation of prometastatic niches, induce EMT, and alter the TME, all of which contribute to tumor invasion and metastasis.^{627–629} Recent research implicates circRNAs in exosomes in the invasion and metastasis of tumors. Pancreatic cancer cells release circPDE8A, and overexpression of exosomal circPDE8A in patient plasma is linked to a poorer prognosis. In pancreatic cancer cells, circPDE8A acts as a miR-338 sponge, activating the metastasis-associated in colon cancer (MACC)/MET/ERK or AKT pathways and promoting invasive development. Additionally, by stimulating the MACC/MET/ERK or AKT pathway, exosomal circPDE8A promotes EMT in recipient cells.⁶³⁰ CircRanGAP1 is upregulated in plasma exosomes from preoperative GC patients compared with those from healthy controls and postoperative GC patients. More significantly, the plasma exosomes from these individuals increased the migratory and invasive rate of GC cells, suggesting that exosomal circRanGAP1 may perform a role in the onset and advancement of GC.⁶³¹ As opposed to nonmetastatic or low-metastatic HCC cells, exosomes from highly metastatic HCC cells have a higher concentration of circPTGR1. The miR-449a/MET pathway, activated by coculture with exosomal circPTGR1, promotes HCC cell invasion and motility. Additionally, patients with HCC have a poorer prognosis and more advanced clinical stages when circPTGR1 expression is high in serum exosomes.⁶³²

Exosoma CircRNA may facilitate the invasion of cancerous cells not only by increasing their invasiveness but also by changing the TME. HUVECs receive circIARS via exosomes secreted from pancreatic cancer cells. Pancreatic cancer cells may more readily invade HUVECs due to the presence of exosomal circIARS, which increases their permeability by upregulating RhoA and sponging miR-122.⁶³³ ExocircRNA-100338, which is increased in an HCC cell line with a high level of metastasis, also enhances the ability of HUVECs to permeate, proliferate, and undergo angiogenesis. CircRNA-100338 may bind RBPs such as NOVA2, which is known to regulate vascular growth and lumen development, as shown by RNA pull-down analysis. These findings suggest that circRNA-100338 could regulate angiogenesis by interacting with NOVA2, but further research is needed to confirm these hypotheses.⁶³

Multiple reports indicate that various circRNAs are implicated in metastasis. CircPRMT5, commonly upregulated in urothelial carcinoma of the bladder (UCB) cells, acts as a miR-30c sponge and modulates the SNAIL1/E-cadherin pathway, stimulating EMT in UCB cells. Additionally, the presence of circPRMT5 in serum and urine exosomes has been positively associated with lymph node metastasis (LNM) and advanced tumor progression.⁵⁴⁸ OC tissues exhibit elevated levels of circWHSC1, which upregulates hTERT and MUC1, acts as a miR-1182 and miR-145 sponge, and enhances cell proliferation, motility, and invasiveness. Exosomal circWHSC1 upregulates N-cadherin and MUC1, causing peritoneal mesothelial cells to adopt a fibroblast-like morphology. Additionally, OC cells, when injected intraperitoneally into mice along with exosomes from cells overexpressing circWHSC1, enhance peritoneal dissemination. This suggests that exosomal circWHSC1 may be transported to peritoneal mesothelial cells, facilitating peritoneal dissemination in vivo.⁶³⁴

Chemoresistance

CircRNAs in exosomes are associated with chemoresistance. In a microarray analysis of exosomal RNAs from chemosensitive and chemoresistant CRC cells, the expression levels of 105 circRNAs were significantly upregulated, while those of 34 circRNAs were downregulated in exosomes from chemoresistant CRC cells. Research suggests that hsa_circ_0032883 could be a potential biomarker for chemotherapy response, as it was found to be significantly elevated in the serum exosomes of chemosensitive patients compared with those who are chemoresistant.⁶³⁵ Another study identified a positive correlation between ciRS-122 and chemoresistance in CRC. ciRS-122 enhances the expression of PKM2 and acts as a miR-122 sponge. ciRS-122, transferred from chemoresistant cells to recipient cells, promotes glycolysis, and reduces drug sensitivity.⁶³⁶

Adipocyte browning

CircRNAs may be transported into adipose tissues by exosomes, potentially causing cancer cachexia in addition to facilitating tumor cells' intracellular crosstalk. Unlike cancer without cachexia, which typically has a better prognosis, cancer cachexia is characterized by an uncontrollable decrease in total body weight. Reports indicate that cancer cachexia is driven by abnormally increased thermogenesis due to adipocyte browning.^{637,638} These findings suggest that exocircRNAs from tumors may contribute to the development of cancer cachexia.

ExocircRNA's potential in clinical settings

CircRNAs can be found in serum,²⁶ urine,⁶⁶ and saliva,¹⁰⁸ with their tertiary structure contributing to their stability. Additionally, various circRNAs are dysregulated in different malignancies.⁶³⁹ To date, circRNAs have shown promise as noninvasive biomarkers for tumor detection. Recent evidence using high-throughput sequencing indicates that various exocircRNAs have potential as diagnostic biomarkers for cancers. Circ-0051443 was shown to be considerably reduced in exosomes generated from the plasma of patients with HCC compared with healthy controls utilizing microarray analysis. The diagnostic potential of exosomal circ-0051443 was evaluated based on plasma exosomes from 60 HCC patients and 60 healthy individuals. An AUC value of 0.8089 for exosomal circ-0051443 indicated moderate diagnostic accuracy.⁶²⁶ Hsa_circ_0000419, circ-KIAA, and hsa_circ_0065149 exhibited lower levels in plasma exosomes from patients with GC than in those from healthy individuals. AUC values of 0.84, 0.75, and 0.64, respectively, for these circRNAs indicated reasonable diagnostic accuracy.^{78,640,641} In a circRNA microarray analysis of three pairs of esophageal squamous cell carcinoma (ESCC) and nontumor tissues, 1045 circRNAs were found to be upregulated and 1032 downregulated in ESCC. Both hsa_circ_0043603 and hsa_circ_0001946 were found to be significantly downregulated in plasma from 50 ESCC patients compared with 50 controls. When used together as a diagnostic tool, these two circRNAs achieved a specificity of 98% and a sensitivity of 84%.⁶⁴² Exosomal hsa-circ-0004771 levels in the circulation were shown to be considerably elevated in the serum samples of 110 CRC patients in contrast to 35 patients with benign intestinal diseases and 35 healthy controls. Exosomal hsa-circ-0004771 in the circulation demonstrated a moderate ability to distinguish between stage I/II CRC patients and healthy controls, with AUC values of 0.86 and 0.88, respectively.⁶⁴³ Poor prognosis and clinical response to treatment in small-cell lung cancer were linked to serum exosomal FECRI.⁶⁴⁴ CircPDAC was elevated and detectable in the sera of pancreatic cancer patients (specificity 0.90, sensitivity 0.45). Additionally, circPDAC was also detected in the sera of patients

with intraductal papillary mucinous neoplasm, a known precancerous lesion.⁶⁴⁵

4.3 | ExocircRNAs and cancer

4.3.1 | ExocircRNAs and NSCLC

ExocircRNAs play crucial roles in the regulation of NSCLC development and progression by targeting cancer-related signaling pathways and/or regulating the expression of genes involved in NSCLC pathology, including cell proliferation, apoptosis, metastasis, stemness, and therapy resistance.⁶⁴⁶ Additionally, certain exocircRNAs are differentially expressed between NSCLC tissues and corresponding normal tissues, highlighting their potential as promising biomarkers for early diagnosis and prognosis of NSCLC. Here, we provide a summary of dysregulated exocircRNAs associated with NSCLC.

Biological properties and activity of exocircRNAs in NSCLC

Continuous proliferation and evasion of apoptosis are characteristic changes in cancer cells.⁶⁴⁷ The specific biological implications of numerous circRNAs on NSCLC are yet unknown. ExocircRNAs are found to be abnormally expressed in body fluids, tissues, plasma, and serum in cases of NSCLC.⁶⁴⁸ This review outlines the research conducted to understand how exocircRNAs are related to NSCLC (Table 3). In recent years, exocircRNAs have been linked to the progression of NSCLC, specifically to proliferation, apoptosis, invasion, metastasis, angiogenesis, glycolysis in NSCLC cells, recurrence, mechanisms of treatment resistance, EMT in NSCLC cells, and mortality, by regulating their target miRNAs and downstream tumor-associated signaling pathways^{649,650} (Figure 8). Table 3 presents the positive correlation between several upregulated circRNAs and NSCLC progression. Additionally, the downregulation of hsa_circ_0102537 and circ_0007761 inhibits the progression of NSCLC.⁶⁵¹

ExocircRNAs target specific organs and cells by transporting exosomes, which subsequently play a role in controlling the proliferative, apoptotic, invasive, and metastatic processes of NSCLC cells. CircRNA_102481 promotes the proliferation of cells sensitive to EGFR-TKIs while inhibiting their apoptosis by acting as a sponge for miR-30a-5p and downregulating ROR1 expression.⁶⁵²

Another study revealed an increase in hsa_circ_0008717 expression in serum exosomes from lung adenocarcinoma (LUAD) cases. Suppression of hsa_circ_0008717 decreased malignant behaviors in LUAD cells, arrested the cell cycle, and induced apoptosis, while repressing their

TABLE 3 The biological functions and potential clinical values of exosomal circular RNAs in NSCLC.

Exosomal circRNA	Target cell	Expression	Pathway	Potential clinical value	Function	References
circRNA_102481	PC9 HCC827	Up	miR-30a-5p/ROR1	Diagnostic biomarker and therapeutic target	Promote EGFR-TKIs sensitive cell proliferation and inhibit cell apoptosis	652
circ_0008717	A549 H1299	Up	miR-1287-5p/PAK2	Therapeutic strategy	Promoted tumorigenesis in NSCLC	653
circSETDB1	A549 PC9	Up	miR-7/Sp1	Occurrence and development	Enhances the proliferation, migration, and invasion of LUAD cells	654
circSHKBP1	A549 H1299	Up	miR-1294/PKM2	Potential biomarker for the diagnosis and treatment of NSCLC	Promotes the proliferation, colony formation, migration, and invasion of NSCLC cells	655
hsa_circ_0102537	A549 H1975 H1299	Down	-	Therapeutic target	Inhibits the migration and invasion of LUAD cells	651
circ-CPA4	A549 H1299	Up	let-7/PD-L1	Therapeutic agents	Regulated cell growth, mobility, stemness, and drug resistance in NSCLC cells	650
circ_0047921	-	UP	-	Diagnostic tool for NSCLC	Promising biomarkers for an NSCLC diagnosis	656
circ_0056285	-	Up	-	-	-	-
circ_0007761	-	Down	-	-	-	-
hsa_circ_0014235	-	UP	-	Potential biomarkers and therapeutic targets	Novel diagnostic biomarkers for LUSC	657
hsa_circ_0025580	-	UP	-	-	-	-
hsa_circ_0026403	-	UP	-	-	-	-
hsa_circ_0001492	-	UP	-	Novel diagnosis and treatment biomarkers	Biomarkers and the pathological effects of lung cancer	658
hsa_circ_0001346	-	UP	-	-	-	-
hsa_circ_0000690	-	UP	-	-	-	-
hsa_circ_0001439	-	UP	-	-	-	-
circDNER	A549	UP	miR139-5p/ITGB8	Potential prognostic biomarker and therapeutic target	Increased lung cancer cell proliferation, invasion and migration	659
circ_0048856	A549 H1299 SK-MES-1	UP	miR-1287-5p	High diagnostic value for NSCLC	Facilitated proliferation, migration and invasion, inhibited apoptosis of NSCLC cells	660
hsa_circ_0069313	-	UP	NER	Discriminate NSCLC and benign lung tumor	The development of noninvasive biomarkers for more aggressive NSCLC	661

(Continues)

TABLE 3 (Continued)

Exosomal circRNA	Target cell	Expression	Pathway	Potential clinical value	Function	References
circ_0007385	A549 H1299	UP	miR-1253/FAM83A	Diagnosis and treatment in NSCLC	Enhances non-small cell lung cancer cell proliferation and stemness	662
circFARSA	A549 PC9	UP	PI3K/AKT	Diagnostic and prognostic biomarker	Increase in vitro migration and invasion	649
circ_PIP5K1A	A549 H1299	UP	miR-101/ABCC1	Diagnosis and treatment in NSCLC	Promoted A549 and H1299 cell migration and invasion	663
circ-MEMO1	A549 H1299	UP	MiR-101-3p/KRAS	Early diagnostic marker for NSCLC	Promotes the Progression and Aerobic Glycolysis of Non-small Cell Lung Cancer	664
hsa_circ_0014235	A549 H1299	UP	miR-520a-5p/CDK4	Promising biomarker for NSCLC	Promoted DDP chemoresistance, leading to increased cell proliferation, migration and invasion	665
circ_0008928	A549 H1299	UP	miR-488/HK2	Potential biomarker for the diagnosis	Knockdown suppressed cell proliferation, migration, invasion, and glycolysis metabolism, and improved CDDP sensitivity in CDDP-resistant NSCLC	666
hsa_circ_0002130	HCC827 H1975	UP	miR-498/GLUT1, HK2 and LDHA	Promotion role in osimertinib-resistant NSCLC	Affected cell growth, apoptosis and glycolysis in NSCLC cells	667
hsa_circ_0000190	A549 H460 H1299	Up	miR-142-5p/PD-L1	Therapeutic strategy of progression in NSCLC	Increased cell migration and invasion in NSCLC cells	668
hsa_circ_0056616	PC9 PC14	Up	-	Potential biomarker for therapeutic of lymph node metastasis in lung adenocarcinoma	Promoted colony formation frequency, proliferation rate, migration rate	669
hsa_circ_0000190 hsa_circ_0001649	A549 HCC827	Up	-	Valuable blood-based biomarker to estimate the prognosis of lung cancer	Associated with clinicopathological features and the treatment response of LC patients	670
circSATB2	A549 H460	Up	miR-326/FSCN1	Potential biomarker for clinical detection of NSCLC and metastatic NSCLC	Promote the progression of NSCLC, and may participate in cell-to-cell communication	671

(Continues)

TABLE 3 (Continued)

Exosomal circRNA	Target cell	Expression	Pathway	Potential clinical value	Function	References
circRNA-002178	A549 PC9 95D	Up	miR-34/PDL1/PD1	Novel diagnosis biomarker for LUAD	As a ceRNA to enhance PDL1 and PD1 expression in cancer cells and T cells	672
hsa_circ_0000519	H2170 A549	Up	miR-1258/RHOV	A new insight into NSCLC development and treatment	Promoted the cell growth and metastasis in NSCLC	673
circPLK1			miR-1294/HMGAI	Potential prognostic marker for NSCLC	Promoted NSCLC progression	674
circ-IARS	A549 H1299	Up	miR-1252-5p/HDGF	A potential diagnostic biomarker for NSCLC and a potential target for the treatment of NSCLC	Promoted cell proliferation, migration, and invasion and inhibited cell apoptosis in NSCLC	675
circUSP7	A549 H1299	Up	miR-934/SHP2	Promoted tumor progression and plays a role in immune evasion in NSCLC	Reduced the therapeutic efficacy of anti-PD1 treatment in NSCLC	676
circRACGAP1	A549 H1299	Up	PTBP1/SIRT3/RIFF1	The development of therapeutic strategies	A driver for stemness and metastasis of NSCLC	677
circ_0076305	A549 H292	Up	miR-186-5p/ABCC1	Regulating Cisplatin resistance of NSCLC	Potential circRNA-targeted therapy for NSCLC	678
circARHGAP10	A549 H292	Up	miR-638/FAM83F	Promoted proliferation, migration, invasion, and glycolysis of NSCLC cells	A theoretical basis for developing effective NSCLC diagnostic biomarkers and therapeutic targets	679
circVMP1	A549 H1299	Up	miR-524-5p-METT13/SOX2	Enhanced the proliferation, sphere formation, migration, invasion, and DDP resistance	Potential promising bio-marker for NSCLC	680
circCD226	A549 H1299	Up	miR-1224-3p/HMGA2	Enhanced NSCLC cell proliferation, migration, invasion and stemness	A potential driver in NSCLC development	681

Abbreviations: ABCC1, ATP binding cassette subfamily C member 1; CDK4, cyclin-dependent kinase 4; DDP/CDDP, cisplatin; FAM83A, family with sequence similarity 83 member A; FAM83F, family with sequence similarity 83 member F; FSCN1, fascin actin-binding protein IRHOV; RAS homolog family member V; GLUT1, glucose transporter 1; HDGF, hepatoma-derived growth factor; HK2, hexokinase 2; HMGA1, high mobility group at-hook 1; HMGA2, high mobility group AT-hook 2; ITGB8, integrin beta8; KRAS, Kirsten rat sarcoma viral oncogene homolog; LDHA, lactate dehydrogenase A; let-7, let-7 microRNA; METTL3/SOX2, methyltransferase Like 3/SRY-Box Transcription Factor 2; NER, nucleotide excision repair; PAK2, p21-activated kinase 2; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; PKM2, pyruvate Kinase M2; PTBP1/SIRT3/RIFF1, polypyrimidine tract-binding protein 1/sirtuin 3/regulator of telomere lengths and telomere C-strand synthesis; ROR1, receptor tyrosine kinase-like orphan receptor 1; SHP2, SH2 domain-containing phosphatase 2; Sp1, specificity protein 1.

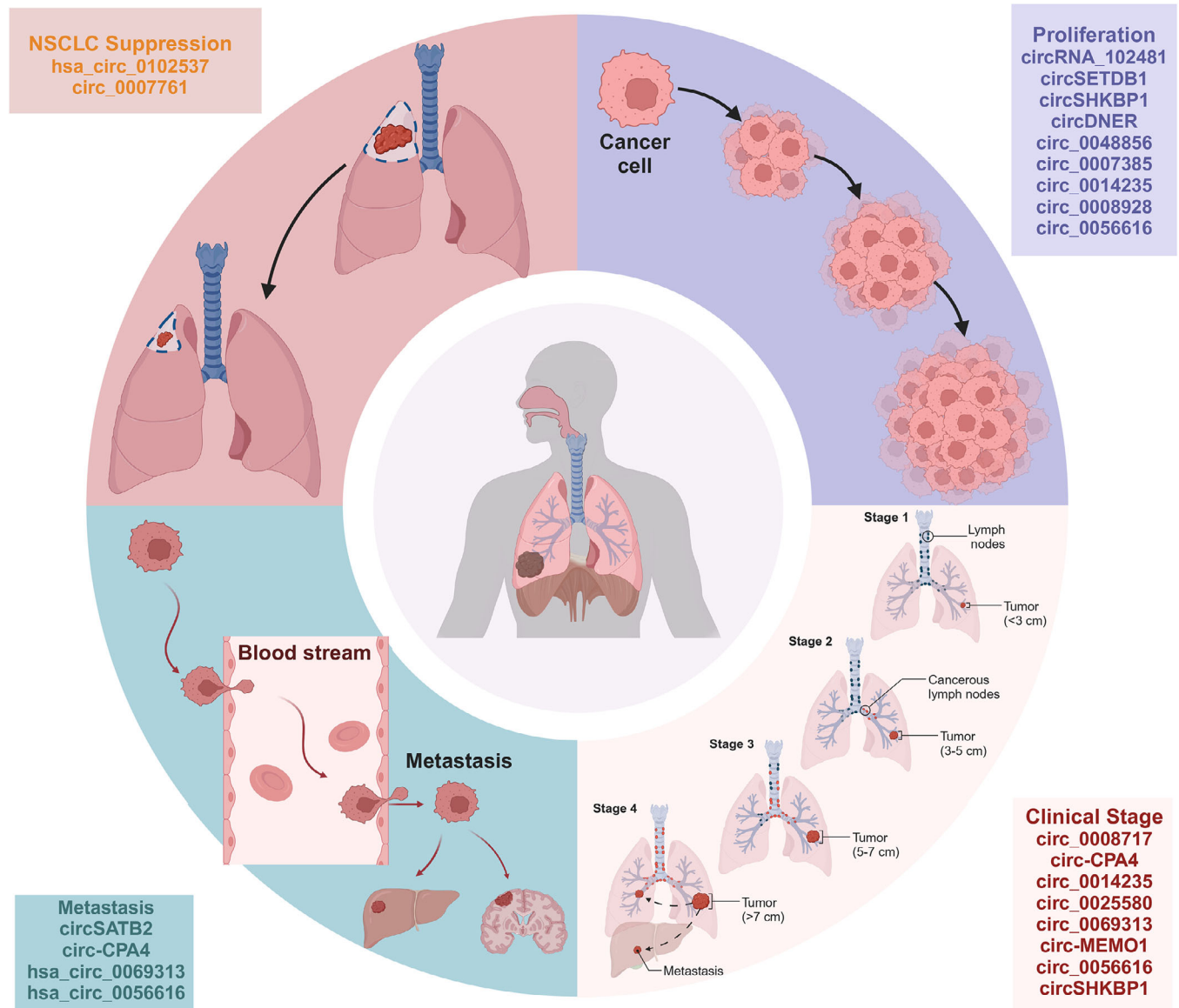


FIGURE 8 Representation of major biological activities of dysregulated exosomal circRNAs in NSCLC. This diagram illustrates the progression of NSCLC from normal lung tissue to advanced stages. The sequence begins with normal lung cells, which undergo proliferation and transformation into malignant cells, leading to the formation of small tumors that progressively enlarge and invade adjacent tissues. As the tumor expands, it disrupts local anatomical structures and has the potential to metastasize via the bloodstream and lymphatic system, ultimately reaching distant organs such as lymph nodes, bones, and internal viscera.

proliferation, migration, and invasiveness, by modulating the miR-1287-5p/PAK2 axis.⁶⁵³

Similarly, circDNER expression is increased in exosomes from LUAD cells and cases. CircDNER acts as a sponge for miR-139-5p, while ITGB8 is the target of miR-139-5p. Consequently, circDNER enhances the ability of LUAD cells to proliferate and migrate by modulating the miR-139-5p/ITGB8 axis.⁶⁵⁹ Circ-CPA4 is also involved in transport within LUAD cells. As discovered by Hong and colleagues, let-7 is sponged by circ-CPA4, while PD-L1 is a target of let-7. Mechanistically, circ-CPA4 knockdown inhibited in

vitro LUAD cell growth and suppressed in vivo LUAD tumor growth via the let-7/PD-L1 axis.⁶⁵⁰

Hsa_circ_0001346, hsa_circ_0000690, and hsa_circ_0001439 were found to be increased in lung cancer, presenting potential novel diagnostic and treatment biomarkers.⁶⁵⁸ Ning et al.⁶⁶² discovered that overexpression of hsa_circ_0007385 enhances NSCLC cell proliferation and stemness via the miR-1253/FAM83A signaling pathway. Circ_0048856 levels are increased in NSCLC cells and tissues, promoting proliferation, migration, and invasion, while inhibiting apoptosis in

NSCLC cells.⁶⁶⁰ Additionally, hsa_circ_0102537 was predominantly packaged in exosomes, but less commonly found in LUAD tissues and plasma compared with normal subjects.⁶⁵¹

ExocircRNAs target signaling pathways in NSCLC

An expanding volume of studies demonstrates that exocircRNAs contribute to the progression of NSCLC by influencing cancer-related signaling pathways, specifically the PI3K/AKT and MAPK pathways. The PI3K/AKT signaling pathway holds significant importance in controlling diverse cellular biological processes such as cell cycle, glucose transport, and the development of cancer.⁶⁸² Aberrations in the PI3K/AKT pathway are tightly linked to the advancement of NSCLC.⁶⁸³ Multiple exocircRNAs have been pinpointed as modulators of NSCLC tumorigenesis through their interaction with the PI3K/AKT signaling cascade. As an illustration, Chen and colleagues⁶⁴⁹ uncovered that exosomal circFARSA stimulates the PI3K/AKT pathway, bolstering the growth of NSCLC cell lines, specifically A549 and PC9. The MAPK signaling pathway is renowned for its role in cancer development. Disturbances in the MAPK/ERK cascade contribute significantly to various facets of cancer progression.⁶⁸⁴ Wang et al.²⁵ revealed that circ-ZKSCAN1 hinders the proliferation of NSCLC cells. This mechanism involves the upregulation of FAM83A expression by sequestering miR-330-5p, thereby suppressing the MAPK signaling pathway.²⁵ Furthermore, reports indicate that hsa_circ_0004050 downregulates DUSP9 expression by sponging miR-1233-3p in the NSCLC cell line A549, thus impeding the ERK/JNK signaling cascade.⁶⁸⁵ Our investigations have demonstrated elevated levels of circ-ZKSCAN1 in both NSCLC tissues and cell lines. This upregulation leads to the suppression of the MAPK signaling pathway by absorbing miR-330-5p, resulting in increased FAM83A expression and consequently, augmented NSCLC cell growth.²⁵ Taken together, these findings underscore the pivotal role of circRNAs in regulating NSCLC signaling cascades (Figure 9).

Relations of exocircRNAs with NSCLC clinicopathological features

Presently, due to the intricate pathological traits of NSCLC, detecting its early symptoms is challenging. Consequently, many patients receive a diagnosis only when the disease has progressed to an advanced stage, thereby missing the optimal window for surgical intervention. Furthermore, the inadequate prognosis evaluation significantly impedes the customization of treatment plans for individual patients and efforts to extend their survival. In the past few years, several traditional biomarkers, including AFP, PD-L1, and ALK, have been utilized for both the diagnosis and prognosis assessment of various cancers, NSCLC being

one of them. Table 4 presents the relations of exocircRNAs with clinicopathological features in NSCLC cases. Wang and colleagues explored the relation of circ_0008717 level with clinicopathological features in 24 LUAD cases, revealing that LUAD cases who had circ_0008717 upregulation showed an advanced TNM and a large tumor size compared with those showing circ_0008717 downregulation.⁶⁵³ According to Hong et al.,⁶⁵⁰ exosomal circ-CAP4 upregulation was tightly associated with TNM and extra-lung metastasis (EM). As discovered by Xian et al.,⁶⁵⁶ upregulation of the serum markers hsa_circ_0025580 and hsa_circ_0014235 in LUAD patients was strongly linked to tumor sizes and TNM stages, which was not the case for sex, age, or smoking status. Moreover, exosomal circ_0047921 and circ_0056285 expression significantly increased among LUAD cases except circ_0007761 was decreased, which showed a positive relation to family history of cancer, but not with other clinical features.⁶⁵⁶ Furthermore, hsa_circ_0026403, hsa_circ_0025580, and hsa_circ_0014235 expression was also related to TNM stage and tumor sizes, rather than to sex, age, and smoking status.⁶⁵⁷ Moreover, hsa_circ_0069313 and Circ-MEMO1 upregulation showed a positive relation to TNM, LNM as well as EM.^{661,664} The expression of hsa_circ_0056616 showed a positive association with tumor size, TNM stages, and EM, which was not the case for age and sex.⁶⁶⁹ Based on the above evidence, tumor size, and TNM stage exhibited the highest association with aberrant exocircRNA expression whereas age, gender, number of tumors, smoking status, and LNM presented no significant relationship.

ExocircRNAs' significance in diagnosing and predicting the prognosis of NSCLC

Although great progresses have been made in surgical, locoregional, and medical treatments, NSCLC still has a high mortality rate due to disease metastasis and relapse postoperatively.⁶⁸⁶ NSCLC-derived exosomes are found to redirect cancer cell metastasis in cells with no specific organ metastatic capacity.⁶⁵⁰ Exosomes can shuttle circRNAs between cells while regulating tissue genesis and cell differentiation. ExocircRNAs have been implicated in recent research as candidate prognostic and diagnostic biological markers for NSCLC.^{651,655,661} Table 5 presents the latest research on the involvement of exocircRNAs in diagnosing and predicting the prognosis of NSCLC.

In NSCLC individuals, there is an increase in the levels of hsa_circ_0025580 and hsa_circ_0014235, which may have an impact on NSCLC progression.⁶⁵⁷ According to Wang and colleagues,⁶⁵⁷ hsa_circ_0014235 was a new marker to diagnose NSCLC, and its AUC value of the ROC curve value was 0.8254 (95 CI%: 0.762–0.889) to discriminate NSCLC.⁶⁵⁷ Moreover, hsa_circ_0025580

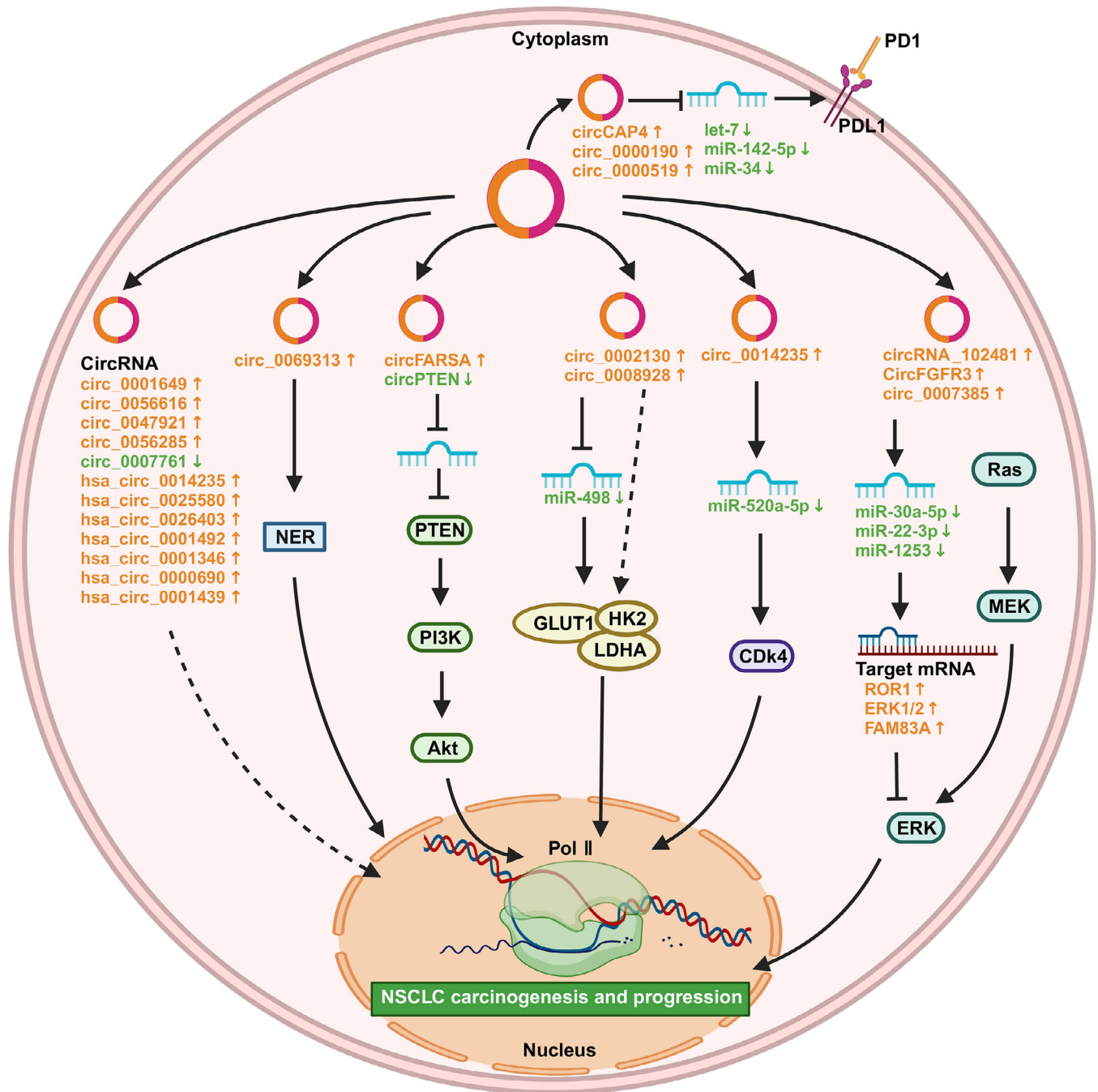


FIGURE 9 Regulation by circRNAs of signaling pathways in NSCLC. CircRNAs participate in the carcinogenesis and progression of NSCLC by regulating the expression of key components involved in cancer-related signaling pathways.

had 0.8003 (95 CI%: 0.741–0.862).⁶⁵⁷ According to He and coworkers,⁶⁶⁰ circ_0048856 showed upregulation in plasma-derived exosomes with better diagnostic ability in NSCLC (AUC = 0.943, and the sensitivity and specificity were 88 and 80%, respectively). In addition, hsa_circ_0069313, circRNA-002178, and circSHKBP1 have the ROC values of 0.724, 0.9967, and 0.853, respectively, to distinguish NSCLC from health, respectively.^{655,660,661} Moreover, Zhang et al.⁶⁷¹ reported that circSATB2 was mostly released via exosomes in NSCLC cells, with

significant upregulation in NSCLC cells and tissues compared with normal lung cells and para-carcinoma tissues. According to the ROC curve, circSATB2 displayed great significance in diagnosing NSCLC, and the AUC was 0.66 (95 CI%: 0.581–0.74).⁶⁷¹ As suggested by Ding and colleagues,⁶⁶⁴ circMEMO1 upregulation in nearby tissues predicted dismal survival for NSCLC cases.

Nevertheless, further study is required before circRNAs can be used in clinical settings since their function in

TABLE 4 Relationship between exocircRNAs and clinicopathologic characteristics in NSCLC.

circRNAs	Expression	N(H/L)	Gender	Age	TS	TNM	LN	PT	SS	EM	References
circ_0008717	Up	24/24	–	–	Y	Y	–	–	–	–	653
circ-CPA4	Up	25/25	N	N	–	Y	–	N	N	Y	650
hsa_circ_0014235	Up	15/15	N	N	Y	Y	–	–	N	–	656
hsa_circ_0025580	Up	15/15	N	N	Y	Y	–	–	N	–	656
hsa_circ_0069313	Up	108	–	–	N	Y	Y	N	–	Y	661
Circ-MEMO1	Up	45/7	N	N	N	Y	Y	–	–	–	664
hsa_circ_0056616	Up	–	N	N	Y	Y	–	–	–	Y	669
circSHKBP1	Up	61/39	N	N	–	Y	Y	N	N	N	655
circSATB2	Up	44/15	N	N	–	N	Y	N	N	N	671
circPLK1	Up	25/25	N	N	N	Y	–	–	–	Y	674
circUSP7	Up	63/63	N	N	N	Y	Y	N	N	–	676

N, no supply; Y, supply.

TABLE 5 ExocircRNAs serve as potential diagnostic biomarkers for NSCLC.

CircRNAs	ROC	95 CI%	Sensitivity (%)	Specificity (%)	References
hsa_circ_0014235	0.8254	0.762–0.889	–	–	657
hsa_circ_0025580	0.8003	0.741–0.862	–	–	657
circ_0048856	0.943	0.904–0.982	88	80	660
hsa_circ_0069313	0.724	–	–	–	661
circ-MEMO1	0.76	0.6259–0.8941	56.67	96	664
hsa_circ_0002130	0.792	0.676–0.909	–	–	667
hsa_circ_0056616	0.812	0.720–0.903	79.2	81	669
hsa_circ_0000190	0.95	0.926–0.974	90	90.2	670
circSATB2	0.66	0.581–0.74	–	–	671
circRNA-002178	0.9967	–	–	–	672
circSHKBP1	0.853	–	–	–	655
circPLK1	0.866	–	–	–	674
circCD226	0.9571	–	–	–	681

NSCLC is still relatively unknown. Moreover, a large number of samples, multiple centers, and independent external cohort validation are required for circRNA to become a widely accepted biomarker. Besides, there are only a very few circRNAs that have been found to have an impact on tumors. In addition, only a limited number of circRNAs have been identified in NSCLC, and further research is required.

4.3.2 | ExocircRNAs and HCC

HCC arises from liver tissue and stands as a predominant cause of mortality worldwide, accounting for approximately 75–85% of primary liver cancers.⁶⁸⁷ HCC is intricately linked with various factors, including chronic hepatitis, cirrhosis, aflatoxin exposure, excessive alcohol

consumption, and genetic predisposition.⁶⁸⁸ CircRNAs derived from HCC cells and their associated exosomes exert multifaceted influences on HCC progression, impacting processes such as tumor cell proliferation, metastasis, and apoptosis regulation. These circRNAs also hold promise as potential markers and therapeutic targets for HCC, examples of which include circTGFB2,⁶⁸⁹ circ_002136,⁶⁹⁰ and hsa_circ_0074854.⁶⁹¹ Conversely, certain exosome-derived circRNAs have been identified as potential inhibitors of HCC, as evidenced by circRNAs like hsa_circ_0004658⁶⁹² and circ_0051443,⁶²⁶ among others. In summary, exosomes play a pivotal and intricate role in the context of HCC, with exosome-derived circRNAs serving as significant contributors. This role opens up novel perspectives and strategies for early HCC diagnosis and treatment. This section will delve into the specific role of exocircRNAs in HCC.

Exosome-derived circRNA promotes HCC

Numerous studies have provided compelling evidence of the significant involvement of exosome-derived circRNAs in advancing the progression of HCC. These specific circRNAs exert a substantial influence on the biological characteristics of HCC cells, including proliferation, metastasis, and drug resistance, thus actively fostering the advancement of HCC.

First, exocircRNAs derived from HCC cells can function as miRNA “sponges,” adsorbing miRNAs and thereby contributing to HCC progression. For example, circWHSC1 absorbs miR-142-3p and promotes proliferation and metastasis of HCC cells by directly targeting homeobox A1 (HOXA1), suggesting that circWHSC1 may become a diagnostic indicator of HCC.⁶⁹³ Circ_MMP2 interacts with miR-136-5p and MMP2, leading to the upregulation of MMP2 and the promotion of HCC cell progression. Elevated MMP2 levels are associated with HCC metastasis and poor overall survival in HCC patients.⁶⁹⁴ Similarly, circPTGR1 promotes cancer cell metastasis by competing for miR449a binding to MET.⁶³² CircRNA Cdr1as promotes AFP expression by adsorbing miR-1270.⁶²⁴ Circ_002136 augments Ras-related expression by blocking miR-19a-3p, increasing Ras-related protein Rab-1A (RAB1A) expression and promotes HCC cell progression.⁶⁹⁰ CircTGFB2 enhances ATG5-mediated cytoprotective autophagy by interfering with the interaction between miR-205-5p and autophagy-related protein 5 (ATG5), thereby promoting HCC progression.⁶⁸⁹ Notably, in arsenite-induced HCC, circRNA_100284 can be transferred into normal hepatocytes and induce cell cycle acceleration, cell proliferation, and malignant transformation of normal hepatocytes by acting as a sponge for miRNA-217, suggesting that circRNAs have the potential to induce malignant transformation in normal cells.⁶²³

Second, exocircRNAs may mediate drug resistance in HCC cells. For example, exosome-derived circZFR from cancer-associated fibroblasts (CAFs) is highly expressed in cisplatin (DDP)-resistant HCC cell lines and can inhibit the STAT3/NF- κ B pathway, promote tumor growth and enhance DDP resistance. Targeting circZFR and related pathways may help improve the efficacy and survival of patients treated with chemotherapy for HCC.⁶⁹⁵ Exosome-derived circRNA-SORE from HCC cells is frequently upregulated in sorafenib-resistant HCC cells, and further studies have shown that circRNA-SORE stabilizes the cytoplasmic oncogenic protein YBX1, which is a key component in the development of HCC. Silencing of circRNA-SORE by siRNA could overcome sorafenib resistance in HCC patients.⁶⁹⁶ CircPAK1 derived from HCC cell exosomes promotes HCC cell proliferation, invasion, and metastasis, while inhibiting apoptosis and angiogenesis. Further studies showed that exosomes from rapastatinib-

resistant HCC cells mediate the transport of circPAK1, contributing to rapastatinib resistance.⁶⁹⁷

In addition, HCC-derived exocircRNAs can inhibit immune cells in the TME and promote angiogenesis to exert pro-cancer effects. For example, circUHRF1 promotes tumor lung metastasis and reduces the number of natural killer group 2, member D (NKG2D)-positive cells in metastatic tumor nodules and contributes to NK cell dysfunction and poor clinical prognosis in HCC patients.⁶⁹⁸ Hsa_circ_0074854 regulates the expression of HCC cells by interacting with HuR protein and regulating its protein expression level, thereby affecting the EMT process in HCC cells. Conversely, exosomes carrying downregulated hsa_circ_0074854 can translocate to macrophages and inhibit their polarization, which may ultimately impede the migration, invasion, and EMT of HCC cells.⁶⁹¹ CircFUT8, whose expression is upregulated in HCC cells, can be modified by m6A, thereby promoting HCC progression. However, M1-type macrophage-derived exosomes can inhibit HCC progression by transfecting miR-628-5p into HCC cells and downregulating m6A modification, suggesting an anticancer role for M1-type macrophage-derived exosomes.⁶⁹⁹ CircGSE1 can maintain the expression of transforming growth factor-beta receptor 1 (TGFBRI) and Smad3, which promotes the expansion of Treg cells and thereby inhibits the activity of effector T cells, such as CD8⁺ T cells, resulting in immune escape from HCC cells.⁷⁰⁰ In addition, circTMEM181 increases CD39 expression on macrophages and inhibits CD8⁺ T cells, leading to resistance to PD-1 treatment in HCC.⁷⁰¹ Similarly, circCCAR1 is able to promote CD8⁺ T cell exhaustion, leading to impaired anti-tumor immunity in TME. The mechanism is that circCCAR1 prevents the ubiquitinated degradation of the PD1 protein by binding directly to PD1, thereby impairing the tumor killing capacity of CD8⁺ T cells.⁷⁰² Notably, in vitro and animal studies have shown that circRNA-100338 promotes the invasion and metastasis of HCC cells and promotes vascular endothelial cell proliferation, angiogenesis, and which correlates with lung metastasis and reduced survival in HCC patients.⁶³

Exosome-derived circRNA inhibits HCC

Conversely, it has also been shown that exosome-derived circRNAs can inhibit HCC progression by adsorbing miRNAs. For example, circ_0051443 can act as a sponge for miR-331-3p, thereby attenuating the regulatory effect of miR-331-3p on BCL2 antagonist/killer 1 (BAK1), which inhibits HCC cell progression.⁶²⁶ Macrophage exosomes overexpressing recombination signal binding protein λ (RBPJ) overexpress hsa_circ_0004658, which led to the upregulation of junctional adhesion molecule 3 through the adsorption of miR-499b-5p, thereby inhibiting HCC

cell proliferation and promoting apoptosis, suggesting the diagnostic and therapeutic potential of hsa_circ_0004658 as a biomarker and target for HCC cell therapy.⁶⁹²

Taken together, these data demonstrate the important role of exosome-derived circRNAs in promoting/inhibiting HCC development, mediating drug resistance, promoting proliferation, metastasis, and regulating immune escape. These findings provide important clues for understanding the mechanism of exosome-derived circRNAs in the pathophysiology of HCC cells and offer new opportunities for their clinical application as diagnostic and prognostic markers as well as therapeutic targets in HCC cells.

4.3.3 | ExocircRNAs and CRC

CRC is a malignant tumor, that starts in the lining of the colon or rectum. It is the third most common cancer worldwide, after lung and breast cancer, and the second leading cause of cancer death after lung cancer.⁷⁰³ Risk factors for CRC include a diet high in processed meat, obesity, smoking, low fruit and vegetable intake, and a history of inflammatory bowel disease.⁷⁰⁴ Patients with hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis and relatives with a positive family history of CRC are also at increased risk.⁷⁰⁵ Several studies have found that circRNAs in exosomes are strongly associated with CRC. These circRNAs may have an important impact on cancer cell proliferation, migration, invasion and resistance to radiotherapy and drugs by regulating the expression of tumor-related genes or modulating signaling pathways, and these findings provide new insights into the mechanism of action of circRNAs in exosomes, as well as clues in the search for biomarkers and new therapeutic targets for CRC. This section focuses on these studies.

Exosome-derived circRNA promotes CRC

CircRNAs in CRC tissues can block downstream signaling pathways by adsorbing miRNAs, thereby affecting cancer cell growth, metastasis and drug resistance.

First, exosome-derived circRNAs in CRC cells can promote tumor invasion, and metastasis by promoting endothelial cell migration and proangiogenesis. For example, circ_001422 was able to inhibit the expression of miR-195-5p, which in turn promotes the kinase insert domain receptor (KDR)/mTOR signaling pathway and facilitates endothelial cell migration and angiogenesis, suggesting that circ_001422 has a role as a biomarker in the diagnosis of CRC.⁷⁰⁶ CircTUBGCP4 activates AKT through regulation of the miR-146b-3p pathway, thereby promoting vascular endothelial cell migration, lumen formation and tumor metastasis, providing important clues to understand the molecular mechanisms of CRC development.⁷⁰⁷ Second,

cancer cell exosome-derived circRNAs can attenuate the sensitivity of CRC cells to radiation, resulting in a reduced effect of radiotherapy. For example, circ_0067835 interacts with miR-296-5p and exerts a procancer effect by regulating the miR-296-5p/insulin-like growth factor 1 receptor (IGF1R) pathway in cancer cells. When downregulated in vivo, circ_0067835 inhibited CRC growth and increased cellular sensitivity to radiation.⁷⁰⁸ In addition, circ_IIFT80 can target miR-296-5p and further inhibit musashi1 (MSI1), a gene associated with tumor progression and radiosensitivity, thereby promoting tumorigenesis and reducing cellular sensitivity to radiation.⁷⁰⁹ In addition, exosome-derived circRNAs can also promote tumorigenesis under hypoxic conditions. For example, under hypoxic conditions, CAFs exosomes can secrete circEIF3K, which in turn promotes CRC cell proliferation, invasion and metastasis. The miR-214/PD-L1 pathway plays an important role in this process.⁷¹⁰ The hypoxic CRC cell-derived exosome circ-133 is able to translocate to normal tumor cells and promote migration via the miR-133a/guanine nucleotide exchange factor-H1 (GEF-H1)/RhoA axis, suggesting a difference in metastatic potential between hypoxic and relatively normoxic cancer cells.⁷¹¹

In terms of drug resistance, circRNAs may act as miRNA sponges to mediate CRC resistance to chemotherapeutic agents. For example, circ_0006174-enriched exosomes from doxorubicin (DOX)-resistant CRC cells promoted DOX resistance by binding miR-1205 and upregulating cyclin D2 (CCND2). This finding has important clinical implications for the treatment of CRC patients and is expected to be a future target for diagnosis and therapy.⁷¹² The exosome-derived hsa_circ_0005963 of oxaliplatin-resistant CRC cells enhances cellular resistance to chemotherapeutic agents by adsorbing miR-122, leading to overexpression of the M2 isoform of pyruvate kinase (PKM2), which subsequently increases cellular glycolytic metabolism. Targeting circRNA with siRNA (si-ciRS-122) can inhibit glycolysis and reverse resistance to oxaliplatin.⁶³⁶ In addition, increased expression of circ_0000338 in CRC cells correlates with increased 5-FU resistance. It has been shown that circ_0000338 negatively regulates the expression of miRNAs miR-217 and miR-485-3p by interacting with these two miRNAs, leading to 5-FU resistance in CRC patients.⁷¹³ Notably, some exosome-derived circRNAs are also capable of encoding proteins, thereby mediating drug resistance. For example, circATG4B is expressed at elevated levels in exosomes released from drug-resistant CRC cells and is capable of encoding the protein circATG4B-222aa. CircATG4B-222aa competitively interacts with the membrane vesicle transport protein transmembrane p24-trafficking protein 10 (TMED10) and acts as a drug resistance blocker. This competitive interaction with transmembrane p24-trafficking

protein 10 (TMED10), acting as a decoy to prevent TMED10 from binding to autophagy-related gene 4B (ATG4B), an interaction that leads to increased autophagy in CRC cells, thereby inducing the development of chemotherapeutic resistance.⁷¹⁴

Exosome-derived circRNAs inhibit CRC

In contrast, the effect of circRNAs on CRC also has therapeutic potential, and certain exosome-derived circRNAs are also able to inhibit CRC, providing an important basis for clinical practice and the development of therapeutic strategies.

It has been suggested that adsorption of miRNAs by circRNAs may also inhibit CRC. For example, circFNDC3B in CRC cell lines and exosomal samples is able to adsorb miR-937-5p and thus inhibit its function. In contrast, miR-937-5p is known to promote EMT. In animal studies, overexpression or exosomal treatment of circFNDC3B was shown to inhibit the growth, angiogenesis and liver metastasis of CRC transplant tumors.⁷¹⁵ CircEPB41L2 acts as a sponge for miR-215p and miR-9425p in exosomes, and overexpression of circEPB41L2 inhibits CRC cell proliferation, enhances apoptosis, and inhibits migration and invasion, which subsequently blocks the regulation of PTEN/AKT signaling pathway by these two miRNAs, ultimately presenting an inhibitory effect on CRC progression in cells and animal models.⁷¹⁶

In addition, some circRNAs act as protein decoys capable of binding proteins to exert inhibitory effects. For example, the plasma exosome circLPAR1 can be internalized by CRC cells and inhibits METTL3–eukaryotic translation initiation factor 3 subunit h (eIF3h) through binding to eIF3h, thereby inhibiting mRNA translation, which in turn inhibits the expression of the oncogene bromodomain-containing protein 4 (BRD4), thereby suppressing CRC cell proliferation, invasion and migration. Clinical studies have shown that downregulation of circLPAR1 is associated with poor survival in CRC patients. Therefore, circLPAR1 may serve as a potential diagnostic marker for CRC.⁶²

Some circRNAs have oncogenic effects in cancer cells, but tumor cell exosomes excrete them, thus escaping their inhibitory effects and maintaining cancer cell adaptation. An example is the exosome-derived circRHOTB3 in CRC cells. In response to this situation, researchers have proposed to intervene in the secretion process of circRHOTB3 through antisense oligonucleotides, thereby increasing its intracellular expression and consequently enhancing its inhibitory effect on CRC.⁷¹⁷

Notably, it has been shown that some circRNAs not only inhibit tumors but also promote resistance to chemotherapeutic agents. For example, hsa_circ_0000338 has a tumor growth inhibitory effect in CRC cells, but its delivery to

other CRC cells via exosomes leads to a role in promoting drug resistance. When knockdown of hsa_circ_0000338 was targeted by siRNA, it was shown to enhance drug resistance, suggesting that hsa_circ_0000338 may have a tumor growth inhibitory effect in CRC cells. These findings provide important clues to further understand the function of circRNAs.⁶³⁵ More studies on exosome-derived circRNAs in CRC have been presented in Table 6.

In summary, exosome-derived circRNAs have important roles in the development and treatment of CRC. These studies provide potential therapeutic targets and theoretical bases by deeply exploring the functions of circRNAs in exosomes, which provide important clues for future clinical practice and the development of therapeutic strategies. However, the different effects of circRNAs further suggest that researchers need to consider their mechanisms of action and regulatory networks more comprehensively in order to better understand their roles in disease development and provide more accurate targets and pathways for future therapeutic strategies.

4.3.4 | ExocircRNAs and pancreatic cancer

Pancreatic cancer is a type of cancer caused by the growth of malignant cells in the pancreatic tissue and is the fourth most common tumor in the world.⁷²⁷ The most common type of pancreatic cancer is PDAC, which accounts for 90% of pancreatic cancer cases.⁷²⁸ Studies have shown that the median survival of patients with pancreatic cancer who do not undergo surgical resection is approximately 2–8 months, and that approximately 94% of patients survive less than 5 years after diagnosis.⁷²⁹ The main risk factors for pancreatic cancer include smoking, obesity, high-fat diet and chronic pancreatitis.⁷³⁰ Because pancreatic cancer is not obvious in its early symptoms and is often detected at an advanced stage, it is more difficult to treat and has a poorer prognosis.⁷³¹ Some studies have found that circRNAs in exosomes are closely associated with pancreatic cancer. These circRNAs may have important effects on cancer cell proliferation, migration, invasion and drug resistance.

First, circRNAs exert oncogenic effects by adsorbing miRNAs and thereby blocking downstream signaling pathways. A study of 85 PDAC tissues, plasma exosomes, pancreatic cancer cells and human microvascular endothelial cells showed that circ-IARS expression was upregulated in plasma exosomes from pancreatic cancer tissues and patients with metastatic disease, which could enter endothelial cells via exosomes and promote tumor invasion and metastasis. Overexpression of circ-IARS significantly downregulated miR-122 and zonula occludens-1 (ZO-1) levels, upregulated RhoA and RhoA-GTP levels,

TABLE 6 Expression of exosome-derived circRNA in CRC.

circRNAs	Samples	Regulation	Signaling pathway	Function	References
circ_001422	Tissues; blood; CRC cells	Upregulated	miR-195-5p/KDR/mTOR	Proangiogenesis	706
circTUBGCP4	Tissues; blood	Upregulated	miR-146b-3p/AKT	Promotes angiogenesis and tumor metastasis	707
circ_0067835	Tissues; CRC cells	Upregulated	miR-296-5p/IGF1R	Promotes CRC development and enhances radioresistance	708
circ_IFT80	Blood; CRC cells	Upregulated	miR-296-5p/MSI1	Promotes tumorigenesis and reduces radiosensitivity	709
circEIF3K	Tissues; cells	Upregulated	miR-214/PD-L1	Induces CRC progression	710
circ-133	Tissues; Blood; CRC cells	Upregulated	miR-133a/GEF-H1/RhoA	Promotes cell migration	711
circ_FMN2	Blood; CRC cells	Upregulated	miR-338-3p/MSI1	Accelerates CRC progression	718
circPACRGL	CRC cells	Upregulated	miR-142-3p/TGF- β 1, miR-506-3p/TGF- β 1	Enhances CRC cell proliferation, migration and invasion, as well as differentiation of N1–N2 neutrophils	719
circCOG2	Blood; tissues; CRC cells	Upregulated	miR-1305/TGF- β 2/SMAD3	Promotes CRC proliferation, migration, and invasion	720
circLONP2	Tissues; CRC cells	Upregulated	circLONP2/DDX1/pri-miR-17	Enhances the invasiveness of CRC cells	721
circCOL1A2	Tissues; CRC cells	Upregulated	miR-665/LASP1	Promotes CRC cell proliferation, migration, invasion, and EMT	722
circFMN2	Blood; tissues; CRC cells	Upregulated	miR-1182/hTERT	Promotes CRC progression	723
circPABPC1	Tissues; CRC cells	Upregulated	miR-874 or miR-1292/ADAM19 or BMP4	Promotes CRC liver metastases	724
circ-RNF121	Tissues; CRC cells	Upregulated	miR-1224-5p/FOXO1	Promotes CRC cell proliferative and metastatic ability	725
circ-HMGCS1	Blood; colon cancer cells	Upregulated	miR-34a-5p/SGP1	Enhances colon cancer cell viability and invasion and suppress apoptosis	726
circ_0006174	Tissues; CRC cells	Upregulated	miR-1205/CCND2	Enhances DOX resistance	712
hsa_circ_0005963	Tissues; CRC cells	Upregulated	miR-122/PKM2	Reduces drug susceptibility in chemosensitive cells	636
circ_0000338	Tissues; CRC cells	Upregulated	miR-217/AEG-1;miR-485-3p/TPX2	Enhances chemotherapy resistance	713
circATG4B	Tissues; CRC cells	Upregulated	TMED10/ATG4B	Participates in the decreased chemosensitivity of CRC cells	714
circLPAR1	Tissues; CRC cells	Downregulated	eIF3h/BRD4	Internalized by CRC cells, and suppresses tumor growth	62
circFNDC3B	Tissues; CRC cells	Downregulated	miR-937-5p/TIMP3	Inhibits tumorigenic, metastatic, and angiogenic properties of CRC	715
circEPB41L2	Blood; CRC cells	Downregulated	miR-21-5p/PTEN/AKT; miR-942-5p/PTEN/AKT	Restraints CRC progression and the activity of PTEN/AKT signaling pathway	716
circRHOBTB3	Tissues	Downregulated	NF- κ B, RAS, and ERK	Represses metabolic pathways and intracellular ROS production in CRC	717
hsa_circ_0000338	Blood; CRC cells	Downregulated	Wnt; cGMP-PKG	May have dual regulatory roles in chemo-resistant CRC	635

Abbreviations: ADAM19, a disintegrin and metalloproteinase-domain-containing protein 19; AKT, protein kinase B; ATG4B, autophagy-related gene 4B; BMP4, bone morphogenetic protein 4; BRD4, bromodomain-containing protein 4; CCND2, cyclin D2; cGMP-PKG, cyclic guanosine monophosphate-dependent protein kinase; DDX1, DEAD box 1; eIF3h, eukaryotic translation initiation factor 3 subunit h; ERK, extracellular signal-regulated kinases; FOXO1, forkhead box O1; GEF-H1, Rho guanine nucleotide exchange factor; HOXB7, Homeobox B7; hTERT, human telomerase reverse transcriptase; IGF1R, insulin-like growth factor 1 receptor; KDR, kinase insert domain receptor; LASP1, multifunctional LIM and SH3 protein 1; MSI1, musashi1; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; PKM2, M2 isoform of pyruvate kinase; PTEN, phosphatase and tensin homolog; RAS, rat sarcoma; SGPP1, sphingosine-1-phosphate phosphatase 1; SMAD3, mothers against decapentaplegic homolog 3; TGF- β 1, transforming growth factor beta 1; TIMP3, tissue inhibitor of metalloproteinase 3; TMED10, transmembrane p24-trafficking protein 10; TPX2, targeting protein for xenopus kinesin-like protein 2; Wnt, wingless-related integration site.

increased filamentous actin (F-actin) expression and adhesive plaques, and increased endothelial monolayer permeability to promote tumor invasion and metastasis.⁶³³ In addition, a study of liver metastasis specimens from PDAC patients showed that high expression of the plasma exosome circ-PDE8A was associated with lymphatic invasion, TNM stage and poorer survival in PDAC patients. Further studies found that circ-PDE8A acted as a sponge for miR-338 and stimulated invasive growth through the MACC/MET/ERK or AKT pathways.⁶³⁰ In addition, the exosome circPDK1 significantly promotes pancreatic cancer cell proliferation, migration and glycolysis both in vitro and in vivo and is associated with poor patient survival. Mechanistically, circPDK1 can be activated at the transcriptional level by HIF-1 alpha and sponge miR-628-3p, thereby activating the bromodomain PHD finger TF (BPTF)/c-MYC axis. In addition, circPDK1 can act as a scaffold to enhance the interaction of ubiquitin conjugating enzyme E2O (UBE2O) with bridging integrator 1 (BIN1) and induce UBE2O-mediated degradation of BIN1.⁷³² In addition, hsa_circ_0000069 was significantly upregulated in exosomes derived from pancreatic cancer cells, which could act as a sponge for miR-144 and thus promote tumor progression. miR-144 targets the SCL/TAL1 interrupting locus (STIL), and knockdown of hsa_circ_0000069 significantly reduced the expression of STIL, CDK1, and cyclin B1 expression. Thus, downregulation of hsa_circ_0000069 induces pancreatic cancer cell cycle arrest in the G2-M phase.⁷³³

Second, exosome-derived circRNAs promote drug resistance in pancreatic cancer cells. For example, it has been shown that exosomes derived from pancreatic cancer cells in a hypoxic environment enhance the resistance of normoxic pancreatic cancer cells to gemcitabine. The mechanism is that the hypoxia-induced exosome circZNF91 can be transfected into normoxic pancreatic cancer cells and competitively binds to miR-23b-3p, which leads to the upregulation of sirtuin 1 (SIRT1) and thereby enhances the deacetylation-dependent stability of the HIF-1 α protein, resulting in the resistance of pancreatic cancer cells to GEM. Thus, the exosome circZNF91 may serve as a potential therapeutic target.⁷³⁴

Conversely, some exosome-derived circRNAs may also inhibit pancreatic cancer progression and impede immune escape of tumor cells, thereby exerting anticancer effects. For example, the bone marrow MSC (BM-MSC)-derived exosome hsa_circ_0006790 promotes the nuclear translocation of chromobox homolog 7 (CBX7), which recruits DNA methyltransferase to the promoter region of S100A11, thereby increasing DNA methylation and inhibiting S100A11 transcription. Inhibition of CBX7 or overexpression of S100A11 eliminates the inhibitory effects of hsa_circ_0006790 on PDAC growth, metastasis

and immune escape.⁷³⁵ In addition, BM-MSC-derived exosomes significantly reduced pancreatic cancer cell invasion, migration, and proliferation, as well as tumor stemness. Further studies showed that circ_0030167 mainly regulates miR-338-5p, increased Wnt inhibitory factor 1 expression and inhibited the Wnt8/ β -catenin signaling pathway, thereby suppressing PC cell stemness and tumor progression.⁷³⁶ Overexpression of serum-derived exosome hsa_circ_0012634 targets MiR-147b, thereby inhibiting homeodomain-interacting protein kinase 2, suppressing PDAC cell growth and glycolysis in vitro and inhibiting tumorigenesis in vivo.⁷³⁷

Taken together, the discovery of these exosome-derived circRNAs provides new perspectives in pancreatic cancer research and reveals important mechanisms associated with cancer development and treatment. As research in this area continues, there is a clearer understanding of how circRNAs can be used for their potential role in the treatment and diagnosis of pancreatic cancer. These findings are promising for further research and clinical applications.

4.3.5 | ExocircRNAs and prostate cancer

Prostate cancer is a malignant tumor that develops in the prostate tissue, usually from prostate epithelial cells, and is a common malignancy of the male genitourinary system.⁷³⁸ Some studies have shown that the incidence is higher worldwide in regions such as North America, Europe, and Oceania.⁷³⁹ With demographic and lifestyle changes, the incidence of prostate cancer is also gradually increasing in some developing countries.⁷⁴⁰ Early-stage prostate cancer usually has no obvious symptoms, so regular physical examinations and screening are crucial for early detection and treatment. Treatment options include surgery, radiotherapy, chemotherapy and endocrine therapy.⁷⁴¹ Fortunately, many prostate cancers can be controlled with early detection and effective treatment. Chemoresistant prostate cancer (CRPC) is a type of prostate cancer that develops after androgen deprivation therapy, which stops the growth of male sex hormones on prostate cancer cells. However, sometimes prostate cancer cells gradually become resistant to this treatment, leading to the development of depot-resistant prostate cancer.⁷⁴² Several studies have found that circRNAs in exosomes are closely associated with prostate cancer development. These circRNAs may have important effects on cancer cell proliferation, migration, invasion and drug resistance. They are highlighted in the following section.

First, in prostate cancer cells, circRNAs can act as sponges for miRNAs and thus act as inhibitors of downstream signaling pathways. For example, in

myeloid-derived suppressor of cellular exocytosis (MDSC-Exo)-treated PC3 cells, MDSC-Exo accelerated PCa cell proliferation, migration, and invasion, whereas circMID1 defects inhibited MDSC-Exo-regulated ex vivo CRPC progression. Mechanistically, MDSC-derived exosome S100A9 adsorbed miR-506-3p by upregulating circMID1 expression, leading to increased midline 1 (MID1) expression and accelerated tumor progression. The results suggest that the S100A9/circMID1/miR-506-3p/MID1 axis is present in the MDSC-exo-regulated progression of castration-resistant prostate cancer (CRPC).⁷⁴³ In addition, circ_0044516 was significantly upregulated in both exosomes and cell lines from prostate cancer patients. Further studies showed that circ_0044516 promoted proliferation and metastasis of prostate cancer cells. The mechanism is that circ_0044516 can downregulate the expression of miR-29a-3p in prostate cancer, thus playing an important role in the survival and metastasis of prostate cancer cells.⁷⁴⁴

Second, exosome-derived circRNAs also promote drug resistance in prostate cancer cells. Circ-XIAP was found to be overexpressed in the exosomes of docetaxel (DTX)-resistant prostate cancer cells and could be delivered via exosomes. Knockdown of circ-XIAP increased DTX sensitivity by inhibiting proliferation, migration and invasion of DTX-resistant cells and inducing cell cycle arrest and apoptosis. The mechanism is that circ-XIAP can directly target miR-1182 and subsequently promote multidrug resistance in prostate cancer by regulating the miR-1182/TPD52 axis, which is a promising therapeutic target for prostate cancer chemotherapy.⁷⁴⁵

In addition, exosome-derived circRNAs may act as protein decoys for cancer-promoting effects. One study showed that exosome-derived circTFDP2 expression was upregulated in prostate cancer tissues and promoted prostate cancer cell proliferation, and metastasis in vitro and in vivo. Mechanistically, circTFDP2 interacts with poly ADP ribose polymerase 1 (PARP1) protein in its DNA-binding domain to block its active caspase-3-dependent cleavage, ultimately alleviating DNA damage in PCa cells. In addition, the RBP eIF4A3 can interact with the flanking region of circTFDP2 to promote circTFDP2 production.⁷⁴⁶

In conclusion, exosome-derived circRNAs play an important role in prostate cancer development and further studies will help to better understand their role in prostate cancer pathogenesis and provide more precise targets and pathways for future treatment.

4.3.6 | ExocircRNAs and breast cancer

ExocircRNAs have been identified as key regulators in cancer progression and carcinogenesis.^{747,748} These circRNAs can distinguish between different breast cancer

subtypes, providing quick guidance on the appropriate therapy protocol for patients, thereby contributing to improved outcomes. ExocircRNAs that have prognostic value may also have therapeutic applications; silencing their expression or targeting them therapeutically could enhance tumor prognosis.⁷⁴⁹ The stability of circRNAs is due to the absence of polyadenylated tails and 5'/3' polarities.⁷⁵⁰ By using alternative splice sites and various splicing mechanisms, circRNAs can directly influence the transcription of linear isoforms. Additionally, circRNAs can regulate transcription by inducing DNA hypomethylation in the promoter region of the parental gene or by modulating intronic enhancers. For instance, FECR1 circRNA interacts with the FLI1 promoter through significant demethylation, thereby regulating the FLI1 gene, which promotes breast cancer growth and metastasis.⁷⁵¹ The role of the circRNA-related ceRNA network in breast cancer development is crucial and requires comprehensive examination.⁷⁵² A microarray study revealed that circTADA2A-E6 acts as a tumor suppressor by targeting SOCS3 as a downstream gene, while another circRNA, circTADA2A-E5/E6, is downregulated in breast cancer.⁷⁵³ Another study reported that circ_000911 also functions as a tumor suppressor.⁷⁵⁴ Breast cancer is linked with the upregulation of circEPSTI1, a prognostic marker and mediator in TNBC.⁷⁵⁵ In TNBC cases with lymph node metastases and advanced clinical stages, circANKS1B is elevated, which inhibits cancer metastasis.⁵⁹¹

Exosomes have the potential to serve as biomarkers for determining cancer cell proliferation.⁷⁵⁶ The expression profile of exosomes and cells from the MDA-MB-231 cell line revealed changes in gene expression. Research by Lin et al.⁷⁵⁷ identified nine circRNAs in plasma EVs that were upregulated, including hsa_circ_0005552, hsa_circ_0007177, hsa_circ_0002190, hsa_circ_0001439, hsa_circ_0000642, hsa_circ_0006404, hsa_circ_0000267, hsa_circ_0001073, and hsa_circ_0001417. Five circRNAs—hsa_circ_0009634, hsa_circ_0020707, hsa_circ_0064923, hsa_circ_0104852, and hsa_circ_0087064—were found to be upregulated in exosomes derived from highly aggressive cells and metastatic tumors in breast cancer patients.⁷⁵⁸ Despite a limited number of investigations on exocircRNA in breast cancer, emerging knowledge in this field may soon provide alternative therapeutic options. Studies on chemoresistant breast cancer have shown that circRNAs might play a role in metastasis or transformation. For instance, exosome-transmitted circHIPK3 induces trastuzumab resistance in initially drug-sensitive breast cancer cells.⁷⁵⁹ Though there are few studies on circRNAs and chemoradiation resistance, circRNAs could be novel biomarkers for evaluating chemotherapy efficacy and predicting recurrence in drug-resistant cancers. Studies indicate that in vitro transduction of circ-UBE2D2 via

exosomes can enhance resistance to tamoxifen in breast cancer, with recent findings showing circ-UBE2D2 expression being 20-fold higher in MCF-7/TAM-R-Exo compared with MCF-7/Par-Exo.⁷⁶⁰

4.3.7 | ExocircRNAs and GC

A set of exocircRNAs exhibit abnormal expression patterns in GC cells and tissues, thereby playing pivotal roles in the initiation and advancement of GC. CircRNAs possess remarkable stability and extended half-life in bodily fluids because of their resistance to exonucleases and ribonucleases. The expression levels of exocircRNAs frequently demonstrate elevated sensitivity and specificity throughout different GC stages.^{761,762}

Shi and colleagues⁷⁶³ found that exosomal circ0088300, originating from CAF cells, sponges miR-1305, boosting GC cell growth, movement, and invasion. Xie's⁶¹⁴ research uncovered that exosomal circSHKBP1 regulates the miR-582-3p/HUR/VEGF pathway, thereby advancing GC progression. This suggests circSHKBP1 as a promising diagnostic biomarker for GC.⁶¹⁴ Highly expressed in GC, exosomal circ0044366 notably hinders the multiplication, migration, and tube formation of HUVECs by adjusting VEGF, thus aiding in GC progression.⁷⁶⁴ Circ-NHSL1, abundant in GC tissues, cells, and their exosomes, has been shown to reduce migration and invasion in GC cells. Its knockdown inhibits tumor growth, highlighting its potential as a diagnostic indicator for GC progression.⁷⁶⁵ CircNEK9 levels are elevated in GC tissues and cells. As reported by Yu et al.,⁷⁶⁶ the transfer of circNEK9 via exosomes hastens GC cell proliferation, migration, and invasion by targeting miR-409-3p. Circ-NRIP1, also prevalent in GC, fuels disease advancement. Studies have shown that exosomal exchange facilitates the transmission of circNRIP1 between GC cells, augmenting progression and metastasis via the miR-149-5p/AKT1/mTOR pathway.⁵³⁶ Exosomes derived from GC can trigger the expression of circ_0004303, aiding the migration and homing of MSCs in neighboring tissues and modulating their biological functions, thereby promoting GC progression.⁷⁶⁷ Lu et al.⁶³¹ demonstrated that circRanGAP1 is upregulated in GC tissues and serum-derived exosomes, facilitating GC invasion and metastasis via the miR-877-3p/VEGFA axis. CircITCH, which is downregulated in GC cell lines, tissues, and serum-derived exosomes, suppresses GC metastasis by sponging miR-199a-5p and increasing Klotho expression, serving as a potential biomarker for GC occurrence and development.⁷⁶⁸ Last, Jiang et al.⁷⁶⁹ found that CDR1as plays a significant suppressive role in GC metastasis through the miR-876-5p/GNG7 axis.

The level of exosomal circSHKBP1 significantly decreased after gastrectomy, and increased expression of exosomal circSHKBP1 was associated with advanced TNM stages and poor survival.⁶¹⁴ There was a statistically significant decrease in plasma exosomal circ0065149 levels in patients with early GC.⁶⁴⁰ This suggests that exosomal circSHKBP1 is a promising biomarker for GC prognosis.⁶⁴⁰ Circ0065149 levels are closely related to the prognosis and survival of patients with GC. Exosomal circ0065149 can be used as an early predictor of the prognosis of GC.

GC serum and exosomes from cisplatin-resistant cells were upregulated with CircPVT1. CircPVT1 regulates autophagy, invasion and apoptosis through miR-30a-5p/YAP1 signaling.⁷⁷⁰ Circ0000260 expression was increased in cancer tissues and serum-derived exosomes of GC patients, and knockdown of circ0000260 reduced resistance to cisplatin.⁷⁷¹ GC cells resistant to oxaliplatin secreted exosomes expressing circ0032821.⁷⁷² Exosomal circ0032821 targeted miR-515-5p/SOX9 pathways to facilitate cell resistance to oxaliplatin.⁷⁷²

ExocircRNAs were associated with advanced TNM stage, drug resistance, poor prognosis, and poor survival of GC, which can serve as stable biomarkers for GC resistance and survival. It is expected that exosome-derived circRNAs will be effective markers for improving drug resistance and prognosis in clinical application once further research and improvements are made.

4.3.8 | ExocircRNAs and glioma

The most common CNS tumor, gliomas are characterized by rapid progression, aggressive growth, substantial heterogeneity, resistance to treatment, and poor prognosis.^{773–775} In the TME, exocircRNAs may play a crucial role in tumor progression.

Exosomal circATP8B4 can sequester miR-766 and contribute to radioresistance in glioma patients undergoing radiotherapy.⁷⁷⁶ CircMMP1 can enhance tumor cell proliferation and inhibit apoptosis, with elevated levels of exosomal circMMP1 observed in gliomas, where it drives oncogenesis through the circMMP1/miR-433/HMGB3 axis.⁷⁷⁷ This suggests that targeting this pathway may offer a viable treatment option for patients. In glioma cells and tissues, circHIPK3 promotes miR-124 sequestration-mediated enhancement of CCND2 expression, leading to an increased proliferation and invasion. Through the miR-421/ZIC5 pathway, exosomal circHIPK3 can promote tumor cell proliferation and resistance to temozolomide (TMZ) treatment.^{778,779} Additionally, TMZ-resistant glioma patients have higher levels of exosomal circNFIX, which can promote oncogenic progression. CircNFIX upregulation reduces glioma cell sensitivity to RPN2 by

inhibiting miR-378e.⁷⁸⁰ TMZ-resistant U251 cells can be sensitized to this drug by knocking down acetyl heparinase, which influences glioma cell TMZ resistance.⁷⁸¹ In TMZ-resistant glioma tissues and cells, circ_0072083 can regulate ALKBH5 via miR-1252-5p, thereby contributing to resistance to TMZ. TMZ-resistant cells may benefit from the Warburg effect by releasing exosomal circ_0072083, which can enhance their TMZ-resistance.⁷⁸²

A high level of serum exosomal circMMP1 (circ_0024108) has been associated with a poor prognosis for glioma patients.⁷⁷⁷ Exosomal circNFIX is associated with TMZ resistance, suggesting that analyses of this circRNA can improve patient care and therapeutic monitoring.^{780,783} In glioblastoma cells, positive cell migration regulator splicing factor 1 (SRSF1) exhibits multiple binding sites for circSMARCA5. Additionally, SRSF3 is expressed at higher levels in glioma, and it may act as a positive regulator of SRSF1-dependent glioma cell migration. By inhibiting the SRSF1/SRSF3/PTB axis, exosomal SMARCA5 can inhibit the migration of GBM cells, suggesting that it may function as a potent tumor suppressor in this type of cancer.⁷⁸⁴ The upregulation of circGLIS3 in high-grade gliomas can also be facilitated by exosomes, which facilitate tumor invasion, angiogenesis, and phosphorylation of Ezrin (T567). Accordingly, high levels of p-Ezrin (T567) are associated with high-grade gliomas and poor outcomes.⁷⁸⁵

5 | CONCLUSION AND PERSPECTIVES

This review examines the role of exocircRNAs in tumor cell proliferation, metastasis, drug resistance, and progression. Research predominantly focuses on tumor-derived exocircRNAs, yet it is imperative to consider the complex and multifaceted TME, which involves various cell types. In future studies, exocircRNAs from CAF, tumor-associated macrophages (TAM), and other immune cells should be investigated.

Research has demonstrated the importance of exocircRNAs in tumorigenesis, but many aspects remain unclear. Primarily synthesized and retained in the nucleus, the mechanisms governing the localization and sorting of circRNAs into exosomes are not comprehensively understood. Recent findings suggest that m6A modification may facilitate the cytoplasmic export of circRNAs,⁷⁸⁶ potentially influencing their incorporation into exosomes. Furthermore, the role of RBPs like argonaute and mannose-binding lectin in binding circRNAs,⁷⁸⁷ and the dependence of miRNA sorting on the ESCRT complex, particularly Ago2,⁷⁸⁸ point toward a regulatory function of exosome-associated RBPs in circRNA sorting. The mediation of exosome sorting by hnRNP A2B1 for specific circRNAs such

as circ-NEIL3 and circ-CCAR1 has been noted.^{702,789} Further research is required to delineate these regulatory mechanisms in detail.

Numerous studies suggest that exocircRNAs may be valuable biomarkers for cancer diagnosis and prognosis due to their highly conserved structures and tissue-specific expression patterns. However, this potential necessitates additional experimental validation, larger cohort studies, and substantial theoretical backing to establish their clinical utility. Moreover, the field of engineered exosomes for targeted cancer therapy, although still nascent, shows promise. Future research should aim at identifying specific exocircRNAs and developing effective and safe engineered exosomes for clinical use.

In summary, our review provides an extensive exploration of the complex roles of exocircRNAs in cancer progression. It underscores the need for further investigation into exocircRNAs from various cellular sources within the TME and elucidates the regulatory mechanisms behind their exosomal sorting. Recognizing their potential in cancer diagnostics and prognostics, we advocate for more rigorous research to validate their clinical application as biomarkers.

AUTHOR CONTRIBUTIONS

Yuanyong Wang, Yuchen Yang, and Rui Li were responsible for drafting the initial manuscript. Jin Zhang, Jie Li, Hui Zhu, Zhuofeng Liu, and Tian Li made substantial contributions to revising the initial draft, ensuring its academic rigor and clarity. Sijia Sun skillfully crafted the illustrations for the paper, enhancing its visual representation. Jin Zheng critically reviewed the manuscript, providing further refinements and insights. Litian Ma, as the corresponding author, carefully reviewed the final manuscript, ensuring that all aspects adhered to high academic standards, and subsequently gave his approval for its publication. All authors have read and approved the final manuscript.

ACKNOWLEDGMENTS

This research was supported by the Joint Research Project of the China Science and Technology Development Center of Traditional Chinese Medicine (Talent Exchange Center of the National Administration of Traditional Chinese Medicine) (grant number CXZH202307 awarded to Jin Zheng); the Single Disease Library Project of the Air Force Medical University (grant number 2023LC2339 awarded to Jin Zheng); the Clinical Research General Program of the Air Force Medical University (grant number 2023LC2330 awarded to Jie Li); the Second Batch of Research Projects of the Science and Technology Department of Shaanxi Province (grant number 2024SF-YBXM-176 awarded to Jie Li); the Natural Science Basic Research Program of

Shaanxi Province (grant number 2021JMJ-245 awarded to Rui Ma); and the Social Talent Fund of the Second Affiliated Hospital of the Air Force Medical University (grant number 2023YFJH016 awarded to Jin Zhang).

Furthermore, we extend our profound gratitude to Ma Rui, the laboratory technician from the Radiotherapy Department of the First Affiliated Hospital of the Air Force Medical University. We sincerely appreciate the professional guidance and invaluable advice she provided during the preparation of our review. Her assistance has significantly enriched our research and imparted immense value to it.

Additionally, I would like to express my gratitude to BioRender for providing the software that assisted me in creating the illustrations for this paper. The utilization of BioRender greatly facilitated the visualization of my research data and enhanced the overall quality of the paper. I deeply appreciate the convenience and efficiency it brought to my work.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

Not applicable.

ORCID

Litian Ma  <https://orcid.org/0000-0002-7177-4439>

REFERENCES

1. Nigro JM, Cho KR, Fearon ER, et al. Scrambled exons. *Cell*. 1991;64(3):607-613.
2. Lasda E, Parker R. Circular RNAs: diversity of form and function. *RNA*. 2014;20(12):1829-1842.
3. Zhang Y, Zhang XO, Chen T, et al. Circular intronic long noncoding RNAs. *Mol Cell*. 2013;51(6):792-806.
4. Toptan T, Abere B, Nalesnik MA, et al. Circular DNA tumor viruses make circular RNAs. *Proc Natl Acad Sci USA*. 2018;115(37):E8737-E8745.
5. Li Z, Huang C, Bao C, et al. Exon-intron circular RNAs regulate transcription in the nucleus. *Nat Struct Mol Biol*. 2015;22(3):256-264.
6. Chen J, Shi P, Zhang J, et al. CircRNA_0044556 diminishes the sensitivity of triplenegative breast cancer cells to adriamycin by sponging miR145 and regulating NRAS. *Mol Med Rep*. 2022;25(2):51.
7. Sun N, Liang Y, Hu B, et al. circSKIL promotes the ossification of cervical posterior longitudinal ligament by activating the JNK/STAT3 pathway. *Exp Ther Med*. 2021;22(1):761.
8. Yuan G, Ding W, Sun B, Zhu L, Gao Y, Chen L. Upregulated circRNA_102231 promotes gastric cancer progression and its clinical significance. *Bioengineered*. 2021;12(1):4936-4945.
9. Cui X, Wang J, Guo Z, et al. Emerging function and potential diagnostic value of circular RNAs in cancer. *Mol Cancer*. 2018;17(1):123.
10. Schmidt CA, Giusto JD, Bao A, Hopper AK, Matera AG. Molecular determinants of metazoan tricRNA biogenesis. *Nucleic Acids Res*. 2019;47(12):6452-6465.
11. Du N, Li M, Yang D. Hsa_circRNA_102541 regulates the development of atherosclerosis by targeting miR-296-5p/PLK1 pathway. *Ir J Med Sci*. 2022;191(3):1153-1159.
12. Sun Y, Zhou Y, Shi X, et al. CircTYW1 serves as a sponge for microRNA-380 in accelerating neurological recovery following spinal cord injury via regulating FGF9. *Cell Cycle*. 2021;20(18):1828-1844.
13. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33.
14. Wei W, Zeng H, Zheng R, et al. Cancer registration in China and its role in cancer prevention and control. *Lancet Oncol*. 2020;21(7):e342-e349.
15. Kilic T, Cho YK, Jeong N, et al. Multielectrode spectroscopy enables rapid and sensitive molecular profiling of extracellular vesicles. *ACS Cent Sci*. 2022;8(1):110-117.
16. Fontana F, Carollo E, Melling GE, Carter DRF. Extracellular vesicles: emerging modulators of cancer drug resistance. *Cancers (Basel)*. 2021;13(4):749.
17. Kallergi G, Kontopodis E, Ntzifa A, et al. Effect of Osimertinib on CTCs and ctDNA in EGFR mutant non-small cell lung cancer patients: the prognostic relevance of liquid biopsy. *Cancers (Basel)*. 2022;14(6):1571.
18. Bonanno L, Dal Maso A, Pavan A, et al. Liquid biopsy and non-small cell lung cancer: are we looking at the tip of the iceberg? *Br J Cancer*. 2022;127(3):383-393.
19. Liu C, Xiang X, Han S, et al. Blood-based liquid biopsy: Insights into early detection and clinical management of lung cancer. *Cancer Lett*. 2022;524:91-102.
20. Clancy JW, Sedgwick A, Rosse C, et al. Regulated delivery of molecular cargo to invasive tumour-derived microvesicles. *Nat Commun*. 2015;6:6919.
21. Rastegari-Pouyani M, Mohammadi-Motlagh HR, Baghaei K, et al. 2-methylpyridine-1-ium-1-sulfonate modifies tumor-derived exosome mediated macrophage polarization: Relevance to the tumor microenvironment. *Int Immunopharmacol*. 2022;106:108581.
22. Kawashima M, Higuchi H, Kotani A. Significance of trogocytosis and exosome-mediated transport in establishing and maintaining the tumor microenvironment in lymphoid malignancies. *J Clin Exp Hematop*. 2021;61(4):192-201.
23. Wang Y, Lu T, Wang Q, Liu J, Jiao W. Circular RNAs: Crucial regulators in the human body (Review). *Oncol Rep*. 2018;40(6):3119-3135.
24. Choi SS, Kim SE, Oh SY, Ahn YH. Clinical implications of circulating circular RNAs in lung cancer. *Biomedicines*. 2022;10(4):871.
25. Wang Y, Xu R, Zhang D, et al. Circ-ZKSCAN1 regulates FAM83A expression and inactivates MAPK signaling by targeting miR-330-5p to promote non-small cell lung cancer progression. *Transl Lung Cancer Res*. 2019;8(6):862-875.
26. Li Y, Zheng Q, Bao C, et al. Circular RNA is enriched and stable in exosomes: a promising biomarker for cancer diagnosis. *Cell Res*. 2015;25(8):981-984.

27. Wang Y, Liu J, Ma J, et al. Exosomal circRNAs: biogenesis, effect and application in human diseases. *Mol Cancer*. 2019;18(1):116.
28. Dou Y, Cha DJ, Franklin JL, et al. Circular RNAs are down-regulated in KRAS mutant colon cancer cells and can be transferred to exosomes. *Sci Rep*. 2016;6:37982.
29. Wang Y, Wo Y, Lu T, et al. Circ-AASDH functions as the progression of early stage lung adenocarcinoma by targeting miR-140-3p to activate E2F7 expression. *Transl Lung Cancer Res*. 2021;10(1):57-70.
30. Liu B, Li J, Cairns MJ. Identifying miRNAs, targets and functions. *Brief Bioinform*. 2014;15(1):1-19.
31. Krek A, Grun D, Poy MN, et al. Combinatorial microRNA target predictions. *Nat Genet*. 2005;37(5):495-500.
32. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell*. 2005;120(1):15-20.
33. Hansen TB, Jensen TI, Clausen BH, et al. Natural RNA circles function as efficient microRNA sponges. *Nature*. 2013;495(7441):384-388.
34. Hansen TB, Wiklund ED, Bramsen JB, et al. miRNA-dependent gene silencing involving Ago2-mediated cleavage of a circular antisense RNA. *EMBO J*. 2011;30(21):4414-4422.
35. Li Y, Shi H, Yuan J, Qiao L, Dong L, Wang Y. Downregulation of circular RNA circPVT1 restricts cell growth of hepatocellular carcinoma through downregulation of Sirtuin 7 via microRNA-3666. *Clin Exp Pharmacol Physiol*. 2020;47(7):1291-1300.
36. Zeng RF, Zhou JJ, Hu CG, Zhang JZ. Transcriptome-wide identification and functional prediction of novel and flowering-related circular RNAs from trifoliate orange (*Poncirus trifoliata* L. Raf.). *Planta*. 2018;247(5):1191-1202.
37. Wang Y, Yang M, Wei S, Qin F, Zhao H, Suo B. Identification of circular RNAs and their targets in leaves of *Triticum aestivum* L. under dehydration stress. *Front Plant Sci*. 2016;7:2024.
38. Ye CY, Chen L, Liu C, Zhu QH, Fan L. Widespread noncoding circular RNAs in plants. *New Phytol*. 2015;208(1):88-95.
39. Zheng X, Chen L, Zhou Y, et al. A novel protein encoded by a circular RNA circPPP1R12A promotes tumor pathogenesis and metastasis of colon cancer via Hippo-YAP signaling. *Mol Cancer*. 2019;18(1):47.
40. Legnini I, Di Timoteo G, Rossi F, et al. Circ-ZNF609 is a circular RNA that can be translated and functions in myogenesis. *Mol Cell*. 2017;66(1):22-37. e9.
41. Yang Y, Gao X, Zhang M, et al. Novel role of FBXW7 circular RNA in repressing glioma tumorigenesis. *J Natl Cancer Inst*. 2018;110(3):304-315.
42. Fontemaggi G, Turco C, Esposito G, Di Agostino S. New molecular mechanisms and clinical impact of circRNAs in human cancer. *Cancers (Basel)*. 2021;13(13):3154.
43. Chen CY, Sarnow P. Initiation of protein synthesis by the eukaryotic translational apparatus on circular RNAs. *Science*. 1995;268(5209):415-417.
44. Wang Y, Wang Z. Efficient backsplicing produces translatable circular mRNAs. *RNA*. 2015;21(2):172-179.
45. Zhang M, Zhao K, Xu X, et al. A peptide encoded by circular form of LINC-PINT suppresses oncogenic transcriptional elongation in glioblastoma. *Nat Commun*. 2018;9(1):4475.
46. Martinez-Salas E, Lozano G, Fernandez-Chamorro J, Francisco-Velilla R, Galan A, Diaz R. RNA-binding proteins impacting on internal initiation of translation. *Int J Mol Sci*. 2013;14(11):21705-21726.
47. Zhou J, Wan J, Gao X, Zhang X, Jaffrey SR, Qian SB. Dynamic m(6)A mRNA methylation directs translational control of heat shock response. *Nature*. 2015;526(7574):591-594.
48. Yang Y, Fan X, Mao M, et al. Extensive translation of circular RNAs driven by N(6)-methyladenosine. *Cell Res*. 2017;27(5):626-641.
49. Zhang M, Huang N, Yang X, et al. A novel protein encoded by the circular form of the SHPRH gene suppresses glioma tumorigenesis. *Oncogene*. 2018;37(13):1805-1814.
50. Xia X, Li X, Li F, et al. A novel tumor suppressor protein encoded by circular AKT3 RNA inhibits glioblastoma tumorigenicity by competing with active phosphoinositide-dependent kinase-1. *Mol Cancer*. 2019;18(1):131.
51. Okholm TLH, Sathe S, Park SS, et al. Transcriptome-wide profiles of circular RNA and RNA-binding protein interactions reveal effects on circular RNA biogenesis and cancer pathway expression. *Genome Med*. 2020;12(1):112.
52. Ashwal-Fluss R, Meyer M, Pamudurti NR, et al. circRNA biogenesis competes with pre-mRNA splicing. *Mol Cell*. 2014;56(1):55-66.
53. Zhang L, Wang Y, Zhang Y, Zhao Y, Li P. Pathogenic mechanisms and the potential clinical value of circFoxo3 in cancers. *Mol Ther Nucleic Acids*. 2021;23:908-917.
54. Du WW, Yang W, Liu E, Yang Z, Dhaliwal P, Yang BB. Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2. *Nucleic Acids Res*. 2016;44(6):2846-2858.
55. Holdt LM, Stahringer A, Sass K, et al. Circular non-coding RNA ANRIL modulates ribosomal RNA maturation and atherosclerosis in humans. *Nat Commun*. 2016;7:12429.
56. Zeng Y, Du WW, Wu Y, et al. A circular RNA binds to and activates AKT phosphorylation and nuclear localization reducing apoptosis and enhancing cardiac repair. *Theranostics*. 2017;7(16):3842-3855.
57. Bose R, Ain R. Regulation of transcription by circular RNAs. *Adv Exp Med Biol*. 2018;1087:81-94.
58. Chia W, Liu J, Huang YG, Zhang C. A circular RNA derived from DAB1 promotes cell proliferation and osteogenic differentiation of BMSCs via RBPJ/DAB1 axis. *Cell Death Dis*. 2020;11(5):372.
59. Li S, Dong R, Kang Z, Li H, Wu X, Li T. Exosomes: Another intercellular lipometabolic communication mediators in digestive system neoplasms? *Cytokine Growth Factor Rev*. 2023;73:93-100.
60. Guo W, Qiao T, Dong B, Li T, Liu Q, Xu X. The effect of hypoxia-induced exosomes on anti-tumor immunity and its implication for immunotherapy. *Front Immunol*. 2022;13:915985.
61. Zhang X, Xu Y, Ma L, et al. Essential roles of exosome and circRNA_101093 on ferroptosis desensitization in lung adenocarcinoma. *Cancer Commun (Lond)*. 2022;42(4):287-313.
62. Zheng R, Zhang K, Tan S, et al. Exosomal circLPAR1 functions in colorectal cancer diagnosis and tumorigenesis through suppressing BRD4 via METTL3-eIF3h interaction. *Mol Cancer*. 2022;21(1):49.
63. Huang XY, Huang ZL, Huang J, et al. Exosomal circRNA-100338 promotes hepatocellular carcinoma metastasis via

- enhancing invasiveness and angiogenesis. *J Exp Clin Cancer Res*. 2020;39(1):20.
64. Lasda E, Parker R. Circular RNAs co-precipitate with extracellular vesicles: a possible mechanism for circRNA clearance. *PLoS One*. 2016;11(2):e0148407.
 65. Alhasan AA, Izuogu OG, Al-Balool HH, et al. Circular RNA enrichment in platelets is a signature of transcriptome degradation. *Blood*. 2016;127(9):e1-e11.
 66. Vo JN, Cieslik M, Zhang Y, et al. The landscape of circular RNA in cancer. *Cell*. 2019;176(4):869-881. e13.
 67. Glazar P, Papavasileiou P, Rajewsky N. circBase: a database for circular RNAs. *RNA*. 2014;20(11):1666-1670.
 68. Ma XK, Xue W, Chen LL, Yang L. CIRCexplorer pipelines for circRNA annotation and quantification from non-polyadenylated RNA-seq datasets. *Methods*. 2021;196:3-10.
 69. Mi Z, Zhongqiang C, Caiyun J, Yanan L, Jianhua W, Liang L. Circular RNA detection methods: a minireview. *Talanta*. 2022;238(Pt 2):123066.
 70. Memczak S, Jens M, Elefsinioti A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature*. 2013;495(7441):333-338.
 71. Zhang XO, Wang HB, Zhang Y, Lu X, Chen LL, Yang L. Complementary sequence-mediated exon circularization. *Cell*. 2014;159(1):134-147.
 72. D'Ambra E, Morlando M. Study of circular RNA expression by nonradioactive northern blot procedure. *Methods Mol Biol*. 2021;2348:371-383.
 73. Jeck WR, Sorrentino JA, Wang K, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats. *RNA*. 2013;19(2):141-157.
 74. Cocquet J, Chong A, Zhang G, Veitia RA. Reverse transcriptase template switching and false alternative transcripts. *Genomics*. 2006;88(1):127-131.
 75. Goo NI, Kim DE. Rolling circle amplification as isothermal gene amplification in molecular diagnostics. *Biochip J*. 2016;10(4):262-271.
 76. Liu Y, Zhang X, Liu M, et al. Direct detection of circRNA in real samples using reverse transcription-rolling circle amplification. *Anal Chim Acta*. 2020;1101:169-175.
 77. Dahl M, Dugaard I, Andersen MS, et al. Enzyme-free digital counting of endogenous circular RNA molecules in B-cell malignancies. *Lab Invest*. 2018;98(12):1657-1669.
 78. Tang W, Fu K, Sun H, Rong D, Wang H, Cao H. CircRNA microarray profiling identifies a novel circulating biomarker for detection of gastric cancer. *Mol Cancer*. 2018;17(1):137.
 79. Li S, Teng S, Xu J, et al. Microarray is an efficient tool for circRNA profiling. *Brief Bioinform*. 2019;20(4):1420-1433.
 80. Chrzanowska NM, Kowalewski J, Lewandowska MA. Use of fluorescence in situ hybridization (FISH) in diagnosis and tailored therapies in solid tumors. *Molecules*. 2020;25(8):1864.
 81. Lim AS, Lim TH. Fluorescence in situ hybridization on tissue sections. *Methods Mol Biol*. 2017;1541:119-125.
 82. Wang Z, Gerstein M, Snyder M. RNA-Seq: a revolutionary tool for transcriptomics. *Nat Rev Genet*. 2009;10(1):57-63.
 83. Zoabi Y, Shomron N. Processing and analysis of RNA-seq data from public resources. *Methods Mol Biol*. 2021;2243:81-94.
 84. Zhao X, Zhong Y, Wang X, Shen J, An W. Advances in circular RNA and its applications. *Int J Med Sci*. 2022;19(6):975-985.
 85. Chen LL. The expanding regulatory mechanisms and cellular functions of circular RNAs. *Nat Rev Mol Cell Biol*. 2020;21(8):475-490.
 86. Jiao J, Gao T, Shi H, et al. A method to directly assay circRNA in real samples. *Chem Commun (Camb)*. 2018;54(95):13451-13454.
 87. Lu T, Cui L, Zhou Y, et al. Transcriptome-wide investigation of circular RNAs in rice. *RNA*. 2015;21(12):2076-2087.
 88. Kristensen LS, Andersen MS, Stagsted LVW, Ebbesen KK, Hansen TB, Kjems J. The biogenesis, biology and characterization of circular RNAs. *Nat Rev Genet*. 2019;20(11):675-691.
 89. Ma XK, Wang MR, Liu CX, et al. CIRCexplorer3: a CLEAR pipeline for direct comparison of circular and linear RNA expression. *Genomics Proteomics Bioinformatics*. 2019;17(5):511-521.
 90. Salzman J, Gawad C, Wang PL, Lacayo N, Brown PO. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. *PLoS One*. 2012;7(2):e30733.
 91. Wesselhoeft RA, Kowalski PS, Parker-Hale FC, Huang Y, Bisaria N, Anderson DG. RNA circularization diminishes immunogenicity and can extend translation duration in vivo. *Mol Cell*. 2019;74(3):508-520. e4.
 92. Meganck RM, Borchardt EK, Castellanos Rivera RM, et al. Tissue-dependent expression and translation of circular RNAs with recombinant AAV vectors in vivo. *Mol Ther Nucleic Acids*. 2018;13:89-98.
 93. Wesselhoeft RA, Kowalski PS, Anderson DG. Engineering circular RNA for potent and stable translation in eukaryotic cells. *Nat Commun*. 2018;9(1):2629.
 94. Qu L, Yi Z, Shen Y, et al. Circular RNA vaccines against SARS-CoV-2 and emerging variants. *Cell*. 2022;185(10):1728-1744. e16.
 95. Chen CK, Cheng R, Demeter J, et al. Structured elements drive extensive circular RNA translation. *Mol Cell*. 2021;81(20):4300-4318. e13.
 96. Liu CX, Guo SK, Nan F, Xu YF, Yang L, Chen LL. RNA circles with minimized immunogenicity as potent PKR inhibitors. *Mol Cell*. 2022;82(2):420-434. e6.
 97. Liao W, Xu J, Li B, Ruan Y, Li T, Liu J. Deciphering the roles of metformin in Alzheimer's disease: a snapshot. *Front Pharmacol*. 2021;12:728315.
 98. Du MR, Gao QY, Liu CL, Bai LY, Li T, Wei FL. Exploring the pharmacological potential of metformin for neurodegenerative diseases. *Front Aging Neurosci*. 2022;14:838173.
 99. Wang W, Liu C, He D, et al. CircRNA CDR1as affects functional repair after spinal cord injury and regulates fibrosis through the SMAD pathway. *Pharmacol Res*. 2024;204:107189.
 100. Liu CX, Li X, Nan F, et al. Structure and degradation of circular RNAs regulate PKR activation in innate immunity. *Cell*. 2019;177(4):865-880. e21.
 101. Yu J, Xu QG, Wang ZG, et al. Circular RNA cSMARCA5 inhibits growth and metastasis in hepatocellular carcinoma. *J Hepatol*. 2018;68(6):1214-1227.
 102. Zhao Q, Liu J, Deng H, et al. Targeting mitochondria-located circRNA SCAR alleviates NASH via reducing mROS output. *Cell*. 2020;183(1):76-93. e22.
 103. Dube U, Del-Aguila JL, Li Z, et al. An atlas of cortical circular RNA expression in Alzheimer disease brains demonstrates clinical and pathological associations. *Nat Neurosci*. 2019;22(11):1903-1912.

104. Wang H, Meng Q, Qian J, Li M, Gu C, Yang Y. Review: RNA-based diagnostic markers discovery and therapeutic targets development in cancer. *Pharmacol Ther.* 2022;234:108123.
105. Enuoka Y, Lauriola M, Feldman ME, Sas-Chen A, Ulitsky I, Yarden Y. Circular RNAs are long-lived and display only minimal early alterations in response to a growth factor. *Nucleic Acids Res.* 2016;44(3):1370-1383.
106. Van Der Steen N, Lyu Y, Hitzler AK, Becker AC, Seiler J, Diederichs S. The circular RNA landscape of non-small cell lung cancer cells. *Cancers (Basel).* 2020;12(5):1091.
107. Zhang L, Liao Y, Tang L. MicroRNA-34 family: a potential tumor suppressor and therapeutic candidate in cancer. *J Exp Clin Cancer Res.* 2019;38(1):53.
108. Bahn JH, Zhang Q, Li F, et al. The landscape of microRNA, Piwi-interacting RNA, and circular RNA in human saliva. *Clin Chem.* 2015;61(1):221-230.
109. Shao Y, Li J, Lu R, et al. Global circular RNA expression profile of human gastric cancer and its clinical significance. *Cancer Med.* 2017;6(6):1173-1180.
110. Xia Q, Ding T, Zhang G, et al. Circular RNA expression profiling identifies prostate cancer-specific circRNAs in prostate cancer. *Cell Physiol Biochem.* 2018;50(5):1903-1915.
111. Wu K, Liao X, Gong Y, et al. Circular RNA F-circSR derived from SLC34A2-ROS1 fusion gene promotes cell migration in non-small cell lung cancer. *Mol Cancer.* 2019;18(1):98.
112. Li M, Ding W, Tariq MA, et al. A circular transcript of ncx1 gene mediates ischemic myocardial injury by targeting miR-133a-3p. *Theranostics.* 2018;8(21):5855-5869.
113. Lim TB, Aliwarga E, Luu TDA, et al. Targeting the highly abundant circular RNA circSlc8a1 in cardiomyocytes attenuates pressure overload induced hypertrophy. *Cardiovasc Res.* 2019;115(14):1998-2007.
114. Yang M, Qi M, Xu L, et al. Differential host circRNA expression profiles in human lung epithelial cells infected with SARS-CoV-2. *Infect Genet Evol.* 2021;93:104923.
115. Wu Y, Zhao T, Deng R, Xia X, Li B, Wang X. A study of differential circRNA and lncRNA expressions in COVID-19-infected peripheral blood. *Sci Rep.* 2021;11(1):7991.
116. Reinhold D, Farztdinov V, Yan Y, et al. The brain reacting to COVID-19: analysis of the cerebrospinal fluid proteome, RNA and inflammation. *J Neuroinflammation.* 2023;20(1):30.
117. Jeck WR, Sharpless NE. Detecting and characterizing circular RNAs. *Nat Biotechnol.* 2014;32(5):453-461.
118. Salzman J, Chen RE, Olsen MN, Wang PL, Brown PO. Cell-type specific features of circular RNA expression. *PLoS Genet.* 2013;9(9):e1003777.
119. You X, Vlatkovic I, Babic A, et al. Neural circular RNAs are derived from synaptic genes and regulated by development and plasticity. *Nat Neurosci.* 2015;18(4):603-610.
120. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? *Cell.* 2011;146(3):353-358.
121. Thomas LF, Saetrom P. Circular RNAs are depleted of polymorphisms at microRNA binding sites. *Bioinformatics.* 2014;30(16):2243-2246.
122. Arora S, Singh P, Dohare R, Jha R, Ali Syed M. Unravelling host-pathogen interactions: ceRNA network in SARS-CoV-2 infection (COVID-19). *Gene.* 2020;762:145057.
123. Qin Z, Wang PY, Su DF, Liu X. miRNA-124 in immune system and immune disorders. *Front Immunol.* 2016;7:406.
124. Zhang X, Chu H, Wen L, et al. Competing endogenous RNA network profiling reveals novel host dependency factors required for MERS-CoV propagation. *Emerg Microbes Infect.* 2020;9(1):733-746.
125. Cadena C, Hur S. Antiviral immunity and circular RNA: no end in sight. *Mol Cell.* 2017;67(2):163-164.
126. Li X, Liu CX, Xue W, et al. Coordinated circRNA biogenesis and function with NF90/NF110 in viral infection. *Mol Cell.* 2017;67(2):214-227. e7.
127. Wang M, Yu F, Wu W, et al. Circular RNAs: a novel type of non-coding RNA and their potential implications in antiviral immunity. *Int J Biol Sci.* 2017;13(12):1497-1506.
128. Chen YG, Kim MV, Chen X, et al. Sensing self and foreign circular RNAs by intron identity. *Mol Cell.* 2017;67(2):228-238. e5.
129. Firoozi Z, Mohammadisoleimani E, Shahi A, et al. Hsa_circ_0000479/Hsa-miR-149-5p/RIG-I, IL-6 axis: a potential novel pathway to regulate immune response against COVID-19. *Can J Infect Dis Med Microbiol.* 2022;2022:2762582.
130. Appelberg S, Gupta S, Svensson Akusjarvi S, et al. Dysregulation in Akt/mTOR/HIF-1 signaling identified by proteo-transcriptomics of SARS-CoV-2 infected cells. *Emerg Microbes Infect.* 2020;9(1):1748-1760.
131. Fajgenbaum DC, June CH. Cytokine storm. *N Engl J Med.* 2020;383(23):2255-2273.
132. Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev.* 2020;53:25-32.
133. Alcamí A. Viral mimicry of cytokines, chemokines and their receptors. *Nat Rev Immunol.* 2003;3(1):36-50.
134. Yan J, Zhang X, Sun S, et al. miR-29b reverses T helper 1 cells/T helper 2 cells imbalance and alleviates airway eosinophils recruitment in OVA-induced murine asthma by targeting inducible co-stimulator. *Int Arch Allergy Immunol.* 2019;180(3):182-194.
135. Feng MJ, Shi F, Qiu C, Peng WK. MicroRNA-181a, -146a and -146b in spleen CD4+ T lymphocytes play proinflammatory roles in a murine model of asthma. *Int Immunopharmacol.* 2012;13(3):347-353.
136. Camoretti-Mercado B, Lockey RF. Airway smooth muscle pathophysiology in asthma. *J Allergy Clin Immunol.* 2021;147(6):1983-1995.
137. Hershenson MB, Brown M, Camoretti-Mercado B, Solway J. Airway smooth muscle in asthma. *Annu Rev Pathol.* 2008;3:523-555.
138. Huang JQ, Wang F, Wang LT, Li YM, Lu JL, Chen JY. Circular RNA ERBB2 contributes to proliferation and migration of airway smooth muscle cells via miR-98-5p/IGF1R signaling in asthma. *J Asthma Allergy.* 2021;14:1197-1207.
139. Kardas G, Daszynska-Kardas A, Marynowski M, Brzakalska O, Kuna P, Panek M. Role of platelet-derived growth factor (PDGF) in asthma as an immunoregulatory factor mediating airway remodeling and possible pharmacological target. *Front Pharmacol.* 2020;11:47.
140. Ito I, Fixman ED, Asai K, et al. Platelet-derived growth factor and transforming growth factor-beta modulate the expression

- of matrix metalloproteinases and migratory function of human airway smooth muscle cells. *Clin Exp Allergy*. 2009;39(9):1370-1380.
141. Spinelli AM, Gonzalez-Cobos JC, Zhang X, et al. Airway smooth muscle STIM1 and Orai1 are upregulated in asthmatic mice and mediate PDGF-activated SOCE, CRAC currents, proliferation, and migration. *Pflugers Arch*. 2012;464(5):481-492.
 142. Ohno I, Nitta Y, Yamauchi K, et al. Eosinophils as a potential source of platelet-derived growth factor B-chain (PDGF-B) in nasal polyposis and bronchial asthma. *Am J Respir Cell Mol Biol*. 1995;13(6):639-647.
 143. Lin H, Wan N. Circular RNA has Circ 001372-Reduced Inflammation in Ovalbumin-Induced Asthma Through Sirt1/NFAT5 Signaling Pathway by miRNA-128-3p. *Mol Biotechnol*. 2022;64(9):1034-1044.
 144. Jiang Y, Guo X, Qin J. Silencing of circHIPK3 hampers platelet-derived growth factor-induced proliferation and migration in airway smooth muscle cells through the miR-375/MMP-16 axis. *Cytotechnology*. 2021;73(4):629-642.
 145. Johnson MT, Xin P, Benson JC, et al. STIM1 is a core trigger of airway smooth muscle remodeling and hyperresponsiveness in asthma. *Proc Natl Acad Sci USA*. 2022;119(1):e2114557118.
 146. Zou JJ, Gao YD, Geng S, Yang J. Role of STIM1/Orai1-mediated store-operated Ca(2+)(+) entry in airway smooth muscle cell proliferation. *J Appl Physiol (1985)*. 2011;110(5):1256-1263.
 147. Ding L, Liu GL, Lu L, Ge L, Wang JY. circ_CSNK1E modulates airway smooth muscle cells proliferation and migration via miR-34a-5p/VAMP2 axis in asthma. *Cell Signal*. 2022;95:110340.
 148. Quan L, Ren G, Liu L, Huang W, Li M. Circular RNA circ_0002594 regulates PDGF-BB-induced proliferation and migration of human airway smooth muscle cells via sponging miR-139-5p/TRIM8 in asthma. *Autoimmunity*. 2022;55(5):339-350.
 149. Wang R, Tan Y, Bao X, et al. Circ_0000029 interacts with the miR-576-5p/KCNA1 axis to hamper the development of pediatric asthma in an asthma-like in vitro assessment. *Ann Clin Lab Sci*. 2023;53(2):200-211.
 150. Zhang H, Sun Z, Yu L, Sun J. MiR-139-5p inhibits proliferation and promoted apoptosis of human airway smooth muscle cells by downregulating the Brg1 gene. *Respir Physiol Neurobiol*. 2017;246:9-16.
 151. Jia Y, Li X, Nan A, et al. Circular RNA 406961 interacts with ILF2 to regulate PM(2.5)-induced inflammatory responses in human bronchial epithelial cells via activation of STAT3/JNK pathways. *Environ Int*. 2020;141:105755.
 152. Su Y, Geng L, Ma Y, Yu X, Kang Z, Kang Z. Identification of circular RNA circVPS33A as a modulator in house dust mite-induced injury in human bronchial epithelial cells. *Exp Lung Res*. 2021;47(8):368-381.
 153. Wang T, Wang P, Chen D, Xu Z, Yang L. circARRDC3 contributes to interleukin-13-induced inflammatory cytokine and mucus production in nasal epithelial cells via the miR-375/KLF4 axis. *Mol Med Rep*. 2021;23(2):141.
 154. Whitsett JA. Airway Epithelial Differentiation and Mucociliary Clearance. *Ann Am Thorac Soc*. 2018;15(Suppl 3):S143-S148.
 155. Kim HT, Yin W, Nakamichi Y, et al. WNT/RYK signaling restricts goblet cell differentiation during lung development and repair. *Proc Natl Acad Sci USA*. 2019;116(51):25697-25706.
 156. Fahy JV, Dickey BF. Airway mucus function and dysfunction. *N Engl J Med*. 2010;363(23):2233-2247.
 157. Rogers DF. Airway goblet cell hyperplasia in asthma: hypersecretory and anti-inflammatory? *Clin Exp Allergy*. 2002;32(8):1124-1127.
 158. Wang X, Xu C, Cai Y, et al. CircZNF652 promotes the goblet cell metaplasia by targeting the miR-452-5p/JAK2 signaling pathway in allergic airway epithelia. *J Allergy Clin Immunol*. 2022;150(1):192-203.
 159. Lommatzsch M. Immune modulation in asthma: current concepts and future strategies. *Respiration*. 2020;99(7):566-576.
 160. Ng WL, Marinov GK, Liao ES, Lam YL, Lim YY, Ea CK. Inducible RasGEF1B circular RNA is a positive regulator of ICAM-1 in the TLR4/LPS pathway. *RNA Biol*. 2016;13(9):861-871.
 161. Wang YH, Yu XH, Luo SS, Han H. Comprehensive circular RNA profiling reveals that circular RNA100783 is involved in chronic CD28-associated CD8(+)T cell ageing. *Immun Ageing*. 2015;12:17.
 162. Li LJ, Zhu ZW, Zhao W, et al. Circular RNA expression profile and potential function of hsa_circ_0045272 in systemic lupus erythematosus. *Immunology*. 2018;155(1):137-149.
 163. Gaffo E, Boldrin E, Dal Molin A, et al. Circular RNA differential expression in blood cell populations and exploration of circRNA deregulation in pediatric acute lymphoblastic leukemia. *Sci Rep*. 2019;9(1):14670.
 164. Zhang C, Wang X, Chen Y, Wu Z, Zhang C, Shi W. The down-regulation of hsa_circ_0012919, the sponge for miR-125a-3p, contributes to DNA methylation of CD11a and CD70 in CD4(+) T cells of systemic lupus erythematosus. *Clin Sci (Lond)*. 2018;132(21):2285-2298.
 165. Ghafouri-Fard S, Shoorei H, Taheri M, Sanak M. Emerging role of non-coding RNAs in allergic disorders. *Biomed Pharmacother*. 2020;130:110615.
 166. Chen D, Wu W, Yi L, et al. A potential circRNA-miRNA-mRNA regulatory network in asthmatic airway epithelial cells identified by integrated analysis of microarray datasets. *Front Mol Biosci*. 2021;8:703307.
 167. DiCosmo BF, Geba GP, Picarella D, et al. Airway epithelial cell expression of interleukin-6 in transgenic mice. Uncoupling of airway inflammation and bronchial hyperreactivity. *J Clin Invest*. 1994;94(5):2028-2035.
 168. Erpenbeck VJ, Hohlfeld JM, Volkmann B, et al. Segmental allergen challenge in patients with atopic asthma leads to increased IL-9 expression in bronchoalveolar lavage fluid lymphocytes. *J Allergy Clin Immunol*. 2003;111(6):1319-1327.
 169. Ferreira MA. Cytokine expression in allergic inflammation: systematic review of in vivo challenge studies. *Mediat Inflamm*. 2003;12(5):259-267.
 170. Fujiwara M, Hirose K, Kagami S, et al. T-bet inhibits both TH2 cell-mediated eosinophil recruitment and TH17 cell-mediated neutrophil recruitment into the airways. *J Allergy Clin Immunol*. 2007;119(3):662-670.
 171. Holgate ST. Pathogenesis of asthma. *Clin Exp Allergy*. 2008;38(6):872-897.
 172. Lloyd CM, Hessel EM. Functions of T cells in asthma: more than just T(H)2 cells. *Nat Rev Immunol*. 2010;10(12):838-848.
 173. Fujimoto M, Nakano M, Terabe F, et al. The influence of excessive IL-6 production in vivo on the development and function of Foxp3+ regulatory T cells. *J Immunol*. 2011;186(1):32-40.

174. Chen H, Xu X, Teng J, et al. CXCR4 inhibitor attenuates allergen-induced lung inflammation by down-regulating MMP-9 and ERK1/2. *Int J Clin Exp Pathol*. 2015;8(6):6700-6707.
175. Cheng S, Chen H, Wang A, et al. Blockade of IL-23 ameliorates allergic lung inflammation via decreasing the infiltration of Tc17 cells. *Arch Med Sci*. 2016;12(6):1362-1369.
176. Hammad H, Lambrecht BN. The basic immunology of asthma. *Cell*. 2021;184(9):2521-2522.
177. Lambrecht BN, Hammad H. The immunology of asthma. *Nat Immunol*. 2015;16(1):45-56.
178. Zhu J, Paul WE. Heterogeneity and plasticity of T helper cells. *Cell Res*. 2010;20(1):4-12.
179. Huang Z, Cao Y, Zhou M, et al. Hsa_circ_0005519 increases IL-13/IL-6 by regulating hsa-let-7a-5p in CD4(+) T cells to affect asthma. *Clin Exp Allergy*. 2019;49(8):1116-1127.
180. Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. *Eur J Immunol*. 2010;40(7):1830-1835.
181. Pope SM, Brandt EB, Mishra A, et al. IL-13 induces eosinophil recruitment into the lung by an IL-5- and eotaxin-dependent mechanism. *J Allergy Clin Immunol*. 2001;108(4):594-601.
182. Shang Y, Sun Y, Xu J, et al. Exosomes from mmu_circ_0001359-modified ADSCs attenuate airway remodeling by enhancing FoxO1 signaling-mediated M2-like macrophage activation. *Mol Ther Nucleic Acids*. 2020;19:951-960.
183. Bao H, Zhou Q, Li Q, et al. Differentially expressed circular RNAs in a murine asthma model. *Mol Med Rep*. 2020;22(6):5412-5422.
184. Nakano T, Inoue Y, Shimojo N, et al. Lower levels of hsa-mir-15a, which decreases VEGFA, in the CD4+ T cells of pediatric patients with asthma. *J Allergy Clin Immunol*. 2013;132(5):1224-1227. e12.
185. Qiu YY, Zhang YW, Qian XF, Bian T. miR-371, miR-138, miR-544, miR-145, and miR-214 could modulate Th1/Th2 balance in asthma through the combinatorial regulation of Runx3. *Am J Transl Res*. 2017;9(7):3184-3199.
186. Duan R, Niu H, Yu T, et al. Identification and bioinformatic analysis of circular RNA expression in peripheral blood mononuclear cells from patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2020;15:1391-1401.
187. Mercer BA, D'Armiento JM. Emerging role of MAP kinase pathways as therapeutic targets in COPD. *Int J Chron Obstruct Pulmon Dis*. 2006;1(2):137-150.
188. Zhou F, Cao C, Chai H, Hong J, Zhu M. Circ-HACE1 aggravates cigarette smoke extract-induced injury in human bronchial epithelial cells via regulating Toll-like receptor 4 by sponging miR-485-3p. *Int J Chron Obstruct Pulmon Dis*. 2021;16:1535-1547.
189. Zeng N, Wang T, Chen M, et al. Cigarette smoke extract alters genome-wide profiles of circular RNAs and mRNAs in primary human small airway epithelial cells. *J Cell Mol Med*. 2019;23(8):5532-5541.
190. Miao Y, Wu J, Wu R, Wang E, Wang J. Circ_0040929 serves as promising biomarker and potential target for chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2079-2092.
191. Qiao D, Hu C, Li Q, Fan J. Circ-RBMS1 knockdown alleviates CSE-induced apoptosis, inflammation and oxidative stress via up-regulating FBXO11 through miR-197-3p in 16HBE cells. *Int J Chron Obstruct Pulmon Dis*. 2021;16:2105-2118.
192. Mei J, Zhang Y, Lu S, Wang J. Long non-coding RNA NNT-AS1 regulates proliferation, apoptosis, inflammation and airway remodeling of chronic obstructive pulmonary disease via targeting miR-582-5p/FBXO11 axis. *Biomed Pharmacother*. 2020;129:110326.
193. Zhou L, Wu B, Yang J, et al. Knockdown of circFOXO3 ameliorates cigarette smoke-induced lung injury in mice. *Respir Res*. 2021;22(1):294.
194. Zheng C, Zhang Y, Zhao Y, Duan Y, Mu Q, Wang X. Circ-OSBP2 contributes to smoke-related chronic obstructive pulmonary disease by targeting miR-193a-5p/BRD4 Axis. *Int J Chron Obstruct Pulmon Dis*. 2021;16:919-931.
195. Ma H, Lu L, Xia H, et al. Circ0061052 regulation of FoxC1/Snail pathway via miR-515-5p is involved in the epithelial-mesenchymal transition of epithelial cells during cigarette smoke-induced airway remodeling. *Sci Total Environ*. 2020;746:141181.
196. Wang C, Tang Y, Hou H, Su C, Gao Y, Yang X. circ_0026466 knockdown protects human bronchial epithelial cells from cigarette smoke extract-induced injury by promoting the mir-153-3P/TRAF6/NF-KappaB pathway. *Shock*. 2023;60(1):121-129.
197. Du Y, Ding Y, Shi T, et al. Suppression of circXPO1 attenuates cigarette smoke-induced inflammation and cellular senescence of alveolar epithelial cells in chronic obstructive pulmonary disease. *Int Immunopharmacol*. 2022;111:109086.
198. Zhang C, Gu S, Kang X. CircRNA circ_0006892 regulates miR-24/PHLPP2 axis to mitigate cigarette smoke extract-induced bronchial epithelial cell injury. *Biotechnol Appl Biochem*. 2022;69(2):735-748.
199. Wang Z, Zuo Y, Gao Z. CircANKRD11 knockdown protects HPMECs from cigarette smoke extract-induced injury by regulating miR-145-5p/BRD4 axis. *Int J Chron Obstruct Pulmon Dis*. 2021;16:887-899.
200. Wang C, Liu Y, Zhang W, et al. circ-BPTF serves as a miR-486-5p sponge to regulate CEMIP and promotes hypoxic pulmonary arterial smooth muscle cell proliferation in COPD. *Acta Biochim Biophys Sin (Shanghai)*. 2022;55(3):438-448.
201. Huang Z, Fu B, Qi X, et al. Diagnostic and therapeutic value of Hsa_circ_0002594 for T helper 2-mediated allergic asthma. *Int Arch Allergy Immunol*. 2021;182(5):388-398.
202. Xu C, Du L, Guo Y, Liang Y. Differential circular RNA expression profiles in induced sputum of patients with asthma. *Int Arch Allergy Immunol*. 2023;184(5):460-470.
203. Guo Z, Wen Z, Qin A, et al. Antisense oligonucleotide treatment enhances the recovery of acute lung injury through IL-10-secreting M2-like macrophage-induced expansion of CD4+ regulatory T cells. *J Immunol*. 2013;190(8):4337-4348.
204. Xu Z, Zhang C, Cheng L, Hu M, Tao H, Song L. The microRNA miR-17 regulates lung FoxA1 expression during lipopolysaccharide-induced acute lung injury. *Biochem Biophys Res Commun*. 2014;445(1):48-53.
205. Wan QQ, Wu D, Ye QF. The expression profiles of circRNAs in lung tissues from rats with lipopolysaccharide-induced acute respiratory distress syndrome: A microarray study. *Biochem Biophys Res Commun*. 2017;493(1):684-689.
206. Ye Z, Liu X, Yang Y, et al. The differential expression of novel circular RNAs in an acute lung injury rat model caused by smoke inhalation. *J Physiol Biochem*. 2018;74(1):25-33.

207. Zhong J, Zhang W, Zhang L, Li J, Kang L, Li X. CircFLNA/miR-214 modulates regulatory T cells by regulating PD-1 in acute lung injury induced by sepsis. *Autoimmunity*. 2023;56(1):2259131.
208. Wang J, Zhu MC, Kalionis B, et al. Characteristics of circular RNA expression in lung tissues from mice with hypoxia-induced pulmonary hypertension. *Int J Mol Med*. 2018;42(3):1353-1366.
209. Miao R, Wang Y, Wan J, et al. Microarray expression profile of circular RNAs in chronic thromboembolic pulmonary hypertension. *Medicine (Baltimore)*. 2017;96(27):e7354.
210. Zhang X, Zhu M, Yang R, Zhao W, Hu X, Gan J. Identification and comparison of novel circular RNAs with associated co-expression and competing endogenous RNA networks in pulmonary tuberculosis. *Oncotarget*. 2017;8(69):113571-113582.
211. Huang ZK, Yao FY, Xu JQ, et al. Microarray expression profile of circular RNAs in peripheral blood mononuclear cells from active tuberculosis patients. *Cell Physiol Biochem*. 2018;45(3):1230-1240.
212. Zhuang ZG, Zhang JA, Luo HL, et al. The circular RNA of peripheral blood mononuclear cells: Hsa_circ_0005836 as a new diagnostic biomarker and therapeutic target of active pulmonary tuberculosis. *Mol Immunol*. 2017;90:264-272.
213. Qian Z, Liu H, Li M, et al. Potential diagnostic power of blood circular RNA expression in active pulmonary tuberculosis. *EBioMedicine*. 2018;27:18-26.
214. Yi Z, Gao K, Li R, Fu Y. Dysregulated circRNAs in plasma from active tuberculosis patients. *J Cell Mol Med*. 2018;22(9):4076-4084.
215. Yang X, Wang J, Zhou Z, et al. Silica-induced initiation of circular ZC3H4 RNA/ZC3H4 pathway promotes the pulmonary macrophage activation. *FASEB J*. 2018;32(6):3264-3277.
216. Zhou Z, Jiang R, Yang X, et al. circRNA mediates silica-induced macrophage activation Via HECTD1/ZC3H12A-dependent ubiquitination. *Theranostics*. 2018;8(2):575-592.
217. Fang S, Guo H, Cheng Y, et al. circHECTD1 promotes the silica-induced pulmonary endothelial-mesenchymal transition via HECTD1. *Cell Death Dis*. 2018;9(3):396.
218. Dayan CM, Besser REJ, Oram RA, et al. Preventing type 1 diabetes in childhood. *Science*. 2021;373(6554):506-510.
219. Li Y, Zhou Y, Zhao M, et al. Differential profile of plasma circular RNAs in type 1 diabetes mellitus. *Diabetes Metab J*. 2020;44(6):854-865.
220. Luo S, Deng M, Xie Z, Li X, Huang G, Zhou Z. Circulating circular RNAs profiles associated with type 1 diabetes. *Diabetes Metab Res Rev*. 2021;37(3):e3394.
221. Zhang C, Han X, Yang L, et al. Circular RNA circPPM1F modulates M1 macrophage activation and pancreatic islet inflammation in type 1 diabetes mellitus. *Theranostics*. 2020;10(24):10908-10924.
222. Cnop M, Welsh N, Jonas JC, Jorns A, Lenzen S, Eizirik DL. Mechanisms of pancreatic beta-cell death in type 1 and type 2 diabetes: many differences, few similarities. *Diabetes*. 2005;54(Suppl 2):S97-S107.
223. Yang L, Han X, Zhang C, et al. Hsa_circ_0060450 negatively regulates type i interferon-induced inflammation by serving as miR-199a-5p sponge in Type 1 diabetes mellitus. *Front Immunol*. 2020;11:576903.
224. Wang Y, Qi Y, Ji T, et al. Circ_LARP4 regulates high glucose-induced cell proliferation, apoptosis, and fibrosis in mouse mesangial cells. *Gene*. 2021;765:145114.
225. Yi X, Cheng X. Understanding competitive endogenous RNA network mechanism in type 1 diabetes mellitus using computational and bioinformatics approaches. *Diabetes Metab Syndr Obes*. 2021;14:3865-3945.
226. Holm K, Li S, Spector N, Hicks F, Carlson E, Lanuza D. Obesity in adults and children: a call for action. *J Adv Nurs*. 2001;36(2):266-269.
227. Li T, Providencia R, Mu N, et al. Association of metformin monotherapy or combined therapy with cardiovascular risks in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol*. 2021;20(1):30.
228. Zhao Z, Li X, Jian D, Hao P, Rao L, Li M. Hsa_circ_0054633 in peripheral blood can be used as a diagnostic biomarker of pre-diabetes and type 2 diabetes mellitus. *Acta Diabetol*. 2017;54(3):237-245.
229. Liang H, Hou L, Wang Q, et al. Serum hsa_circ_0054633 is elevated and correlated with clinical features in type 2 diabetes mellitus. *Ann Clin Lab Sci*. 2021;51(1):90-96.
230. Lu YK, Chu X, Wang S, et al. Identification of circulating hsa_circ_0063425 and hsa_circ_0056891 as novel biomarkers for detection of type 2 diabetes. *J Clin Endocrinol Metab*. 2021;106(7):e2688-e2699.
231. Rezaeinejad F, Mirzaei A, Khalvati B, Sabz G, Alipoor B. Circulating expression levels of CircHIPK3 and CDR1as circular-RNAs in type 2 diabetes patients. *Mol Biol Rep*. 2022;49(1):131-138.
232. Kaur S, Mirza AH, Pociot F. Cell type-selective expression of circular RNAs in human pancreatic islets. *Noncoding RNA*. 2018;4(4):38.
233. Cai H, Jiang Z, Yang X, Lin J, Cai Q, Li X. Circular RNA HIPK3 contributes to hyperglycemia and insulin homeostasis by sponging miR-192-5p and upregulating transcription factor forkhead box O1. *Endocr J*. 2020;67(4):397-408.
234. Stoll L, Sobel J, Rodriguez-Trejo A, et al. Circular RNAs as novel regulators of beta-cell functions in normal and disease conditions. *Mol Metab*. 2018;9:69-83.
235. Baroukh N, Ravier MA, Loder MK, et al. MicroRNA-124a regulates Foxa2 expression and intracellular signaling in pancreatic beta-cell lines. *J Biol Chem*. 2007;282(27):19575-19588.
236. Bagge A, Clausen TR, Larsen S, et al. MicroRNA-29a is up-regulated in beta-cells by glucose and decreases glucose-stimulated insulin secretion. *Biochem Biophys Res Commun*. 2012;426(2):266-272.
237. Jacovetti C, Jimenez V, Ayuso E, et al. Contribution of intronic miR-338-3p and its hosting gene AATK to compensatory beta-cell mass expansion. *Mol Endocrinol*. 2015;29(5):693-702.
238. Joglekar MV, Patil D, Joglekar VM, et al. The miR-30 family microRNAs confer epithelial phenotype to human pancreatic cells. *Islets*. 2009;1(2):137-147.
239. Hansen TB, Kjems J, Damgaard CK. Circular RNA and miR-7 in cancer. *Cancer Res*. 2013;73(18):5609-5612.
240. Xu H, Guo S, Li W, Yu P. The circular RNA Cdr1as, via miR-7 and its targets, regulates insulin transcription and secretion in islet cells. *Sci Rep*. 2015;5:12453.

241. Wu L, Xiong L, Li J, et al. Circ-Tulp4 promotes beta-cell adaptation to lipotoxicity by regulating *soat1* expression. *J Mol Endocrinol.* 2020;65(4):149-161.
242. Xiong L, Chen L, Wu L, et al. Lipotoxicity-induced circGlis3 impairs beta cell function and is transmitted by exosomes to promote islet endothelial cell dysfunction. *Diabetologia.* 2022;65(1):188-205.
243. Das D, Das A, Sahu M, et al. Identification and characterization of circular intronic RNAs derived from insulin gene. *Int J Mol Sci.* 2020;21(12):4302.
244. Stoll L, Rodriguez-Trejo A, Guay C, et al. A circular RNA generated from an intron of the insulin gene controls insulin secretion. *Nat Commun.* 2020;11(1):5611.
245. Fang Y, Wang X, Li W, et al. Screening of circular RNAs and validation of circANKRD36 associated with inflammation in patients with type 2 diabetes mellitus. *Int J Mol Med.* 2018;42(4):1865-1874.
246. Bai C, Yang W, Lu Y, Wei W, Li Z, Zhang L. Identification of circular RNAs regulating islet beta-cell autophagy in type 2 diabetes mellitus. *Biomed Res Int.* 2019;2019:4128315.
247. She W, Li T, Liu Y, Liu X. CircRNA circVEGFC is highly expressed in gestational diabetes mellitus (GDM) and it is correlated with multiple adverse events. *Diabetes Metab Syndr Obes.* 2021;14:4409-4414.
248. Zhu C, Liu Y, Wu H. Overexpression of circACTR2 in Gestational Diabetes Mellitus Predicts Intrauterine Death, Fetal Malformation, and Intrauterine Infection. *Diabetes Metab Syndr Obes.* 2021;14:4655-4660.
249. Yan L, Feng J, Cheng F, et al. Circular RNA expression profiles in placental villi from women with gestational diabetes mellitus. *Biochem Biophys Res Commun.* 2018;498(4):743-750.
250. Tang L, Li P, Li L. Whole transcriptome expression profiles in placenta samples from women with gestational diabetes mellitus. *J Diabetes Investig.* 2020;11(5):1307-1317.
251. Chen H, Zhang S, Wu Y, et al. The role of circular RNA circ_0008285 in gestational diabetes mellitus by regulating the biological functions of trophoblasts. *Biol Res.* 2021;54(1):14.
252. Wang H, Zhou W, She G, Yu B, Sun L. Downregulation of *hsa_circ_0005243* induces trophoblast cell dysfunction and inflammation via the beta-catenin and NF-kappaB pathways. *Reprod Biol Endocrinol.* 2020;18(1):51.
253. Zhang L, Zeng M, Tang F, Chen J, Cao D, Tang ZN. Circ-PNPT1 contributes to gestational diabetes mellitus (GDM) by regulating the function of trophoblast cells through miR-889-3p/PAK1 axis. *Diabetol Metab Syndr.* 2021;13(1):58.
254. Kollias AN, Ulbig MW. Diabetic retinopathy: Early diagnosis and effective treatment. *Dtsch Arztebl Int.* 2010;107(5):75-83; quiz 84.
255. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet.* 2010;376(9735):124-136.
256. Wu Z, Liu B, Ma Y, Chen H, Wu J, Wang J. Discovery and validation of *hsa_circ_0001953* as a potential biomarker for proliferative diabetic retinopathy in human blood. *Acta Ophthalmol.* 2021;99(3):306-313.
257. Memczak S, Papavasileiou P, Peters O, Rajewsky N. Identification and characterization of circular RNAs as a new class of putative biomarkers in human blood. *PLoS One.* 2015;10(10):e0141214.
258. He H, Zhang J, Gong W, et al. Involvement of CircRNA expression profile in diabetic retinopathy and its potential diagnostic value. *Front Genet.* 2022;13:833573.
259. Shan K, Liu C, Liu BH, et al. Circular noncoding RNA HIPK3 mediates retinal vascular dysfunction in diabetes mellitus. *Circulation.* 2017;136(17):1629-1642.
260. Zou J, Liu KC, Wang WP, Xu Y. Circular RNA COL1A2 promotes angiogenesis via regulating miR-29b/VEGF axis in diabetic retinopathy. *Life Sci.* 2020;256:117888.
261. Guo J, Xiao F, Ren W, et al. Circular ribonucleic acid circFTO promotes angiogenesis and impairs blood-retinal barrier via targeting the miR-128-3p/thioredoxin interacting protein axis in diabetic retinopathy. *Front Mol Biosci.* 2021;8:685466.
262. Jiewei Y, Jingjing Z, Jingjing X, Guilan Z. Downregulation of circ-UBAP2 ameliorates oxidative stress and dysfunctions of human retinal microvascular endothelial cells (hRMECs) via miR-589-5p/EGR1 axis. *Bioengineered.* 2021;12(1):7508-7518.
263. Li X, Wang J, Qian H, et al. Serum exosomal circular RNA expression profile and regulative role in proliferative diabetic retinopathy. *Front Genet.* 2021;12:719312.
264. Wang S, Yu Q, Wang Y, Xu C, Niu G, Liu R. Circ-SLC16A12 absence inhibits high glucose-induced dysfunction in retinal microvascular endothelial cells through mediating miR-140-3p/FGF2 axis in diabetic retinopathy. *Curr Eye Res.* 2022;47(5):759-769.
265. Zhu K, Hu X, Chen H, et al. Downregulation of circRNA DMNT3B contributes to diabetic retinal vascular dysfunction through targeting miR-20b-5p and BAMBI. *EBioMedicine.* 2019;49:341-353.
266. Wang F, Zhang M. Circ_001209 aggravates diabetic retinal vascular dysfunction through regulating miR-15b-5p/COL12A1. *J Transl Med.* 2021;19(1):294.
267. Liu C, Ge HM, Liu BH, et al. Targeting pericyte-endothelial cell crosstalk by circular RNA-cPWWP2A inhibition aggravates diabetes-induced microvascular dysfunction. *Proc Natl Acad Sci USA.* 2019;116(15):7455-7464.
268. Ye L, Guo H, Wang Y, et al. Exosomal circEhmt1 released from hypoxia-pretreated pericytes regulates high glucose-induced microvascular dysfunction via the NFIA/NLRP3 pathway. *Oxid Med Cell Longev.* 2021;2021:8833098.
269. Sun H, Kang X. *hsa_circ_0041795* contributes to human retinal pigment epithelial cells (ARPE 19) injury induced by high glucose via sponging miR-646 and activating VEGFC. *Gene.* 2020;747:144654.
270. Li Y, Cheng T, Wan C, Cang Y. circRNA_0084043 contributes to the progression of diabetic retinopathy via sponging miR-140-3p and inducing TGFA gene expression in retinal pigment epithelial cells. *Gene.* 2020;747:144653.
271. Liang Z, Lu C, Feng T, et al. Circ-ADAM9 promotes high glucose-induced retinal pigment epithelial cell injury in DR via regulating miR-338-3p/CARM1 axis. *J Ophthalmol.* 2022;2022:2522249.
272. Zhu Z, Duan P, Song H, Zhou R, Chen T. Downregulation of Circular RNA PSEN1 ameliorates ferroptosis of the high glucose treated retinal pigment epithelial cells via miR-200b-3p/cofilin-2 axis. *Bioengineered.* 2021;12(2):12555-12567.
273. Jiang Q, Liu C, Li CP, et al. Circular RNA-ZNF532 regulates diabetes-induced retinal pericyte degeneration and vascular dysfunction. *J Clin Invest.* 2020;130(7):3833-3847.

274. Liang GH, Luo YN, Wei RZ, et al. CircZNF532 knockdown protects retinal pigment epithelial cells against high glucose-induced apoptosis and pyroptosis by regulating the miR-20b-5p/STAT3 axis. *J Diabetes Investig*. 2022;13(5):781-795.
275. Wang T, Li C, Shi M, Zhou S, Chen J, Wang F. Circular RNA circZNF532 facilitates angiogenesis and inflammation in diabetic retinopathy via regulating miR-1243/CARM1 axis. *Diabetol Metab Syndr*. 2022;14(1):14.
276. Zhou L, Li FF, Wang SM. Circ-ITCH restrains the expression of MMP-2, MMP-9 and TNF-alpha in diabetic retinopathy by inhibiting miR-22. *Exp Mol Pathol*. 2021;118:104594.
277. Yao MD, Jiang Q, Ma Y, et al. Targeting circular RNA-MET for anti-angiogenesis treatment via inhibiting endothelial tip cell specialization. *Mol Ther*. 2022;30(3):1252-1264.
278. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA consensus conference. *Diabetes Care*. 2014;37(10):2864-2883.
279. Wang XB, Zhu H, Song W, Su JH. Gremlin regulates podocyte apoptosis via transforming growth factor-beta (TGF-beta) pathway in diabetic nephropathy. *Med Sci Monit*. 2018;24:183-189.
280. Zhang K, Wan X, Khan MA, et al. Peripheral blood circRNA microarray profiling identifies hsa_circ_0001831 and hsa_circ_0000867 as two novel circRNA biomarkers for early type 2 diabetic nephropathy. *Diabetes Metab Syndr Obes*. 2022;15:2789-2801.
281. Hu F, Sha W, Dai H, et al. Lower expression of Hsa_circRNA_102682 in diabetic hyperhomocysteinemia negatively related to creatinemia is associated with TGF-beta and CTGF. *J Clin Lab Anal*. 2021;35(8):e23860.
282. Xu B, Wang Q, Li W, et al. Circular RNA circEIF4G2 aggravates renal fibrosis in diabetic nephropathy by sponging miR-218. *J Cell Mol Med*. 2022;26(6):1799-1805.
283. Yun J, Ren J, Liu Y, et al. Circ-ACR2 aggravates the high glucose-induced cell dysfunction of human renal mesangial cells through mediating the miR-205-5p/HMGA2 axis in diabetic nephropathy. *Diabetol Metab Syndr*. 2021;13(1):72.
284. Li B, Sun G, Yu H, Meng J, Wei F. Exosomal circTAOK1 contributes to diabetic kidney disease progression through regulating SMAD3 expression by sponging miR-520h. *Int Urol Nephrol*. 2022;54(9):2343-2354.
285. Zhu Y, Zha F, Tang B, et al. Exosomal hsa_circ_0125310 promotes cell proliferation and fibrosis in diabetic nephropathy via sponging miR-422a and targeting the IGF1R/p38 axis. *J Cell Mol Med*. 2022;26(1):151-162.
286. Sun A, Sun N, Liang X, Hou Z. Circ-FBXW12 aggravates the development of diabetic nephropathy by binding to miR-31-5p to induce LIN28B. *Diabetol Metab Syndr*. 2021;13(1):141.
287. Hu W, Han Q, Zhao L, Wang L. Circular RNA circRNA_15698 aggravates the extracellular matrix of diabetic nephropathy mesangial cells via miR-185/TGF-beta1. *J Cell Physiol*. 2019;234(2):1469-1476.
288. Wu R, Niu Z, Ren G, Ruan L, Sun L. CircSMAD4 alleviates high glucose-induced inflammation, extracellular matrix deposition and apoptosis in mouse glomerulus mesangial cells by relieving miR-377-3p-mediated BMP7 inhibition. *Diabetol Metab Syndr*. 2021;13(1):137.
289. Liu H, Wang X, Wang ZY, Li L. Circ_0080425 inhibits cell proliferation and fibrosis in diabetic nephropathy via sponging miR-24-3p and targeting fibroblast growth factor 11. *J Cell Physiol*. 2020;235(5):4520-4529.
290. Zhao L, Chen H, Zeng Y, et al. Circular RNA circ_0000712 regulates high glucose-induced apoptosis, inflammation, oxidative stress, and fibrosis in (DN) by targeting the miR-879-5p/SOX6 axis. *Endocr J*. 2021;68(10):1155-1164.
291. Wang J, Yang S, Li W, Zhao M, Li K. Circ_0000491 promotes apoptosis, inflammation, oxidative stress, and fibrosis in high glucose-induced mesangial cells by regulating miR-455-3p/Hmgb1 axis. *Nephron*. 2022;146(1):72-83.
292. Peng F, Gong W, Li S, et al. circRNA_010383 acts as a sponge for miR-135a and its downregulated expression contributes to renal fibrosis in diabetic nephropathy. *Diabetes*. 2020;70(2):603-615.
293. Yao T, Zha D, Hu C, Wu X. Circ_0000285 promotes podocyte injury through sponging miR-654-3p and activating MAPK6 in diabetic nephropathy. *Gene*. 2020;747:144661.
294. Wang Q, Cang Z, Shen L, et al. circ_0037128/miR-17-3p/AKT3 axis promotes the development of diabetic nephropathy. *Gene*. 2021;765:145076.
295. Tang B, Li W, Ji TT, et al. Circ-AKT3 inhibits the accumulation of extracellular matrix of mesangial cells in diabetic nephropathy via modulating miR-296-3p/E-cadherin signals. *J Cell Mol Med*. 2020;24(15):8779-8788.
296. Jin J, Wang Y, Zheng D, Liang M, He Q. A novel identified circular RNA, mmu_mmu_circRNA_0000309, involves in germacrone-mediated improvement of diabetic nephropathy through regulating ferroptosis by targeting miR-188-3p/GPX4 signaling axis. *Antioxid Redox Signal*. 2022;36(10-12):740-759.
297. Liu J, Duan P, Xu C, Xu D, Liu Y, Jiang J. CircRNA circ-ITCH improves renal inflammation and fibrosis in streptozotocin-induced diabetic mice by regulating the miR-33a-5p/SIRT6 axis. *Inflamm Res*. 2021;70(7):835-846.
298. Zhuang L, Wang Z, Hu X, Yang Q, Pei X, Jin G. CircHIPK3 alleviates high glucose toxicity to human renal tubular epithelial HK-2 cells through regulation of miR-326/miR-487a-3p/SIRT1. *Diabetes Metab Syndr Obes*. 2021;14:729-740.
299. Liu R, Zhang M, Ge Y. Circular RNA HIPK3 exacerbates diabetic nephropathy and promotes proliferation by sponging miR-185. *Gene*. 2021;765:145065.
300. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. *Nat Rev Dis Primers*. 2019;5(1):41.
301. He J, Wang HB, Huang JJ, et al. Diabetic neuropathic pain induced by streptozotocin alters the expression profile of non-coding RNAs in the spinal cord of mice as determined by sequencing analysis. *Exp Ther Med*. 2021;22(1):775.
302. Zhang HH, Zhang Y, Wang X, et al. Circular RNA profile in diabetic peripheral neuropathy: analysis of coexpression networks of circular RNAs and mRNAs. *Epigenomics*. 2020;12(10):843-857.
303. Wang L, Luo T, Bao Z, Li Y, Bu W. Intrathecal circHIPK3 shRNA alleviates neuropathic pain in diabetic rats. *Biochem Biophys Res Commun*. 2018;505(3):644-650.
304. Dillmann WH. Diabetic cardiomyopathy. *Circ Res*. 2019;124(8):1160-1162.
305. Zhang M, Wang S, Cheng Z, et al. Polydatin ameliorates diabetic cardiomyopathy via Sirt3 activation. *Biochem Biophys Res Commun*. 2017;493(3):1280-1287.

306. Jia G, Whaley-Connell A, Sowers JR. Diabetic cardiomyopathy: a hyperglycaemia- and insulin-resistance-induced heart disease. *Diabetologia*. 2018;61(1):21-28.
307. Zhou B, Yu JW. A novel identified circular RNA, circRNA_010567, promotes myocardial fibrosis via suppressing miR-141 by targeting TGF- β 1. *Biochem Biophys Res Commun*. 2017;487(4):769-775.
308. Tang CM, Zhang M, Huang L, et al. CircRNA_000203 enhances the expression of fibrosis-associated genes by derepressing targets of miR-26b-5p, Col1a2 and CTGF, in cardiac fibroblasts. *Sci Rep*. 2017;7:40342.
309. Wang W, Zhang S, Xu L, et al. Involvement of circHIPK3 in the pathogenesis of diabetic cardiomyopathy in mice. *Diabetologia*. 2021;64(3):681-692.
310. Jiang J, Gao G, Pan Q, Liu J, Tian Y, Zhang X. Circular RNA circHIPK3 is downregulated in diabetic cardiomyopathy and overexpression of circHIPK3 suppresses PTEN to protect cardiomyocytes from high glucose-induced cell apoptosis. *Bioengineered*. 2022;13(3):6272-6279.
311. Fu L, Zhang J, Lin Z, Li Y, Qin G. CircularRNA circ_0071269 knockdown protects against from diabetic cardiomyopathy injury by microRNA-145/gasdermin A axis. *Bioengineered*. 2022;13(2):2398-2411.
312. Yang F, Li A, Qin Y, et al. A novel circular RNA mediates pyroptosis of diabetic cardiomyopathy by functioning as a competing endogenous RNA. *Mol Ther Nucleic Acids*. 2019;17:636-643.
313. Sumpio BE, Riley JT, Dardik A. Cells in focus: endothelial cell. *Int J Biochem Cell Biol*. 2002;34(12):1508-1512.
314. Kaur R, Kaur M, Singh J. Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: molecular insights and therapeutic strategies. *Cardiovasc Diabetol*. 2018;17(1):121.
315. Grassi D, Desideri G, Necozione S, et al. Protective effects of flavanol-rich dark chocolate on endothelial function and wave reflection during acute hyperglycemia. *Hypertension*. 2012;60(3):827-832.
316. Ceriello A. Point: postprandial glucose levels are a clinically important treatment target. *Diabetes Care*. 2010;33(8):1905-1907.
317. Shang FF, Luo S, Liang X, Xia Y. Alterations of circular RNAs in hyperglycemic human endothelial cells. *Biochem Biophys Res Commun*. 2018;499(3):551-555.
318. Cheng J, Liu Q, Hu N, et al. Downregulation of hsa_circ_0068087 ameliorates TLR4/NF- κ B/NLRP3 inflammasome-mediated inflammation and endothelial cell dysfunction in high glucose conditioned by sponging miR-197. *Gene*. 2019;709:1-7.
319. Zhang W, Sui Y. CircBPTF knockdown ameliorates high glucose-induced inflammatory injuries and oxidative stress by targeting the miR-384/LIN28B axis in human umbilical vein endothelial cells. *Mol Cell Biochem*. 2020;471(1-2):101-111.
320. Zhang Q, Long J, Li N, Ma X, Zheng L. Circ_CLASP2 regulates high glucose-induced dysfunction of human endothelial cells through targeting miR-140-5p/FBXW7 axis. *Front Pharmacol*. 2021;12:594793.
321. Chen J, Cui L, Yuan J, Zhang Y, Sang H. Circular RNA WDR77 target FGF-2 to regulate vascular smooth muscle cells proliferation and migration by sponging miR-124. *Biochem Biophys Res Commun*. 2017;494(1-2):126-132.
322. Bai Y, Liu F, Yang Z. CircRNA LRP6 promotes high-glucose induced proliferation and migration of vascular smooth muscle cells through regulating miR-545-3p/HMGA1 signaling axis. *Am J Transl Res*. 2021;13(8):8909-8920.
323. Yuan J, Liu Y, Zhou L, Xue Y, Lu Z, Gan J. YTHDC2-mediated circYTHDC2 N6-methyladenosine modification promotes vascular smooth muscle cells dysfunction through inhibiting ten-eleven translocation 2. *Front Cardiovasc Med*. 2021;8:686293.
324. Wang Z, Feng C, Liu H, et al. Hypoxic pretreatment of adipose-derived stem cells accelerates diabetic wound healing via circ-gcap14 and HIF-1 α /VEGF mediated angiopoiesis. *Int J Stem Cells*. 2021;14(4):447-454.
325. Shang B, Xu T, Hu N, Mao Y, Du X. Circ-Klhl8 overexpression increased the therapeutic effect of EPCs in diabetic wound healing via the miR-212-3p/SIRT5 axis. *J Diabetes Complications*. 2021;35(11):108020.
326. Shi R, Jin Y, Hu W, et al. Exosomes derived from mmu_circ_0000250-modified adipose-derived mesenchymal stem cells promote wound healing in diabetic mice by inducing miR-128-3p/SIRT1-mediated autophagy. *Am J Physiol Cell Physiol*. 2020;318(5):C848-C856.
327. Meng F, Shen F, Ling H, Jin P, Zhou D, Li Q. CircARHGAP12 triggers mesenchymal stromal cell autophagy to facilitate its effect on repairing diabetic wounds by sponging miR-301b-3p/ATG16L1 and miR-301b-3p/ULK2. *J Invest Dermatol*. 2022;142(7):1976-1989. e4.
328. Iqbal J, Al Qarni A, Hawwari A, Alghanem AF, Ahmed G. Metabolic syndrome, dyslipidemia and regulation of lipoprotein metabolism. *Curr Diabetes Rev*. 2018;14(5):427-433.
329. Turer CB, Brady TM, de Ferranti SD. Obesity, hypertension, and dyslipidemia in childhood are key modifiable antecedents of adult cardiovascular disease: a call to action. *Circulation*. 2018;137(12):1256-1259.
330. Chen C, Zhang X, Deng Y, et al. Regulatory roles of circRNAs in adipogenesis and lipid metabolism: emerging insights into lipid-related diseases. *FEBS J*. 2021;288(12):3663-3682.
331. Sun J, Li B, Shu C, Ma Q, Wang J. Functions and clinical significance of circular RNAs in glioma. *Mol Cancer*. 2020;19(1):34.
332. Zhu Y, Gui W, Lin X, Li H. Knock-down of circular RNA H19 induces human adipose-derived stem cells adipogenic differentiation via a mechanism involving the polypyrimidine tract-binding protein 1. *Exp Cell Res*. 2020;387(2):111753.
333. Arcinas C, Tan W, Fang W, et al. Adipose circular RNAs exhibit dynamic regulation in obesity and functional role in adipogenesis. *Nat Metab*. 2019;1(7):688-703.
334. Liu Y, Liu H, Li Y, et al. Circular RNA SAMD4A controls adipogenesis in obesity through the miR-138-5p/EZH2 axis. *Theranostics*. 2020;10(10):4705-4719.
335. Zhang X, Chen L, Xiao B, Liu H, Su Y. Circ_0075932 in adipocyte-derived exosomes induces inflammation and apoptosis in human dermal keratinocytes by directly binding with PUM2 and promoting PUM2-mediated activation of AuroraA/NF- κ B pathway. *Biochem Biophys Res Commun*. 2019;511(3):551-558.
336. Zhang D, Ni N, Wang Y, et al. CircRNA-vgll3 promotes osteogenic differentiation of adipose-derived mesenchymal stem cells via modulating miRNA-dependent integrin α 5 expression. *Cell Death Differ*. 2021;28(1):283-302.

337. Chen G, Wang Q, Li Z, et al. Circular RNA CDR1as promotes adipogenic and suppresses osteogenic differentiation of BMSCs in steroid-induced osteonecrosis of the femoral head. *Bone*. 2020;133:115258.
338. Long T, Guo Z, Han L, et al. Differential expression profiles of circular RNAs during osteogenic differentiation of mouse adipose-derived stromal cells. *Calcif Tissue Int*. 2018;103(3):338-352.
339. Liu H, Sun Q, Wan C, Li L, Zhang L, Chen Z. MicroRNA-338-3p regulates osteogenic differentiation of mouse bone marrow stromal stem cells by targeting Runx2 and Fgfr2. *J Cell Physiol*. 2014;229(10):1494-1502.
340. Guo Z, Zhao L, Ji S, et al. CircRNA-23525 regulates osteogenic differentiation of adipose-derived mesenchymal stem cells via miR-30a-3p. *Cell Tissue Res*. 2021;383(2):795-807.
341. Chen Q, Liu M, Luo Y, et al. Maternal obesity alters circRNA expression and the potential role of mmu_circRNA_0000660 via sponging miR_693 in offspring liver at weaning age. *Gene*. 2020;731:144354.
342. Guo XY, Sun F, Chen JN, Wang YQ, Pan Q, Fan JG. circRNA_0046366 inhibits hepatocellular steatosis by normalization of PPAR signaling. *World J Gastroenterol*. 2018;24(3):323-337.
343. Guo XY, Chen JN, Sun F, Wang YQ, Pan Q, Fan JG. circRNA_0046367 prevents hepatotoxicity of lipid peroxidation: an inhibitory role against hepatic steatosis. *Oxid Med Cell Longev*. 2017;2017:3960197.
344. Guo XY, He CX, Wang YQ, et al. Circular RNA profiling and bioinformatic modeling identify its regulatory role in hepatic steatosis. *Biomed Res Int*. 2017;2017:5936171.
345. Li P, Shan K, Liu Y, Zhang Y, Xu L, Xu L. CircScd1 promotes fatty liver disease via the janus kinase 2/Signal transducer and activator of transcription 5 pathway. *Dig Dis Sci*. 2019;64(1):113-122.
346. Zhang Z, Zhang T, Feng R, Huang H, Xia T, Sun C. circARF3 alleviates mitophagy-mediated inflammation by targeting miR-103/TRAF3 in mouse adipose tissue. *Mol Ther Nucleic Acids*. 2019;14:192-203.
347. Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. *Nat Rev Immunol*. 2008;8(9):726-736.
348. Wang Y, Li M, Wang Y, et al. A Zfp609 circular RNA regulates myoblast differentiation by sponging miR-194-5p. *Int J Biol Macromol*. 2019;121:1308-1313.
349. Cherubini A, Barilani M, Rossi RL, et al. FOXP1 circular RNA sustains mesenchymal stem cell identity via microRNA inhibition. *Nucleic Acids Res*. 2019;47(10):5325-5340.
350. Musso G, Gambino R, Cassader M. Recent insights into hepatic lipid metabolism in non-alcoholic fatty liver disease (NAFLD). *Prog Lipid Res*. 2009;48(1):1-26.
351. Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology*. 2003;37(4):917-923.
352. Neuschwander-Tetri BA. Hepatic lipotoxicity and the pathogenesis of nonalcoholic steatohepatitis: the central role of non-triglyceride fatty acid metabolites. *Hepatology*. 2010;52(2):774-788.
353. Jin X, Feng CY, Xiang Z, Chen YP, Li YM. CircRNA expression pattern and circRNA-miRNA-mRNA network in the pathogenesis of nonalcoholic steatohepatitis. *Oncotarget*. 2016;7(41):66455-66467.
354. Zheng J, Zhang Q, Mul JD, et al. Maternal high-calorie diet is associated with altered hepatic microRNA expression and impaired metabolic health in offspring at weaning age. *Endocrine*. 2016;54(1):70-80.
355. An T, Zhang J, Lv B, et al. Salvianolic acid B plays an anti-obesity role in high fat diet-induced obese mice by regulating the expression of mRNA, circRNA, and lncRNA. *PeerJ*. 2019;7:e6506.
356. Chien Y, Tsai PH, Lai YH, et al. CircularRNA as novel biomarkers in liver diseases. *J Chin Med Assoc*. 2020;83(1):15-17.
357. Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology*. 2006;44(4):865-873.
358. Evans MA, Sano S, Walsh K. Cardiovascular disease, aging, and clonal hematopoiesis. *Annu Rev Pathol*. 2020;15:419-438.
359. Zhang F, Liu L, Zhang C, Ji S, Mei Z, Li T. Association of metabolic syndrome and its components with risk of stroke recurrence and mortality: a meta-analysis. *Neurology*. 2021;97(7):e695-e705.
360. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovasc Diabetol*. 2018;17(1):83.
361. Tsao CW, Aday AW, Almarazgo ZI, et al. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. *Circulation*. 2022;145(8):e153-e639.
362. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76(25):2982-3021.
363. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. *Lancet*. 2014;383(9921):999-1008.
364. Wu R, Gao W, Yao K, Ge J. Roles of exosomes derived from immune cells in cardiovascular diseases. *Front Immunol*. 2019;10:648.
365. Lu M, Yuan S, Li S, Li L, Liu M, Wan S. The exosome-derived biomarker in atherosclerosis and its clinical application. *J Cardiovasc Transl Res*. 2019;12(1):68-74.
366. Pang Y, Ma M, Wang D, et al. Embryonic stem cell-derived exosomes attenuate transverse aortic constriction induced heart failure by increasing angiogenesis. *Front Cardiovasc Med*. 2021;8:638771.
367. Gao XF, Wang ZM, Wang F, Gu Y, Zhang JJ, Chen SL. Exosomes in coronary artery disease. *Int J Biol Sci*. 2019;15(11):2461-2470.
368. Gong M, Yu B, Wang J, et al. Mesenchymal stem cells release exosomes that transfer miRNAs to endothelial cells and promote angiogenesis. *Oncotarget*. 2017;8(28):45200-45212.
369. Qiao L, Hu S, Liu S, et al. microRNA-21-5p dysregulation in exosomes derived from heart failure patients impairs regenerative potential. *J Clin Invest*. 2019;129(6):2237-2250.
370. Nowbar AN, Howard JP, Finegold JA, Asaria P, Francis DP. 2014 global geographic analysis of mortality from ischaemic heart disease by country, age and income: statistics from World Health Organisation and United Nations. *Int J Cardiol*. 2014;174(2):293-298.

371. Moriya J. Critical roles of inflammation in atherosclerosis. *J Cardiol*. 2019;73(1):22-27.
372. Nawaz B, Fromm A, Øygarden H, et al. Vascular risk factors and staging of atherosclerosis in patients and controls: The Norwegian Stroke in the Young Study. *European stroke journal*. 2022;7(3):289-298.
373. Tabas I, Lichtman AH. Monocyte-macrophages and T cells in atherosclerosis. *Immunity*. 2017;47(4):621-634.
374. Vilades D, Martínez-Camblor P, Ferrero-Gregori A, et al. Plasma circular RNA hsa_circ_0001445 and coronary artery disease: performance as a biomarker. *Faseb j*. 2020;34(3):4403-4414.
375. Wang L, Shen C, Wang Y, et al. Identification of circular RNA Hsa_circ_0001879 and Hsa_circ_0004104 as novel biomarkers for coronary artery disease. *Atherosclerosis*. 2019;286:88-96.
376. Wu WP, Pan YH, Cai MY, et al. Plasma-derived exosomal circular RNA hsa_circ_0005540 as a novel diagnostic biomarker for coronary artery disease. *Dis Markers*. 2020;2020:3178642.
377. Miao L, Yin RX, Zhang QH, et al. A novel circRNA-miRNA-mRNA network identifies circ-YOD1 as a biomarker for coronary artery disease. *Sci Rep*. 2019;9(1):18314.
378. Xiong F, Mao R, Zhang L, et al. CircNPHP4 in monocyte-derived small extracellular vesicles controls heterogeneous adhesion in coronary heart atherosclerotic disease. *Cell Death Dis*. 2021;12(10):948.
379. Liu X, Zheng M, Han R, et al. Circulating exosomal CircRNAs as diagnostic biomarkers for chronic coronary syndrome. *Metabolites*. 2023;13(10):1066.
380. Liu J, Zhang X, Yu Z, Zhang T. Circ_0026218 ameliorates oxidized low-density lipoprotein-induced vascular endothelial cell dysfunction by regulating miR-188-3p/TLR4/NF- κ B pathway. *Cardiovasc Drugs Ther*. 2022;38(2):263-277.
381. Yamamoto E, Yonetsu T, Kakuta T, et al. Clinical and laboratory predictors for plaque erosion in patients with acute coronary syndromes. *J Am Heart Assoc*. 2019;8(21):e012322.
382. Kolodgie FD, Burke AP, Farb A, et al. The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes. *Curr Opin Cardiol*. 2001;16(5):285-292.
383. Huang S, Wu Z, Zhou Y. Hypoxia-induced circRNAs encoded by PPARG are highly expressed in human cardiomyocytes and are potential clinical biomarkers of acute myocardial infarction. *Eur J Med Res*. 2024;29(1):159.
384. Liu R, Hu L, Zhou Y, Cao Y. Serum circPRDM5 as a novel diagnostic biomarker for acute myocardial infarction. *Gene*. 2024;899:148142.
385. Tian M, Xue J, Dai C, Jiang E, Zhu B, Pang H. CircSLC8A1 and circNFIX can be used as auxiliary diagnostic markers for sudden cardiac death caused by acute ischemic heart disease. *Sci Rep*. 2021;11(1):4695.
386. Tong X, Zhao X, Dang X, Kou Y, Kou J. circRNA, a novel diagnostic biomarker for coronary heart disease. *Front Cardiovasc Med*. 2023;10:1070616.
387. Pang P, Si W, Wu H, et al. The circular RNA circHelz enhances cardiac fibrosis by facilitating the nuclear translocation of YAP1. *Transl Res*. 2023;257:30-42.
388. Wang Y, Li C, Zhao R, et al. CircUbe3a from M2 macrophage-derived small extracellular vesicles mediates myocardial fibrosis after acute myocardial infarction. *Theranostics*. 2021;11(13):6315-6333.
389. Deng Y, Wang J, Xie G, Zeng X, Li H. Circ-HIPK3 strengthens the effects of adrenaline in heart failure by MiR-17-3p - ADCY6 axis. *Int J Biol Sci*. 2019;15(11):2484-2496.
390. Huang C, Qu Y, Feng F, et al. Cardioprotective effect of circ_SMG6 knockdown against myocardial ischemia/reperfusion injury correlates with miR-138-5p-mediated EGRI/TLR4/TRIF inactivation. *Oxid Med Cell Longev*. 2022;2022:1927260.
391. Zhu J, Chen Z, Peng X, et al. Extracellular vesicle-derived circITGB1 regulates dendritic cell maturation and cardiac inflammation via miR-342-3p/NFAM1. *Oxid Med Cell Longev*. 2022;2022:8392313.
392. Ye X, Hang Y, Lu Y, et al. CircRNA circ-NNT mediates myocardial ischemia/reperfusion injury through activating pyroptosis by sponging miR-33a-5p and regulating USP46 expression. *Cell Death Discov*. 2021;7(1):370.
393. Zhang Y, Liu S, Ding L, Wang D, Li Q, Li D. Circ_0030235 knockdown protects H9c2 cells against OGD/R-induced injury via regulation of miR-526b. *PeerJ*. 2021;9:e11482.
394. Zhu Y, Zou C, Jia Y, Zhang H, Ma X, Zhang J. Knockdown of circular RNA circMAT2B reduces oxygen-glucose deprivation-induced inflammatory injury in H9c2 cells through up-regulating miR-133. *Cell Cycle*. 2020;19(20):2622-2630.
395. Li X, Guo L, Wang J, Yang X. Pro-fibrotic and apoptotic activities of circARAP1 in myocardial ischemia-reperfusion injury. *Eur J Med Res*. 2023;28(1):84.
396. Chen TP, Zhang NJ, Wang HJ, Hu SG, Geng X. Knockdown of circROBO2 attenuates acute myocardial infarction through regulating the miR-1184/TRADD axis. *Mol Med (Cambridge, Mass)*. 2021;27(1):21.
397. Liao H, Xiao C, Li W, Chen W, Xiang D. Silencing hsa_circ_0049271 attenuates hypoxia-reoxygenation (H/R)-induced myocardial cell injury via the miR-17-3p/FZD4 signaling axis. *Ann Transl Med*. 2023;11(2):99.
398. Huang L, Guo B, Yan J, Wei H, Liu S, Li Y. CircHSPG2 knockdown attenuates hypoxia-induced apoptosis, inflammation, and oxidative stress in human AC16 cardiomyocytes by regulating the miR-1184/MAP3K2 axis. *Cell Stress Chaperones*. 2023;28(2):177-190.
399. Ren K, Li B, Jiang L, et al. circ_0023461 silencing protects cardiomyocytes from hypoxia-induced dysfunction through targeting miR-370-3p/PDE4D signaling. *Oxid Med Cell Longev*. 2021;2021:8379962.
400. Liu B, Guo K. CircRbms1 knockdown alleviates hypoxia-induced cardiomyocyte injury via regulating the miR-742-3p/FOXO1 axis. *Cell Mol Biol Lett*. 2022;27(1):31.
401. Tan J, Pan W, Chen H, et al. Circ_0124644 serves as a ceRNA for miR-590-3p to promote hypoxia-induced cardiomyocytes injury via regulating SOX4. *Front Genet*. 2021;12:667724.
402. Xu C, Jia Z, Cao X, Wang S, Wang J, An L. Hsa_circ_0007059 promotes apoptosis and inflammation in cardiomyocytes during ischemia by targeting microRNA-378 and microRNA-383. *Cell Cycle*. 2022;21(10):1003-1019.
403. Chen YE, Yang H, Pang HB, Shang FQ. Circ-CBFB exacerbates hypoxia/reoxygenation-triggered cardiomyocyte injury via regulating miR-495-3p in a VDAC1-dependent manner. *J Biochem Mol Toxicol*. 2022;36(11):e23189.

404. Zhao Y, Wang S, Liu S, Yan Q, Li Y, Liu Y. CircHSPG2 absence weakens hypoxia-induced dysfunction in cardiomyocytes by targeting the miR-25-3p/PAWR axis. *Cardiovasc Diagn Ther.* 2022;12(5):589-602.
405. Zhou D, Dai Z, Ren M, Yang M. Adipose-derived stem cells-derived exosomes with high amounts of Circ_0001747 alleviate hypoxia/reoxygenation-induced injury in myocardial cells by targeting MiR-199b-3p/MCL1 axis. *Int Heart J.* 2022;63(2):356-366.
406. Gao XQ, Liu CY, Zhang YH, et al. The circRNA CNEACR regulates necroptosis of cardiomyocytes through Foxa2 suppression. *Cell Death Differ.* 2022;29(3):527-539.
407. Zhao Q, Li W, Pan W, Wang Z. CircRNA 010567 plays a significant role in myocardial infarction via the regulation of the miRNA-141/DAPK1 axis. *J Thorac Dis.* 2021;13(4):2447-2459.
408. Liu X, Dou B, Tang W, et al. Cardioprotective effects of circ_0002612 in myocardial ischemia/reperfusion injury correlate with disruption of miR-30a-5p-dependent Ppargc1a inhibition. *Int Immunopharmacol.* 2023;117:110006.
409. Wang Y, Zhao R, Shen C, et al. Exosomal CircHIPK3 released from hypoxia-induced cardiomyocytes regulates cardiac angiogenesis after myocardial infarction. *Oxid Med Cell Longev.* 2020;2020:8418407.
410. Garikipati VNS, Verma SK, Cheng Z, et al. Circular RNA CircFndc3b modulates cardiac repair after myocardial infarction via FUS/VEGF-A axis. *Nat Commun.* 2019;10(1):4317.
411. Ju J, Li XM, Zhao XM, et al. Circular RNA FEACR inhibits ferroptosis and alleviates myocardial ischemia/reperfusion injury by interacting with NAMPT. *J Biomed Sci.* 2023;30(1):45.
412. Li XX, Mu B, Li X, Bie ZD. circCELF1 Inhibits Myocardial Fibrosis by Regulating the Expression of DKK2 Through FTO/m(6)A and miR-636. *J Cardiovasc Transl Res.* 2022;15(5):998-1009.
413. Zhu Y, Pan W, Yang T, et al. Upregulation of circular RNA CircNFIB attenuates cardiac fibrosis by sponging miR-433. *Front Genet.* 2019;10:564.
414. Zhou LY, Zhai M, Huang Y, et al. The circular RNA ACR attenuates myocardial ischemia/reperfusion injury by suppressing autophagy via modulation of the Pink1/FAM65B pathway. *Cell Death Differ.* 2019;26(7):1299-1315.
415. Sun G, Shen JF, Wei XF, Qi GX. Circular RNA Foxo3 relieves myocardial ischemia/reperfusion injury by suppressing autophagy via inhibiting HMGB1 by repressing KAT7 in myocardial infarction. *J Inflamm Res.* 2021;14:6397-6407.
416. Wang K, Gan TY, Li N, et al. Circular RNA mediates cardiomyocyte death via miRNA-dependent upregulation of MTP18 expression. *Cell Death Differ.* 2017;24(6):1111-1120.
417. Zhao B, Li G, Peng J, et al. CircMACF1 attenuates acute myocardial infarction through miR-500b-5p-EMP1 axis. *J Cardiovasc Transl Res.* 2021;14(1):161-172.
418. Wei G, Li C, Jia X, et al. Extracellular vesicle-derived CircWhsc1 promotes cardiomyocyte proliferation and heart repair by activating TRIM59/STAT3/Cyclin B2 pathway. *J Adv Res.* 2023;53:199-218.
419. Yu L, Liang Y, Zhang M, Yang PC, Hinek A, Mao S. Extracellular vesicle-derived circCEBPZOS attenuates postmyocardial infarction remodeling by promoting angiogenesis via the miR-1178-3p/PDPK1 axis. *Commun Biol.* 2023;6(1):133.
420. Fan M, Liang T, Xie F, Ma P, Li J. Exosomal circ_HIPK3 reduces apoptosis in H2O2-induced AC16 cardiomyocytes through miR-33a-5p/IRS1 axis. *Transpl Immunol.* 2023;80:101862.
421. Chen S, Sun L, Hao M, Liu X. Circ-SWT1 ameliorates H(2)O(2)-induced apoptosis, oxidative stress and endoplasmic reticulum stress in cardiomyocytes via miR-192-5p/SOD2 axis. *Cardiovasc Toxicol.* 2022;22(4):378-389.
422. Feng Y, Yan B, Cheng H, et al. Knockdown circ_0040414 inhibits inflammation, apoptosis and promotes the proliferation of cardiomyocytes via miR-186-5p/PTEN/AKT axis in chronic heart failure. *Cell Biol Int.* 2021;45(11):2304-2315.
423. Sun Y, Jiang X, Lv Y, et al. Circular RNA expression profiles in plasma from patients with heart failure related to platelet activity. *Biomolecules.* 2020;10(2):187.
424. Han J, Zhang L, Hu L, et al. Circular RNA-expression profiling reveals a potential role of Hsa_circ_0097435 in heart failure via sponging multiple MicroRNAs. *Front Genet.* 2020;11:212.
425. Guo J, Chen LW, Huang ZQ, et al. Suppression of the inhibitory effect of circ_0036176-translated Myo9a-208 on cardiac fibroblast proliferation by miR-218-5p. *J Cardiovasc Transl Res.* 2022;15(3):548-559.
426. Zhu Y, Zheng C, Zhang R, et al. Circ-Ddx60 contributes to the antihypertrophic memory of exercise hypertrophic preconditioning. *J Adv Res.* 2023;46:113-121.
427. Wang Y, Wang H, Zhang L, Zhang J, Liu N, Zhao P. A novel identified circular RNA, circSnap47, promotes heart failure progression via regulation of miR-223-3p/MAPK axis. *Mol Cell Biochem.* 2023;478(3):459-469.
428. Yan J, Ai C, Chen Q, et al. CircMap4k2 reactivated by aneurysm plication alleviates residual cardiac remodeling after SVR by enhancing cardiomyocyte proliferation in post-MI mice. *J Adv Res.* 2023.
429. Hu Y, Cao H, Sheng J, et al. The functional role of circRNA CHRC through miR-431-5p/KLF15 signaling axis in the progression of heart failure. *J Genet Genomics.* 2024.
430. Li B, Bai WW, Guo T, et al. Statins improve cardiac endothelial function to prevent heart failure with preserved ejection fraction through upregulating circRNA-RBCK1. *Nat Commun.* 2024;15(1):2953.
431. Wang K, Long B, Liu F, et al. A circular RNA protects the heart from pathological hypertrophy and heart failure by targeting miR-223. *Eur Heart J.* 2016;37(33):2602-2011.
432. Zuo H, Li L, Wang X, et al. A novel circ_0018553 protects against angiotensin-induced cardiac hypertrophy in cardiomyocytes by modulating the miR-4731/SIRT2 signaling pathway. *Hypertens Res.* 2023;46(2):421-436.
433. Zhu X, Tang X, Chong H, et al. Expression profiles of circular RNA in human atrial fibrillation with valvular heart diseases. *Front Cardiovasc Med.* 2020;7:597932.
434. Wu N, Li C, Xu B, et al. Circular RNA mmu_circ_0005019 inhibits fibrosis of cardiac fibroblasts and reverses electrical remodeling of cardiomyocytes. *BMC Cardiovasc Disorders.* 2021;21(1):308.
435. Li J, Jiang R, Hou Y, Lin A. Mesenchymal stem cells-derived exosomes prevent sepsis-induced myocardial injury by a CircRTN4/miR-497-5p/MG53 pathway. *Biochem Biophys Res Commun.* 2022;618:133-140.
436. Zuk A, Bonventre JV. Acute kidney injury. *Annu Rev Med.* 2016;67:293-307.

437. Yu Z, Zhou Y, Zhang Y, et al. Cell profiling of acute kidney injury to chronic kidney disease reveals novel oxidative stress characteristics in the failed repair of proximal tubule cells. *Int J Mol Sci.* 2023;24(14):11617.
438. Nelson RG, Grams ME, Ballew SH, et al. Development of risk prediction equations for incident chronic kidney disease. *JAMA.* 2019;322(21):2104-2114.
439. Kuang F, Wang B, You T, et al. circ_0001818 targets mir-136-5P to increase lipopolysaccharide-induced HK2 cell injuries by activating TXNIP/NLRP3 inflammasome pathway. *Shock.* 2023;60(1):110-120.
440. Li H, Zhang X, Wang P, Zhou X, Liang H, Li C. Knockdown of circ-FANCA alleviates LPS-induced HK2 cell injury via targeting miR-93-5p/OXSR1 axis in septic acute kidney injury. *Diabetol Metab Syndr.* 2021;13(1):7.
441. Kölling M, Haddad G, Wegmann U, et al. Circular RNAs in urine of kidney transplant patients with acute T cell-mediated allograft rejection. *Clin Chem.* 2019;65(10):1287-1294.
442. Yang B, Wang J, Qiao J, et al. Circ DENND4C inhibits pyroptosis and alleviates ischemia-reperfusion acute kidney injury by exosomes secreted from human urine-derived stem cells. *Chem Biol Interact.* 2024;391:110922.
443. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. *Lancet.* 2018;392(10141):61-74.
444. Lee JM, Kronbichler A, Shin JJ, Oh J. Current understandings in treating children with steroid-resistant nephrotic syndrome. *Pediatr Nephrol.* 2021;36(4):747-761.
445. Kodner C. Nephrotic syndrome in adults: diagnosis and management. *Am Fam Physician.* 2009;80(10):1129-1134.
446. Nawata A, Hisano S, Shimajiri S, Wang KY, Tanaka Y, Nakayama T. Podocyte and endothelial cell injury lead to nephrotic syndrome in proliferative lupus nephritis. *Histopathology.* 2018;72(7):1084-1092.
447. Fu W, Liu Y, Liu F, et al. A novel autoantibody induced by bacterial biofilm conserved components aggravates lupus nephritis. *Front Immunol.* 2021;12:656090.
448. Menke J, Amann K, Cavagna L, et al. Colony-stimulating factor-1: a potential biomarker for lupus nephritis. *J Am Soc Nephrol.* 2015;26(2):379-389.
449. Zhang W, Tang Z, Shi Y, et al. Association between gamma-glutamyl transferase, total bilirubin and systemic lupus erythematosus in Chinese women. *Front Immunol.* 2021;12:682400.
450. Mohan C, Putterman C. Genetics and pathogenesis of systemic lupus erythematosus and lupus nephritis. *Nat Rev Nephrol.* 2015;11(6):329-341.
451. Miao X, Tian Y, Wu L, et al. CircRTN4 aggravates mesangial cell dysfunction by activating the miR-513a-5p/FN axis in lupus nephritis. *Lab Invest.* 2022;102(9):966-978.
452. Ouyang Q, Huang Q, Jiang Z, Zhao J, Shi GP, Yang M. Using plasma circRNA_002453 as a novel biomarker in the diagnosis of lupus nephritis. *Mol Immunol.* 2018;101:531-538.
453. Zhang C, Gao C, Di X, et al. Hsa_circ_0123190 acts as a competitive endogenous RNA to regulate APLNR expression by sponging hsa-miR-483-3p in lupus nephritis. *Arthritis Res Ther.* 2021;23(1):24.
454. Luan J, Jiao C, Ma C, et al. circMTND5 participates in renal mitochondrial injury and fibrosis by sponging MIR6812 in lupus nephritis. *Oxid Med Cell Longev.* 2022;2022:2769487.
455. Li Q, Xu M, Zhang Z, Yin M, Zhang Y, Liu F. Urinary exosomal hsa_circ_0001250 as a novel diagnostic biomarker of idiopathic membranous nephropathy. *J Transl Med.* 2022;20(1):607.
456. Sun Z, Xu Q, Ma Y, Yang S, Shi J. Circ_0000524/miR-500a-5p/CXCL16 axis promotes podocyte apoptosis in membranous nephropathy. *Eur J Clin Invest.* 2021;51(3):e13414.
457. Qiu D, Zhao N, Chen Q, Wang M. Knockdown of circ_CDYL contributes to inhibit angiotensin II-induced podocytes apoptosis in membranous nephropathy via the miR-149-5p/TNFSF11 pathway. *J Cardiovasc Pharmacol.* 2022;79(6):887-895.
458. Cui X, Fu J, Luan J, et al. CircZNF609 is involved in the pathogenesis of focal segmental glomerulosclerosis by sponging miR-615-5p. *Biochem Biophys Res Commun.* 2020;531(3):341-349.
459. van Delft MAM, Huizinga TWJ. An overview of autoantibodies in rheumatoid arthritis. *J Autoimmun.* 2020;110:102392.
460. Wang J, Yan S, Yang J, Lu H, Xu D, Wang Z. Non-coding RNAs in rheumatoid arthritis: from bench to bedside. *Front Immunol.* 2019;10:3129.
461. Wang Y, Huang Y, Cheng C, et al. Dysregulation of circRNAs in rheumatoid arthritis, with special emphasis on circRNAs secreted by exosomes and the crosstalk between circRNAs and RNA methylations. *Int Immunopharmacol.* 2023;122:110549.
462. Ouyang Q, Wu J, Jiang Z, et al. Microarray expression profile of circular RNAs in peripheral blood mononuclear cells from rheumatoid arthritis patients. *Cell Physiol Biochem.* 2017;42(2):651-659.
463. Hao J, Chen Y, Yu Y. Circular RNA circ_0008360 inhibits the proliferation, migration, and inflammation and promotes apoptosis of fibroblast-like synoviocytes by regulating miR-135b-5p/HDAC4 Axis in rheumatoid arthritis. *Inflammation.* 2022;45(1):196-211.
464. Geng X, Zhao C, Zhang Z, Liu Y, Zhang X, Ding P. Circ_0088036 facilitates the proliferation and inflammation and inhibits the apoptosis of fibroblast-like synoviocytes through targeting miR-326/FZD4 axis in rheumatoid arthritis. *Autoimmunity.* 2022;55(3):157-167.
465. Zhong S, Ouyang Q, Zhu D, et al. Hsa_circ_0088036 promotes the proliferation and migration of fibroblast-like synoviocytes by sponging miR-140-3p and upregulating SIRT1 expression in rheumatoid arthritis. *Mol Immunol.* 2020;125:131-139.
466. Zhao P, Ma G, Ma L. Circ_0000479 promotes proliferation, invasion, migration and inflammation and inhibits apoptosis of rheumatoid arthritis fibroblast-like synoviocytes via miR-766/FKBP5 axis. *J Orthop Surg Res.* 2023;18(1):220.
467. Yang C, Ni B, Li C, et al. circRNA_17725 promotes macrophage polarization towards M2 by targeting FAM46C to alleviate arthritis. *Mediat Inflamm.* 2023;2023:6818524.
468. Wang X, Zhou D, Zhou W, et al. Clematichinenoside AR inhibits the pathology of rheumatoid arthritis by blocking the circPTN/miR-145-5p/FZD4 signal axis. *Int Immunopharmacol.* 2022;113(Pt A):109376.
469. Peng Y, Zhang M, Hu J. Non-coding RNAs involved in fibroblast-like synoviocyte functioning in arthritis rheumatoid: from pathogenesis to therapy. *Cytokine.* 2024;173:156418.
470. Yang Y, Lin S, Yang Z, Huang Y, Zhan F. Circ_0001947 promotes cell proliferation, invasion, migration and inflammation and inhibits apoptosis in human rheumatoid arthritis

- fibroblast-like synoviocytes through miR-671-5p/STAT3 axis. *J Orthop Surg Res.* 2022;17(1):54.
471. Lu JZ, Yang J, Zhou ST, Xie KL. Circ_0002984 promotes proliferation, migration and inflammatory cytokine secretion and inhibits apoptosis of rheumatoid arthritis fibroblast-like synoviocytes by inducing PCSK6 through miR-543. *J Orthop Surg Res.* 2023;18(1):335.
 472. Qu W, Jiang L, Hou G. Circ-AFF2/miR-650/CNP axis promotes proliferation, inflammatory response, migration, and invasion of rheumatoid arthritis synovial fibroblasts. *J Orthop Surg Res.* 2021;16(1):165.
 473. Luo Z, Chen S, Chen X. CircMAPK9 promotes the progression of fibroblast-like synoviocytes in rheumatoid arthritis via the miR-140-3p/PPM1A axis. *J Orthop Surg Res.* 2021;16(1):395.
 474. Zhang S, Zhao J, Ma W. Circ-Sirt1 inhibits proliferation, induces apoptosis, and ameliorates inflammation in human rheumatoid arthritis fibroblast-like synoviocytes. *Autoimmunity.* 2021;54(8):514-525.
 475. Zhang S, Shen Z, Chao G, et al. Circ_0004712 silencing suppresses the aggressive changes of rheumatoid arthritis fibroblast-like synoviocytes by targeting miR-633/TRAF6 Axis. *Biochem Genet.* 2023;61(2):521-537.
 476. Wang R, Li H, Han Y, Li L. Knockdown of circ_0025908 inhibits proliferation, migration, invasion, and inflammation while stimulates apoptosis in fibroblast-like synoviocytes by regulating miR-650-dependent SCUBE2. *Autoimmunity.* 2022;55(7):473-484.
 477. Zuo Y, Xu H, Li Y, Zhang Z, Tao R, Wang M. Hsa_circ_0007707 participates in PDE3B-mediated apoptosis inhibition and inflammation promotion in fibroblast-like synoviocytes. *Int Immunopharmacol.* 2023;119:110157.
 478. Feng L, Jing W, Jin S, Wang B. Circ_0088194 regulates proliferation, migration, apoptosis, and inflammation by miR-30a-3p/ADAM10 axis in rheumatoid arthritis fibroblastic synovial cells. *Inflammation.* 2023;46(1):161-174.
 479. Chen L, Huang H, Chen L, Xu L, Chen J, Lu Q. circ-PTTG1IP/miR-671-5p/TLR4 axis regulates proliferation, migration, invasion and inflammatory response of fibroblast-like synoviocytes in rheumatoid arthritis. *Gen Physiol Biophys.* 2021;40(3):207-219.
 480. Xu Y, Zai Z, Lu Z, et al. Circular RNA CircCDKN2B-AS_006 promotes the tumor-like growth and metastasis of rheumatoid arthritis synovial fibroblasts by targeting the miR-1258/RUNX1 Axis. *Int J Mol Sci.* 2023;24(6):5880.
 481. Li G, Fang Y, Xu N, Ding Y, Liu D. Fibroblast-like synoviocytes-derived exosomal circFTO deteriorates rheumatoid arthritis by enhancing N6-methyladenosine modification of SOX9 in chondrocytes. *Arthritis Res Ther.* 2024;26(1):56.
 482. Zhang J, Zhang Y, Ma Y, Luo L, Chu M, Zhang Z. Therapeutic potential of exosomal circRNA derived from synovial mesenchymal cells via targeting circEDIL3/miR-485-3p/PIAS3/STAT3/VEGF functional module in rheumatoid arthritis. *Int J Nanomedicine.* 2021;16:7977-7994.
 483. Chang L, Kan L. Mesenchymal stem cell-originated exosomal circular RNA circFBXW7 attenuates cell proliferation, migration and inflammation of fibroblast-like synoviocytes by targeting miR-216a-3p/HDAC4 in rheumatoid arthritis. *J Inflamm Res.* 2021;14:6157-6171.
 484. Xue Q, Huang Y, Chang J, et al. CircRNA-mediated ceRNA mechanism in OA: special emphasis on circRNAs in exosomes and the crosstalk of circRNAs and RNA methylation. *Biochem Pharmacol.* 2023;212:115580.
 485. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol.* 2014;28(1):5-15.
 486. Zhang Y, Liu L, Liu K, Wang M, Su X, Wang J. Regulatory mechanism of circular RNA involvement in osteoarthritis. *Frontiers in surgery.* 2022;9:1049513.
 487. Lin S, Li H, Wu B, et al. TGF-beta1 regulates chondrocyte proliferation and extracellular matrix synthesis via circPhf21a-Vegfa axis in osteoarthritis. *Cell Commun Signal.* 2022;20(1):75.
 488. Wang Z, Rao Z, Wang X, Jiang C, Yang Y. circPhc3 sponging microRNA-93-3p is involved in the regulation of chondrocyte function by mechanical instability in osteoarthritis. *Int J Mol Med.* 2022;49(1):6.
 489. Feng X, Xiang Q, Jia J, et al. CircHGF suppressed cell proliferation and osteogenic differentiation of BMSCs in ONFH via inhibiting miR-25-3p binding to SMAD7. *Mol Ther Nucleic Acids.* 2022;28:99-113.
 490. Li B, Ding T, Chen H, et al. CircStrn3 targeting microRNA-9-5p is involved in the regulation of cartilage degeneration and subchondral bone remodelling in osteoarthritis. *Bone Joint Res.* 2023;12(1):33-45.
 491. Shuai S, Cai Q, Ou Y. Circular RNA circ_0008365 regulates SOX9 by targeting miR-338-3p to inhibit IL-1 β -induced chondrocyte apoptosis and extracellular matrix degradation. *J Orthop Surg Res.* 2022;17(1):452.
 492. Zhang L, Sui C, Zhang Y, Wang G, Yin Z. Knockdown of hsa_circ_0134111 alleviates the symptom of osteoarthritis via sponging microRNA-224-5p. *Cell Cycle.* 2021;20(11):1052-1066.
 493. Li Z, Meng D, Liu Y, et al. Circular RNA VMA21 ameliorates IL-1 β -engendered chondrocyte injury through the miR-495-3p/FBWX7 signaling axis. *Clin Immunol.* 2022;238:108995.
 494. Liu W, Yang H, Feng X, Song J, Zhong W. Circular RNA circCTNNA1 is downregulated in osteoarthritis and sponges miR-29a to suppress LPS-induced apoptosis of synoviocytes. *Immunopharmacol Immunotoxicol.* 2022;44(1):1-6.
 495. Zhang J, Cheng F, Rong G, Tang Z, Gui B. Circular RNA hsa_circ_0005567 overexpression promotes M2 type macrophage polarization through miR-492/SOCS2 axis to inhibit osteoarthritis progression. *Bioengineered.* 2021;12(1):8920-8930.
 496. Man G, Yang H, Shen K, et al. Circular RNA RHOT1 regulates miR-142-5p/CCND1 to participate in chondrocyte autophagy and proliferation in osteoarthritis. *J Immunol Res.* 2022;2022:4370873.
 497. Yang Y, Shen P, Yao T, et al. Novel role of circRSU1 in the progression of osteoarthritis by adjusting oxidative stress. *Theranostics.* 2021;11(4):1877-1900.
 498. Wu X, Bian B, Lin Z, et al. Identification of exosomal mRNA, lncRNA and circRNA signatures in an osteoarthritis synovial fluid-exosomal study. *Exp Cell Res.* 2022;410(1):112881.
 499. Chen J, Yu X, Zhang X. Advances on biological functions of exosomal non-coding RNAs in osteoarthritis. *Cell Biochem Funct.* 2022;40(1):49-59.
 500. Guo Z, Wang H, Zhao F, et al. Exosomal circ-BRWD1 contributes to osteoarthritis development through the modulation of miR-1277/TRAF6 axis. *Arthritis Res Ther.* 2021;23(1):159.

501. Mao G, Xu Y, Long D, et al. Exosome-transported circRNA_0001236 enhances chondrogenesis and suppress cartilage degradation via the miR-3677-3p/Sox9 axis. *Stem Cell Res Ther.* 2021;12(1):389.
502. Tao SC, Huang JY, Gao Y, et al. Small extracellular vesicles in combination with sleep-related circRNA3503: A targeted therapeutic agent with injectable thermosensitive hydrogel to prevent osteoarthritis. *Bioactive Mater.* 2021;6(12):4455-4469.
503. Mao X, Cao Y, Guo Z, Wang L, Xiang C. Biological roles and therapeutic potential of circular RNAs in osteoarthritis. *Mol Ther Nucleic Acids.* 2021;24:856-867.
504. Shen S, Wu Y, Chen J, et al. CircSERPINE2 protects against osteoarthritis by targeting miR-1271 and ETS-related gene. *Ann Rheum Dis.* 2019;78(6):826-836.
505. Wu Y, Hong Z, Xu W, et al. Circular RNA circPDE4D protects against osteoarthritis by binding to miR-103a-3p and regulating FGF18. *Mol Ther.* 2021;29(1):308-323.
506. Shen P, Yang Y, Liu G, et al. CircCDK14 protects against Osteoarthritis by sponging miR-125a-5p and promoting the expression of Smad2. *Theranostics.* 2020;10(20):9113-9131.
507. Zhou Z, Ma J, Lu J, Chen A, Zhu L. Circular RNA CircCDH13 contributes to the pathogenesis of osteoarthritis via CircCDH13/miR-296-3p/PTEN axis. *J Cell Physiol.* 2021;236(5):3521-3535.
508. Thorlacius GE, Bjork A, Wahren-Herlenius M. Genetics and epigenetics of primary Sjogren syndrome: implications for future therapies. *Nat Rev Rheumatol.* 2023;19(5):288-306.
509. Huang Y, Li R, Ye S, Lin S, Yin G, Xie Q. Recent advances in the use of exosomes in Sjögren's Syndrome. *Front Immunol.* 2020;11:1509.
510. Li F, Liu Z, Zhang B, et al. Circular RNA sequencing indicates circ-IQGAP2 and circ-ZC3H6 as noninvasive biomarkers of primary Sjögren's syndrome. *Rheumatology (Oxford).* 2020;59(9):2603-2615.
511. Ji W, Lu Y, Ma Z, et al. Triptolide attenuates inhibition of ankylosing spondylitis-derived mesenchymal stem cells on the osteoclastogenesis through modulating exosomal transfer of circ-0110634. *J Orthopaedic Transl.* 2022;36:132-144.
512. Ogata K, Katagiri W, Hibi H. Secretomes from mesenchymal stem cells participate in the regulation of osteoclastogenesis in vitro. *Clin Oral Investig.* 2017;21(6):1979-1988.
513. Luo Q, Liu J, Fu B, et al. Circular RNAs Hsa_circ_0002715 and Hsa_circ_0035197 in peripheral blood are novel potential biomarkers for new-onset rheumatoid arthritis. *Dis Markers.* 2019;2019:2073139.
514. Zhang L, Qu L, Zhang Y, Xu Z, Tang H. Differential expression of circular RNAs in plasma exosomes from patients with ankylosing spondylitis. *Cell Biol Int.* 2022;46(4):649-659.
515. Wang S, Chen F, Zeng C, et al. RNA sequencing reveals the expression profiles of circRNAs and indicates Hsa_circ_0070562 as a pro-osteogenic factor in bone marrow-derived mesenchymal stem cells of patients with ankylosing spondylitis. *Front Genet.* 2022;13:947120.
516. Dong Q, Han Z, Tian L. Identification of serum exosome-derived circRNA-miRNA-TF-mRNA regulatory network in postmenopausal osteoporosis using bioinformatics analysis and validation in peripheral blood-derived mononuclear cells. *Front Endocrinol.* 2022;13:899503.
517. Zheng ZG, Cheng HM, Zhou YP, et al. Dual targeting of SREBP2 and ERRalpha by carnosic acid suppresses RANKL-mediated osteoclastogenesis and prevents ovariectomy-induced bone loss. *Cell Death Differ.* 2020;27(7):2048-2065.
518. Chen Z, Lin W, Zhao S, et al. Identification of circRNA expression profiles in BMSCs from glucocorticoid-induced osteoporosis model. *Stem Cells Int.* 2022;2022:3249737.
519. Yu L, Liu Y. circRNA_0016624 could sponge miR-98 to regulate BMP2 expression in postmenopausal osteoporosis. *Biochem Biophys Res Commun.* 2019;516(2):546-550.
520. Liu S, Wang C, Bai J, et al. Involvement of circRNA_0007059 in the regulation of postmenopausal osteoporosis by promoting the microRNA-378/BMP-2 axis. *Cell Biol Int.* 2021;45(2):447-455.
521. Qiao L, Li CG, Liu D. CircRNA_0048211 protects postmenopausal osteoporosis through targeting miRNA-93-5p to regulate BMP2. *Eur Rev Med Pharmacol Sci.* 2020;24(7):3459-3466.
522. Wang H, Zhou K, Xiao F, et al. Identification of circRNA-associated ceRNA network in BMSCs of OVX models for postmenopausal osteoporosis. *Sci Rep.* 2020;10(1):10896.
523. Pan X, Cen X, Zhang B, et al. Circular RNAs as potential regulators in bone remodeling: a narrative review. *Ann Transl Med.* 2021;9(19):1505.
524. Chen W, Zhang B, Chang X. Emerging roles of circular RNAs in osteoporosis. *J Cell Mol Med.* 2021;25(19):9089-9101.
525. Huang Y, Xie J, Li E. Comprehensive circular RNA profiling reveals circ_0002060 as a potential diagnostic biomarkers for osteoporosis. *J Cell Biochem.* 2019;120(9):15688-15694.
526. Shen W, Sun B, Zhou C, Ming W, Zhang S, Wu X. Circ-FOXP1/FOXP1 promotes osteogenic differentiation in adipose-derived mesenchymal stem cells and bone regeneration in osteoporosis via miR-33a-5p. *J Cell Mol Med.* 2020;24(21):12513-12524.
527. Schunk SJ, Floege J, Fliser D, Speer T. WNT-beta-catenin signalling - a versatile player in kidney injury and repair. *Nat Rev Nephrol.* 2021;17(3):172-184.
528. Louis C, Coulouarn C. One stone, two birds: circACTN4, a nexus for a coordinated activation of Hippo and Wnt/beta-catenin pathways in cholangiocarcinoma. *J Hepatol.* 2022;76(1):8-10.
529. Meng J, Chen S, Han JX, et al. Twist1 regulates vimentin through Cul2 circular RNA to promote EMT in hepatocellular carcinoma. *Cancer Res.* 2018;78(15):4150-4162.
530. Yang Z, Xie L, Han L, et al. Circular RNAs: regulators of cancer-related signaling pathways and potential diagnostic biomarkers for human cancers. *Theranostics.* 2017;7(12):3106-3117.
531. Jiang M, Fang S, Zhao X, Zhou C, Gong Z. Epithelial-mesenchymal transition-related circular RNAs in lung carcinoma. *Cancer Biol Med.* 2021;18(2):411-420.
532. Cui W, Dai J, Ma J, Gu H. circCDYL/microRNA-105-5p participates in modulating growth and migration of colon cancer cells. *Gen Physiol Biophys.* 2019;38(6):485-495.
533. Tu FL, Guo XQ, Wu HX, et al. Circ-0001313/miRNA-510-5p/AKT2 axis promotes the development and progression of colon cancer. *Am J Transl Res.* 2020;12(1):281-291.
534. Wu M, Kong C, Cai M, et al. Hsa_circRNA_002144 promotes growth and metastasis of colorectal cancer through

- regulating miR-615-5p/LARP1/mTOR pathway. *Carcinogenesis*. 2021;42(4):601-610.
535. Jiang T, Wang H, Liu L, et al. CircIL4R activates the PI3K/AKT signaling pathway via the miR-761/TRIM29/PHLPP1 axis and promotes proliferation and metastasis in colorectal cancer. *Mol Cancer*. 2021;20(1):167.
 536. Zhang X, Wang S, Wang H, et al. Circular RNA circNRIP1 acts as a microRNA-149-5p sponge to promote gastric cancer progression via the AKT1/mTOR pathway. *Mol Cancer*. 2019;18(1):20.
 537. Qiu BQ, Zhang PF, Xiong D, et al. CircRNA fibroblast growth factor receptor 3 promotes tumor progression in non-small cell lung cancer by regulating Galectin-1-AKT/ERK1/2 signaling. *J Cell Physiol*. 2019;234(7):11256-11264.
 538. Huang XY, Huang ZL, Zhang PB, et al. CircRNA-100338 is associated with mTOR signaling pathway and poor prognosis in hepatocellular carcinoma. *Front Oncol*. 2019;9:392.
 539. Shi F, Shi Z, Zhao Y, Tian J. CircRNA hsa-circ-0014359 promotes glioma progression by regulating miR-153/PI3K signaling. *Biochem Biophys Res Commun*. 2019;510(4):614-620.
 540. Zhang L, Zhou Q, Qiu Q, et al. CircPLEKHM3 acts as a tumor suppressor through regulation of the miR-9/BRCA1/DNAJB6/KLF4/AKT1 axis in ovarian cancer. *Mol Cancer*. 2019;18(1):144.
 541. Guo XY, Liu TT, Zhu WJ, et al. CircKDM4B suppresses breast cancer progression via the miR-675/NEDD4L axis. *Oncogene*. 2022;41(13):1895-1906.
 542. Tang J, Zhang C, Huang Y, et al. CircRNA circ_0124554 blocked the ubiquitination of AKT promoting the skip lymphovascular invasion on hepatic metastasis in colorectal cancer. *Cell Death Dis*. 2021;12(3):270.
 543. Wang H, Yan X, Zhang H, Zhan X. CircRNA circ_0067934 overexpression correlates with poor prognosis and promotes thyroid carcinoma progression. *Med Sci Monit*. 2019;25:1342-1349.
 544. Su W, Wang Y, Wang F, et al. Circular RNA hsa_circ_0007059 indicates prognosis and influences malignant behavior via AKT/mTOR in oral squamous cell carcinoma. *J Cell Physiol*. 2019;234(9):15156-15166.
 545. Shi X, Yang J, Liu M, et al. Circular RNA ANAPC7 inhibits tumor growth and muscle wasting via PHLPP2-AKT-TGF-beta signaling axis in pancreatic cancer. *Gastroenterology*. 2022;162(7):2004-2017. e2.
 546. Geng Y, Zheng X, Hu W, et al. Hsa_circ_0009361 acts as the sponge of miR-582 to suppress colorectal cancer progression by regulating APC2 expression. *Clin Sci (Lond)*. 2019;133(10):1197-1213.
 547. Liang WC, Wong CW, Liang PP, et al. Translation of the circular RNA circbeta-catenin promotes liver cancer cell growth through activation of the Wnt pathway. *Genome Biol*. 2019;20(1):84.
 548. Chen X, Chen RX, Wei WS, et al. PRMT5 circular RNA promotes metastasis of urothelial carcinoma of the bladder through sponging miR-30c to induce epithelial-mesenchymal transition. *Clin Cancer Res*. 2018;24(24):6319-6330.
 549. Zhao CX, Yan ZX, Wen JJ, et al. CircEAF2 counteracts Epstein-Barr virus-positive diffuse large B-cell lymphoma progression via miR-BART19-3p/APC/beta-catenin axis. *Mol Cancer*. 2021;20(1):153.
 550. Wo D, Peng J, Ren DN, et al. Opposing roles of Wnt inhibitors IGFBP-4 and Dkk1 in cardiac ischemia by differential targeting of LRP5/6 and beta-catenin. *Circulation*. 2016;134(24):1991-2007.
 551. Fang G, Ye BL, Hu BR, Ruan XJ, Shi YX. CircRNA_100290 promotes colorectal cancer progression through miR-516b-induced downregulation of FZD4 expression and Wnt/beta-catenin signaling. *Biochem Biophys Res Commun*. 2018;504(1):184-189.
 552. Chen Z, Duan X. hsa_circ_0000177-miR-638-FZD7-Wnt signaling cascade contributes to the malignant behaviors in glioma. *DNA Cell Biol*. 2018;37(9):791-797.
 553. Jin Y, Yu LL, Zhang B, Liu CF, Chen Y. Circular RNA hsa_circ_0000523 regulates the proliferation and apoptosis of colorectal cancer cells as miRNA sponge. *Braz J Med Biol Res*. 2018;51(12):e7811.
 554. Wang Z, Sun A, Yan A, et al. Circular RNA MTCL1 promotes advanced laryngeal squamous cell carcinoma progression by inhibiting C1QBP ubiquitin degradation and mediating beta-catenin activation. *Mol Cancer*. 2022;21(1):92.
 555. Shen Q, He T, Yuan H. Hsa_circ_0002577 promotes endometrial carcinoma progression via regulating miR-197/CTNND1 axis and activating Wnt/beta-catenin pathway. *Cell Cycle*. 2019;18(11):1229-1240.
 556. Bi W, Huang J, Nie C, et al. CircRNA circRNA_102171 promotes papillary thyroid cancer progression through modulating CTNNBIP1-dependent activation of beta-catenin pathway. *J Exp Clin Cancer Res*. 2018;37(1):275.
 557. Peng Y, Xu Y, Zhang X, et al. A novel protein AXIN1-295aa encoded by circAXIN1 activates the Wnt/beta-catenin signaling pathway to promote gastric cancer progression. *Mol Cancer*. 2021;20(1):158.
 558. Li Y, Wang Z, Su P, et al. circ-EIF6 encodes EIF6-224aa to promote TNBC progression via stabilizing MYH9 and activating the Wnt/beta-catenin pathway. *Mol Ther*. 2022;30(1):415-430.
 559. Pan Z, Cai J, Lin J, et al. A novel protein encoded by circFNDC3B inhibits tumor progression and EMT through regulating Snail in colon cancer. *Mol Cancer*. 2020;19(1):71.
 560. Gao S, Yu Y, Liu L, Meng J, Li G. Circular RNA hsa_circ_0007059 restrains proliferation and epithelial-mesenchymal transition in lung cancer cells via inhibiting microRNA-378. *Life Sci*. 2019;233:116692.
 561. Gong LJ, Wang XY, Yao XD, Wu X, Gu WY. CircESRP1 inhibits clear cell renal cell carcinoma progression through the CTCF-mediated positive feedback loop. *Cell Death Dis*. 2021;12(11):1081.
 562. Feng H, Li F, Tang P. Circ_0000745 regulates NOTCH1-mediated cell proliferation and apoptosis in pediatric T-cell acute lymphoblastic leukemia through adsorbing miR-193b-3p. *Hematology*. 2021;26(1):885-895.
 563. Xu H, Zhang Y, Qi L, Ding L, Jiang H, Yu H. NFIX Circular RNA promotes glioma progression by regulating miR-34a-5p via Notch signaling pathway. *Front Mol Neurosci*. 2018;11:225.
 564. Yao Y, Li X, Cheng L, Wu X, Wu B. Circular RNA FAT atypical cadherin 1 (circFAT1)/microRNA-525-5p/spindle and kinetochore-associated complex subunit 1 (SKA1) axis regulates oxaliplatin resistance in breast cancer by activating the notch and Wnt signaling pathway. *Bioengineered*. 2021;12(1):4032-4043.

565. Chen Y, Li Z, Zhang M, et al. Circ-ASH2L promotes tumor progression by sponging miR-34a to regulate Notch1 in pancreatic ductal adenocarcinoma. *J Exp Clin Cancer Res.* 2019;38(1):466.
566. Wu HB, Huang SS, Lu CG, Tian SD, Chen M. CircALP2 regulates the proliferation and metastasis of colorectal cancer by targeting miR-101-3p to activate the Notch signalling pathway. *Am J Transl Res.* 2020;12(6):2554-2569.
567. Wu N, Yuan Z, Du KY, et al. Translation of yes-associated protein (YAP) was antagonized by its circular RNA via suppressing the assembly of the translation initiation machinery. *Cell Death Differ.* 2019;26(12):2758-2773.
568. Shimoda M, Moroishi T. The emerging link between the Hippo pathway and non-coding RNA. *Biol Pharm Bull.* 2020;43(1):1-10.
569. Liu Z, Huang S, Cao Y, et al. YAP1 inhibits circRNA-000425 expression and thus promotes oncogenic activities of miR-17 and miR-106. *Biochem Biophys Res Commun.* 2018;503(4):2370-2375.
570. Zhang X, Xu Y, Qian Z, et al. circRNA_104075 stimulates YAP-dependent tumorigenesis through the regulation of HNF4a and may serve as a diagnostic marker in hepatocellular carcinoma. *Cell Death Dis.* 2018;9(11):1091.
571. Shi P, Li Y, Guo Q. Circular RNA circPIP5K1A contributes to cancer stemness of osteosarcoma by miR-515-5p/YAP axis. *J Transl Med.* 2021;19(1):464.
572. An Y, Xu B, Yan G, Wang N, Yang Z, Sun M. YAP derived circ-LECRC functions as a “brake signal” to suppress hyperactivation of oncogenic YAP signalling in colorectal cancer. *Cancer Lett.* 2022;532:215589.
573. Chen C, Yuan W, Zhou Q, et al. N6-methyladenosine-induced circ1662 promotes metastasis of colorectal cancer by accelerating YAP1 nuclear localization. *Theranostics.* 2021;11(9):4298-4315.
574. Yang G, Wang X, Liu B, et al. circ-BIRC6, a circular RNA, promotes hepatocellular carcinoma progression by targeting the miR-3918/Bcl2 axis. *Cell Cycle.* 2019;18(9):976-989.
575. Lu C, Jiang W, Hui B, et al. The circ_0021977/miR-10b-5p/P21 and P53 regulatory axis suppresses proliferation, migration, and invasion in colorectal cancer. *J Cell Physiol.* 2020;235(3):2273-2285.
576. Verduci L, Ferraiuolo M, Sacconi A, et al. The oncogenic role of circPVT1 in head and neck squamous cell carcinoma is mediated through the mutant p53/YAP/TEAD transcription-competent complex. *Genome Biol.* 2017;18(1):237.
577. Xu J, Ni L, Zhao F, et al. Overexpression of hsa_circ_0002874 promotes resistance of non-small cell lung cancer to paclitaxel by modulating miR-1273f/MDM2/p53 pathway. *Aging (Albany NY).* 2021;13(4):5986-6009.
578. Liang M, Huang G, Liu Z, et al. Elevated levels of hsa_circ_006100 in gastric cancer promote cell growth and metastasis via miR-195/GPRC5A signalling. *Cell Prolif.* 2019;52(5):e12661.
579. Li S, Pei Y, Wang W, Liu F, Zheng K, Zhang X. Circular RNA 0001785 regulates the pathogenesis of osteosarcoma as a ceRNA by sponging miR-1200 to upregulate HOXB2. *Cell Cycle.* 2019;18(11):1281-1291.
580. Lou J, Hao Y, Lin K, et al. Circular RNA CDR1as disrupts the p53/MDM2 complex to inhibit gliomagenesis. *Mol Cancer.* 2020;19(1):138.
581. Vousden KH, Prives C. Blinded by the light: the growing complexity of p53. *Cell.* 2009;137(3):413-431.
582. Bizzarri AR, Cannistraro S. Direct interaction of miRNA and circRNA with the oncosuppressor p53: an intriguing perspective in cancer research. *Cancers (Basel).* 2021;13(23):6108.
583. Fang L, Du WW, Lyu J, et al. Enhanced breast cancer progression by mutant p53 is inhibited by the circular RNA circ-Ccnb1. *Cell Death Differ.* 2018;25(12):2195-2208.
584. Du WW, Yang W, Li X, et al. A circular RNA circ-DNMT1 enhances breast cancer progression by activating autophagy. *Oncogene.* 2018;37(44):5829-5842.
585. Lu C, Jiang W, Hui B, et al. The circ_0021977/miR-10b-5p/P21 and P53 regulatory axis suppresses proliferation, migration, and invasion in colorectal cancer. *J Cell Physiol.* 2020;235(3):2273-2285.
586. Zhang X, Zhao Y, Kong P, Han M, Li B. Expression of circ-cZNF609 is down-regulated in colorectal cancer tissue and promotes apoptosis in colorectal cancer cells by upregulating p53. *Med Sci Monit.* 2019;25:5977-5985.
587. Li B, Li X. Overexpression of hsa_circ_0007534 predicts unfavorable prognosis for osteosarcoma and regulates cell growth and apoptosis by affecting AKT/GSK-3beta signaling pathway. *Biomed Pharmacother.* 2018;107:860-866.
588. Jiang Y, Wang Z, Ying C, Hu J, Zeng T, Gao L. FMR1/circCHAF1A/miR-211-5p/HOXC8 feedback loop regulates proliferation and tumorigenesis via MDM2-dependent p53 signaling in GSCs. *Oncogene.* 2021;40(24):4094-4110.
589. Bai Y, Li LD, Li J, et al. A FXDY5/TGF-beta/SMAD positive feedback loop drives epithelial-to-mesenchymal transition and promotes tumor growth and metastasis in ovarian cancer. *Int J Oncol.* 2020;56(1):301-314.
590. Wang L, Tong X, Zhou Z, et al. Circular RNA hsa_circ_0008305 (circPTK2) inhibits TGF-beta-induced epithelial-mesenchymal transition and metastasis by controlling TIF1gamma in non-small cell lung cancer. *Mol Cancer.* 2018;17(1):140.
591. Zeng K, He B, Yang BB, et al. The pro-metastasis effect of circANKS1B in breast cancer. *Mol Cancer.* 2018;17(1):160.
592. Su Y, Feng W, Shi J, Chen L, Huang J, Lin T. circRIP2 accelerates bladder cancer progression via miR-1305/Tgf-beta2/smad3 pathway. *Mol Cancer.* 2020;19(1):23.
593. Yan J, Xu H. Regulation of transforming growth factor-beta1 by circANKS1B/miR-515-5p affects the metastatic potential and cisplatin resistance in oral squamous cell carcinoma. *Bioengineered.* 2021;12(2):12420-12430.
594. Zheng L, Liang H, Zhang Q, et al. circPTEN1, a circular RNA generated from PTEN, suppresses cancer progression through inhibition of TGF-beta/Smad signaling. *Mol Cancer.* 2022;21(1):41.
595. Meng L, Zheng Y, Liu S, et al. ZEB1 represses biogenesis of circ-DOCK5 to facilitate metastasis in esophageal squamous cell carcinoma via a positive feedback loop with TGF-beta. *Cancer Lett.* 2021;519:117-129.
596. Zhao W, Cui Y, Liu L, et al. Splicing factor derived circular RNA circUHRF1 accelerates oral squamous cell carcinoma tumorigenesis via feedback loop. *Cell Death Differ.* 2020;27(3):919-933.
597. Papatsirou M, Artemaki PI, Karousi P, Scorilas A, Kontos CK. Circular RNAs: emerging regulators of the major signaling pathways involved in cancer progression. *Cancers (Basel).* 2021;13(11):2744.

598. Pan BT, Teng K, Wu C, Adam M, Johnstone RM. Electron microscopic evidence for externalization of the transferrin receptor in vesicular form in sheep reticulocytes. *J Cell Biol.* 1985;101(3):942-948.
599. Simons M, Raposo G. Exosomes—vesicular carriers for intercellular communication. *Curr Opin Cell Biol.* 2009;21(4):575-581.
600. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol.* 2018;19(4):213-228.
601. Kumar P, Becker JC, Gao K, et al. Neuroprotective effect of placenta-derived mesenchymal stromal cells: role of exosomes. *FASEB J.* 2019;33(5):5836-5849.
602. Hessvik NP, Llorente A. Current knowledge on exosome biogenesis and release. *Cell Mol Life Sci.* 2018;75(2):193-208.
603. Palmulli R, van Niel G. To be or not to be... secreted as exosomes, a balance finely tuned by the mechanisms of biogenesis. *Essays Biochem.* 2018;62(2):177-191.
604. Phan J, Kumar P, Hao D, Gao K, Farmer D, Wang A. Engineering mesenchymal stem cells to improve their exosome efficacy and yield for cell-free therapy. *J Extracell Vesicles.* 2018;7(1):1522236.
605. Thakur A, Qiu G, Xu C, et al. Label-free sensing of exosomal MCT1 and CD147 for tracking metabolic reprogramming and malignant progression in glioma. *Sci Adv.* 2020;6(26):eaaz6119.
606. Gurunathan S, Kang MH, Jeyaraj M, Qasim M, Kim JH. Review of the isolation, characterization, biological function, and multifarious therapeutic approaches of exosomes. *Cells.* 2019;8(4):307.
607. Bebelman MP, Smit MJ, Pegtel DM, Baglio SR. Biogenesis and function of extracellular vesicles in cancer. *Pharmacol Ther.* 2018;188:1-11.
608. Zhou Q, Xie D, Wang R, et al. The emerging landscape of exosomal CircRNAs in solid cancers and hematological malignancies. *Biomark Res.* 2022;10(1):28.
609. Xu JL, Xu WX, Tang JH. Exosomal circRNAs: a new communication method in cancer. *Am J Transl Res.* 2021;13(11):12913-12928.
610. Vakhshiteh F, Hassani S, Momenifar N, Pakdaman F. Exosomal circRNAs: new players in colorectal cancer. *Cancer Cell Int.* 2021;21(1):483.
611. Wang S, Dong Y, Gong A, et al. Exosomal circRNAs as novel cancer biomarkers: challenges and opportunities. *Int J Biol Sci.* 2021;17(2):562-573.
612. Mao M, Zhang J, Xiang Y, Gong M, Deng Y, Ye D. Role of exosomal competitive endogenous RNA (ceRNA) in diagnosis and treatment of malignant tumors. *Bioengineered.* 2022;13(5):12156-12168.
613. Shang A, Gu C, Wang W, et al. Exosomal circPACRGL promotes progression of colorectal cancer via the miR-142-3p/miR-506-3p- TGF-beta1 axis. *Mol Cancer.* 2020;19(1):117.
614. Xie M, Yu T, Jing X, et al. Exosomal circSHKBP1 promotes gastric cancer progression via regulating the miR-582-3p/HUR/VEGF axis and suppressing HSP90 degradation. *Mol Cancer.* 2020;19(1):112.
615. Preusser C, Hung LH, Schneider T, et al. Selective release of circRNAs in platelet-derived extracellular vesicles. *J Extracell Vesicles.* 2018;7(1):1424473.
616. O'Brien K, Breyne K, Ughetto S, Laurent LC, Breakefield XO. RNA delivery by extracellular vesicles in mammalian cells and its applications. *Nat Rev Mol Cell Biol.* 2020;21(10):585-606.
617. Wang M, Yu F, Li P, Wang K. Emerging function and clinical significance of exosomal circRNAs in cancer. *Mol Ther Nucleic Acids.* 2020;21:367-383.
618. Suzuki H, Zuo Y, Wang J, Zhang MQ, Malhotra A, Mayeda A. Characterization of RNase R-digested cellular RNA source that consists of lariat and circular RNAs from pre-mRNA splicing. *Nucleic Acids Res.* 2006;34(8):e63.
619. Rybak-Wolf A, Stottmeister C, Glazar P, et al. Circular RNAs in the mammalian brain are highly abundant, conserved, and dynamically expressed. *Mol Cell.* 2015;58(5):870-885.
620. Zhang Y, Xue W, Li X, et al. The biogenesis of nascent circular RNAs. *Cell Rep.* 2016;15(3):611-624.
621. Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, Lotvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol.* 2007;9(6):654-659.
622. Skog J, Wurdinger T, van Rijn S, et al. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. *Nat Cell Biol.* 2008;10(12):1470-1476.
623. Dai X, Chen C, Yang Q, et al. Exosomal circRNA_100284 from arsenite-transformed cells, via microRNA-217 regulation of EZH2, is involved in the malignant transformation of human hepatic cells by accelerating the cell cycle and promoting cell proliferation. *Cell Death Dis.* 2018;9(5):454.
624. Su Y, Lv X, Yin W, et al. CircRNA Cdr1as functions as a competitive endogenous RNA to promote hepatocellular carcinoma progression. *Aging (Albany NY).* 2019;11(19):8183-8203.
625. Wang S, Hu Y, Lv X, et al. Circ-0000284 arouses malignant phenotype of cholangiocarcinoma cells and regulates the biological functions of peripheral cells through cellular communication. *Clin Sci (Lond).* 2019;133(18):1935-1953.
626. Chen W, Quan Y, Fan S, et al. Exosome-transmitted circular RNA hsa_circ_0051443 suppresses hepatocellular carcinoma progression. *Cancer Lett.* 2020;475:119-128.
627. Kalluri R. The biology and function of exosomes in cancer. *J Clin Invest.* 2016;126(4):1208-1215.
628. Maia J, Caja S, Strano Moraes MC, Couto N, Costa-Silva B. Exosome-based cell-cell communication in the tumor microenvironment. *Front Cell Dev Biol.* 2018;6:18.
629. Wortzel I, Dror S, Kenific CM, Lyden D. Exosome-mediated metastasis: communication from a distance. *Dev Cell.* 2019;49(3):347-360.
630. Li Z, Yanfang W, Li J, et al. Tumor-released exosomal circular RNA PDE8A promotes invasive growth via the miR-338/MACCl1/MET pathway in pancreatic cancer. *Cancer Lett.* 2018;432:237-250.
631. Lu J, Wang YH, Yoon C, et al. Circular RNA circ-RanGAP1 regulates VEGFA expression by targeting miR-877-3p to facilitate gastric cancer invasion and metastasis. *Cancer Lett.* 2020;471:38-48.
632. Wang G, Liu W, Zou Y, et al. Three isoforms of exosomal circPTGR1 promote hepatocellular carcinoma metastasis via the miR449a-MET pathway. *EBioMedicine.* 2019;40:432-445.
633. Li J, Li Z, Jiang P, et al. Circular RNA IARS (circ-IARS) secreted by pancreatic cancer cells and located within exosomes

- regulates endothelial monolayer permeability to promote tumor metastasis. *J Exp Clin Cancer Res.* 2018;37(1):177.
634. Zong ZH, Du YP, Guan X, Chen S, Zhao Y. CircWHSC1 promotes ovarian cancer progression by regulating MUC1 and hTERT through sponging miR-145 and miR-1182. *J Exp Clin Cancer Res.* 2019;38(1):437.
 635. Hon KW, Ab-Mutalib NS, Abdullah NMA, Jamal R, Abu N. Extracellular vesicle-derived circular RNAs confers chemoresistance in colorectal cancer. *Sci Rep.* 2019;9(1):16497.
 636. Wang X, Zhang H, Yang H, et al. Exosome-delivered circRNA promotes glycolysis to induce chemoresistance through the miR-122-PKM2 axis in colorectal cancer. *Mol Oncol.* 2020;14(3):539-555.
 637. Kir S, White JP, Kleiner S, et al. Tumour-derived PTH-related protein triggers adipose tissue browning and cancer cachexia. *Nature.* 2014;513(7516):100-104.
 638. Petruzzelli M, Schweiger M, Schreiber R, et al. A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. *Cell Metab.* 2014;20(3):433-447.
 639. Naeli P, Pourhanifeh MH, Karimzadeh MR, et al. Circular RNAs and gastrointestinal cancers: Epigenetic regulators with a prognostic and therapeutic role. *Crit Rev Oncol Hematol.* 2020;145:102854.
 640. Shao Y, Tao X, Lu R, et al. Hsa_circ_0065149 is an indicator for early gastric cancer screening and prognosis prediction. *Pathol Oncol Res.* 2020;26(3):1475-1482.
 641. Tao X, Shao Y, Lu R, et al. Clinical significance of hsa_circ_0000419 in gastric cancer screening and prognosis estimation. *Pathol Res Pract.* 2020;216(1):152763.
 642. Fan L, Cao Q, Liu J, Zhang J, Li B. Circular RNA profiling and its potential for esophageal squamous cell cancer diagnosis and prognosis. *Mol Cancer.* 2019;18(1):16.
 643. Pan B, Qin J, Liu X, et al. Identification of serum exosomal hsa-circ-0004771 as a novel diagnostic biomarker of colorectal cancer. *Front Genet.* 2019;10:1096.
 644. Li L, Li W, Chen N, et al. FLI1 exonic circular RNAs as a novel oncogenic driver to promote tumor metastasis in small cell lung cancer. *Clin Cancer Res.* 2019;25(4):1302-1317.
 645. Seimiya T, Otsuka M, Iwata T, et al. Aberrant expression of a novel circular RNA in pancreatic cancer. *J Hum Genet.* 2021;66(2):181-191.
 646. Harper KL, McDonnell E, Whitehouse A. CircRNAs: From anonymity to novel regulators of gene expression in cancer (Review). *Int J Oncol.* 2019;55(6):1183-1193.
 647. Wei L, Yang Y, Wang W, Xu R. Circular RNAs in the pathogenesis of sepsis and their clinical implications: A narrative review. *Ann Acad Med Singap.* 2022;51(4):221-227.
 648. Seimiya T, Otsuka M, Iwata T, et al. Emerging roles of exosomal circular RNAs in cancer. *Front Cell Dev Biol.* 2020;8:568366.
 649. Chen T, Liu Y, Li C, et al. Tumor-derived exosomal circFARSA mediates M2 macrophage polarization via the PTEN/PI3K/AKT pathway to promote non-small cell lung cancer metastasis. *Cancer Treat Res Commun.* 2021;28:100412.
 650. Hong W, Xue M, Jiang J, Zhang Y, Gao X. Circular RNA circ-CPA4/let-7 miRNA/PD-L1 axis regulates cell growth, stemness, drug resistance and immune evasion in non-small cell lung cancer (NSCLC). *J Exp Clin Cancer Res.* 2020;39(1):149.
 651. Lin S, Xiong W, Liu H, Pei L, Yi H, Guan Y. Profiling and integrated analysis of differentially expressed circular RNAs in plasma exosomes as novel biomarkers for advanced-stage lung adenocarcinoma. *Onco Targets Ther.* 2020;13:12965-12977.
 652. Yang B, Teng F, Chang L, et al. Tumor-derived exosomal circRNA_102481 contributes to EGFR-TKIs resistance via the miR-30a-5p/ROR1 axis in non-small cell lung cancer. *Aging (Albany NY).* 2021;13(9):13264-13286.
 653. Wang H, Tang Z, Duan J, Zhou C, Xu K, Mu H. Cancer-released exosomal circular RNA circ_0008717 promotes cell tumorigenicity through microRNA-1287-5p/P21-activated kinase 2 (PAK2) axis in non-small cell lung cancer. *Bioengineered.* 2022;13(4):8937-8949.
 654. Xu L, Liao WL, Lu QJ, Zhang P, Zhu J, Jiang GN. Hypoxic tumor-derived exosomal circular RNA SETDB1 promotes invasive growth and EMT via the miR-7/Sp1 axis in lung adenocarcinoma. *Mol Ther Nucleic Acids.* 2021;23:1078-1092.
 655. Chen W, Tang D, Lin J, et al. Exosomal circSHKBP1 participates in non-small cell lung cancer progression through PKM2-mediated glycolysis. *Mol Ther Oncolytics.* 2022;24:470-485.
 656. Xian J, Su W, Liu L, et al. Identification of three circular RNA cargoes in serum exosomes as diagnostic biomarkers of non-small-cell lung cancer in the Chinese population. *J Mol Diagn.* 2020;22(8):1096-1108.
 657. Wang Y, Zhang H, Wang J, Li B, Wang X. Circular RNA expression profile of lung squamous cell carcinoma: identification of potential biomarkers and therapeutic targets. *Biosci Rep.* 2020;40(4):BSR20194512.
 658. Chen F, Huang C, Wu Q, Jiang L, Chen S, Chen L. Circular RNAs expression profiles in plasma exosomes from early-stage lung adenocarcinoma and the potential biomarkers. *J Cell Biochem.* 2020;121(3):2525-2533.
 659. Li J, Zhu T, Weng Y, et al. Exosomal circDNER enhances paclitaxel resistance and tumorigenicity of lung cancer via targeting miR-139-5p/ITGB8. *Thorac Cancer.* 2022;13(9):1381-1390.
 660. He Y, Liu Y, Cha N, et al. Exosomal circ_0048856 derived from non-small cell lung cancer contributes to aggressive cancer progression through downregulation of miR-1287-5p. *Pathol Res Pract.* 2022;232:153659.
 661. Chen Y, Lou C, Ma X, et al. Serum exosomal hsa_circ_0069313 has a potential to diagnose more aggressive non-small cell lung cancer. *Clin Biochem.* 2022;102:56-64.
 662. Ning Z, Tian Y, Li Y, et al. Exosomal circ_0007385 enhances non-small cell lung cancer cell proliferation and stemness via regulating miR-1253/FAM83A axis. *Anticancer Drugs.* 2022;33(1):61-74.
 663. Shao N, Song L, Sun X. Exosomal circ_PIP5K1A regulates the progression of non-small cell lung cancer and cisplatin sensitivity by miR-101/ABCC1 axis. *Mol Cell Biochem.* 2021;476(6):2253-2267.
 664. Ding C, Xi G, Wang G, et al. Exosomal Circ-MEMO1 promotes the progression and aerobic glycolysis of non-small cell lung cancer through targeting MiR-101-3p/KRAS axis. *Front Genet.* 2020;11:962.
 665. Xu X, Tao R, Sun L, Ji X. Exosome-transferred hsa_circ_0014235 promotes DDP chemoresistance and deteriorates the development of non-small cell lung cancer by mediating the miR-520a-5p/CDK4 pathway. *Cancer Cell Int.* 2020;20(1):552.
 666. Shi Q, Ji T, Ma Z, Tan Q, Liang J. Serum exosomes-based biomarker circ_0008928 regulates cisplatin sensitivity, tumor

- progression, and glycolysis metabolism by miR-488/HK2 axis in cisplatin-resistant non-small cell lung carcinoma. *Cancer Biother Radiopharm.* 2021;38(8):558-571.
667. Ma J, Qi G, Li L. A novel serum exosomes-based biomarker hsa_circ_0002130 facilitates osimertinib-resistance in non-small cell lung cancer by sponging miR-498. *Onco Targets Ther.* 2020;13:5293-5307.
 668. Luo YH, Yang YP, Chien CS, et al. Circular RNA hsa_circ_0000190 facilitates the tumorigenesis and immune evasion by upregulating the expression of soluble PD-L1 in non-small-cell lung cancer. *Int J Mol Sci.* 2021;23(1):64.
 669. He F, Zhong X, Lin Z, et al. Plasma exo-hsa_circRNA_0056616: a potential biomarker for lymph node metastasis in lung adenocarcinoma. *J Cancer.* 2020;11(14):4037-4046.
 670. Luo YH, Yang YP, Chien CS, et al. Plasma level of circular RNA hsa_circ_0000190 correlates with tumor progression and poor treatment response in advanced lung cancers. *Cancers (Basel).* 2020;12(7):1740.
 671. Zhang N, Nan A, Chen L, et al. Circular RNA circSATB2 promotes progression of non-small cell lung cancer cells. *Mol Cancer.* 2020;19(1):101.
 672. Wang J, Zhao X, Wang Y, et al. circRNA-002178 act as a ceRNA to promote PDL1/PD1 expression in lung adenocarcinoma. *Cell Death Dis.* 2020;11(1):32.
 673. Wang R, Liu H, Dong M, Huang D, Yi J. Exosomal hsa_circ_0000519 modulates the NSCLC cell growth and metastasis via miR-1258/RHOV axis. *Open Med (Wars).* 2022;17(1):826-840.
 674. Li C, Wang G, Ma X, et al. Upregulation of exosomal circ-PLK1 promotes the development of non-small cell lung cancer through the miR-1294/high mobility group protein A1 axis. *Bioengineered.* 2022;13(2):4185-4200.
 675. Yang J, Yang C, Li P. circ-IARS depletion inhibits the progression of non-small-cell lung cancer by circ-IARS/miR-1252-5p/HDGF ceRNA pathway. *Open Med (Wars).* 2023;18(1):20220613.
 676. Chen SW, Zhu SQ, Pei X, et al. Cancer cell-derived exosomal circUSP7 induces CD8(+) T cell dysfunction and anti-PD1 resistance by regulating the miR-934/SHP2 axis in NSCLC. *Mol Cancer.* 2021;20(1):144.
 677. Xiong H, Liu B, Liu XY, et al. circ_rac GTPase-activating protein 1 facilitates stemness and metastasis of non-small cell lung cancer via polypyrimidine tract-binding protein 1 recruitment to promote sirtuin-3-mediated replication timing regulatory factor 1 deacetylation. *Lab Invest.* 2023;103(1):100010.
 678. Wang X, Wang H, Jiang H, Qiao L, Guo C. Circular RNACirc_0076305 promotes cisplatin (DDP) resistance of non-small cell lung cancer cells by regulating ABCC1 through miR-186-5p. *Cancer Biother Radiopharm.* 2023;38(5):293-304.
 679. Fang K, Chen X, Qiu F, Xu J, Xiong H, Zhang Z. Serum-derived exosomes-mediated circular RNA ARHGAP10 modulates the progression of non-small cell lung cancer through the miR-638/FAM83F axis. *Cancer Biother Radiopharm.* 2022;37(2):96-110.
 680. Xie H, Yao J, Wang Y, Ni B. Exosome-transmitted circVMP1 facilitates the progression and cisplatin resistance of non-small cell lung cancer by targeting miR-524-5p-METTL3/SOX2 axis. *Drug Deliv.* 2022;29(1):1257-1271.
 681. Peng L, Cao Y, Hu C. Identification of exosomal circRNA CD226 as a potent driver of non-small cell lung cancer through miR-1224-3p/high mobility group AT-hook 2 axis. *Anticancer Drugs.* 2022;33(10):1126-1138.
 682. Curtis D, Bandyopadhyay S. Mini-review: role of the PI3K/Akt pathway and tyrosine phosphatases in Alzheimer's disease susceptibility. *Ann Hum Genet.* 2021;85(1):1-6.
 683. Yu R, Bai H, Gao B, et al. Rare case of apatinib acquired resistance induced by point mutation of WRN p.V697F through activation of the PI3K/AKT apoptosis-inhibiting pathway. *Thorac Cancer.* 2021;12(1):128-132.
 684. Li K, Liu Y, Ding Y, et al. BCL6 is regulated by the MAPK/ELK1 axis and promotes KRAS-driven lung cancer. *J Clin Invest.* 2022;132(22):e161308.
 685. Wang Y, Zang RK, Du YN. HSA_CIRC_0004050 on proliferation and apoptosis of A549 cells through ERK/JNK signaling pathway. *J Biol Regul Homeost Agents.* 2020;34(6):2037-2047.
 686. Ma Z, Liu D, Di S, et al. Histone deacetylase 9 downregulation decreases tumor growth and promotes apoptosis in non-small cell lung cancer after melatonin treatment. *J Pineal Res.* 2019;67(2):e12587.
 687. Xiang D, Hu S, Mai T, et al. Worldwide cancer statistics of adults over 75 years old in 2019: a systematic analysis of the global burden of disease study 2019. *BMC Public Health.* 2022;22(1):1979.
 688. Singal AG, Kanwal F, Llovet JM. Global trends in hepatocellular carcinoma epidemiology: implications for screening, prevention and therapy. *Nat Rev Clin Oncol.* 2023;20(12):864-884.
 689. Wang X, Dong FL, Wang YQ, Wei HL, Li T, Li J. Exosomal circTGFB2 promotes hepatocellular carcinoma progression via enhancing ATG5 mediated protective autophagy. *Cell Death Dis.* 2023;14(7):451.
 690. Yuan P, Song J, Wang F, Chen B. Exosome-transmitted circ_002136 promotes hepatocellular carcinoma progression by miR-19a-3p/RAB1A pathway. *BMC Cancer.* 2022;22(1):1284.
 691. Wang Y, Gao R, Li J, et al. Downregulation of hsa_circ_0074854 suppresses the migration and invasion in hepatocellular carcinoma via interacting with HuR and via suppressing exosomes-mediated macrophage M2 polarization. *Int J Nanomedicine.* 2021;16:2803-2818.
 692. Zhang L, Zhang J, Li P, Li T, Zhou Z, Wu H. Exosomal hsa_circ_0004658 derived from RBPJ overexpressed-macrophages inhibits hepatocellular carcinoma progression via miR-499b-5p/JAM3. *Cell Death Dis.* 2022;13(1):32.
 693. Lyu P, Zhai Z, Hao Z, Zhang H, He J. CircWHSC1 serves as an oncogene to promote hepatocellular carcinoma progression. *Eur J Clin Invest.* 2021;51(6):e13487.
 694. Lv X, Huang H, Feng H, Wei Z. Circ-MMP2 (circ-0039411) induced by FOXM1 promotes the proliferation and migration of lung adenocarcinoma cells in vitro and in vivo. *Cell Death Dis.* 2020;11(6):426.
 695. Zhou Y, Tang W, Zhuo H, et al. Cancer-associated fibroblast exosomes promote chemoresistance to cisplatin in hepatocellular carcinoma through circZFR targeting signal transducers and activators of transcription (STAT3)/nuclear factor-kappa B (NF-kappaB) pathway. *Bioengineered.* 2022;13(3):4786-4797.

696. Xu J, Ji L, Liang Y, et al. CircRNA-SORE mediates sorafenib resistance in hepatocellular carcinoma by stabilizing YBX1. *Signal Transduct Target Ther.* 2020;5(1):298.
697. Hao X, Zhang Y, Shi X, et al. CircPAK1 promotes the progression of hepatocellular carcinoma via modulation of YAP nucleus localization by interacting with 14-3-3zeta. *J Exp Clin Cancer Res.* 2022;41(1):281.
698. Zhang PF, Gao C, Huang XY, et al. Cancer cell-derived exosomal circUHRF1 induces natural killer cell exhaustion and may cause resistance to anti-PD1 therapy in hepatocellular carcinoma. *Mol Cancer.* 2020;19(1):110.
699. Wang L, Yi X, Xiao X, Zheng Q, Ma L, Li B. Exosomal miR-628-5p from M1 polarized macrophages hinders m6A modification of circFUT8 to suppress hepatocellular carcinoma progression. *Cell Mol Biol Lett.* 2022;27(1):106.
700. Huang M, Huang X, Huang N. Exosomal circGSE1 promotes immune escape of hepatocellular carcinoma by inducing the expansion of regulatory T cells. *Cancer Sci.* 2022;113(6):1968-1983.
701. Lu JC, Zhang PF, Huang XY, et al. Amplification of spatially isolated adenosine pathway by tumor-macrophage interaction induces anti-PD1 resistance in hepatocellular carcinoma. *J Hematol Oncol.* 2021;14(1):200.
702. Hu Z, Chen G, Zhao Y, et al. Exosome-derived circCCAR1 promotes CD8 + T-cell dysfunction and anti-PD1 resistance in hepatocellular carcinoma. *Mol Cancer.* 2023;22(1):55.
703. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209-249.
704. Tang X, Peng J, Huang S, et al. Global burden of early-onset colorectal cancer among people aged 40–49 years from 1990 to 2019 and predictions to 2030. *J Cancer Res Clin Oncol.* 2023;149(18):16537-16550.
705. Weitz J, Koch M, Debus J, Hohler T, Galle PR, Buchler MW. Colorectal cancer. *Lancet.* 2005;365(9454):153-165.
706. Ghafouri I, Pakravan K, Razmara E, Montazeri M, Rouhollah F, Babashah S. Colorectal cancer-secreted exosomal circ_001422 plays a role in regulating KDR expression and activating mTOR signaling in endothelial cells by targeting miR-195-5p. *J Cancer Res Clin Oncol.* 2023;149(13):12227-12240.
707. Chen C, Liu Y, Liu L, et al. Exosomal circTUBGCP4 promotes vascular endothelial cell tipping and colorectal cancer metastasis by activating Akt signaling pathway. *J Exp Clin Cancer Res.* 2023;42(1):46.
708. Wang P, Sun Y, Yang Y, Chen Y, Liu H. Circ_0067835 knock-down enhances the radiosensitivity of colorectal cancer by miR-296-5p/IGF1R axis. *Oncotargets Ther.* 2021;14:491-502.
709. Li L, Jiang Z, Zou X, Hao T. Exosomal circ_IFT80 enhances tumorigenesis and suppresses radiosensitivity in colorectal cancer by regulating miR-296-5p/MSI1 axis. *Cancer Manag Res.* 2021;13:1929-1941.
710. Yang K, Zhang J, Bao C. Exosomal circEIF3K from cancer-associated fibroblast promotes colorectal cancer (CRC) progression via miR-214/PD-L1 axis. *BMC Cancer.* 2021;21(1):933.
711. Yang H, Zhang H, Yang Y, et al. Hypoxia induced exosomal circRNA promotes metastasis of colorectal cancer via targeting GEF-H1/RhoA axis. *Theranostics.* 2020;10(18):8211-8226.
712. Zhang Y, Tan X, Lu Y. Exosomal transfer of circ_0006174 contributes to the chemoresistance of doxorubicin in colorectal cancer by depending on the miR-1205/CCND2 axis. *J Physiol Biochem.* 2022;78(1):39-50.
713. Zhao K, Cheng X, Ye Z, et al. Exosome-mediated transfer of circ_0000338 enhances 5-fluorouracil resistance in colorectal cancer through regulating MicroRNA 217 (miR-217) and miR-485-3p. *Mol Cell Biol.* 2021;41(5):e00517.
714. Pan Z, Zheng J, Zhang J, et al. A novel protein encoded by exosomal CircATG4B induces oxaliplatin resistance in colorectal cancer by promoting autophagy. *Adv Sci (Weinh).* 2022;9(35):e2204513.
715. Zeng W, Liu Y, Li WT, Li Y, Zhu JF. CircFNDC3B sequesters miR-937-5p to derepress TIMP3 and inhibit colorectal cancer progression. *Mol Oncol.* 2020;14(11):2960-2984.
716. Jiang Z, Hou Z, Li L, Liu W, Yu Z, Chen S. Exosomal circEPB41L2 serves as a sponge for miR-21-5p and miR-942-5p to suppress colorectal cancer progression by regulating the PTEN/AKT signalling pathway. *Eur J Clin Invest.* 2021;51(9):e13581.
717. Chen C, Yu H, Han F, et al. Tumor-suppressive circRHOBTB3 is excreted out of cells via exosome to sustain colorectal cancer cell fitness. *Mol Cancer.* 2022;21(1):46.
718. Yu Q, Zhang Y, Tian Y, et al. Exosomal Circ_FMN2 derived from the serum of colorectal cancer patients promotes cancer progression by miR-338-3p/MSI1 AXIS. *Appl Biochem Biotechnol.* 2023;195(12):7322-7337.
719. Shang A, Gu C, Wang W, et al. Exosomal circPACRGL promotes progression of colorectal cancer via the miR-142-3p/miR-506-3p- TGF- β 1 axis. *Mol Cancer.* 2020;19(1):117.
720. Gao L, Tang X, He Q, Sun G, Wang C, Qu H. Exosome-transmitted circCOG2 promotes colorectal cancer progression via miR-1305/TGF- β 2/SMAD3 pathway. *Cell Death Discov.* 2021;7(1):281.
721. Han K, Wang FW, Cao CH, et al. CircLONP2 enhances colorectal carcinoma invasion and metastasis through modulating the maturation and exosomal dissemination of microRNA-17. *Mol Cancer.* 2020;19(1):60.
722. Miao Z, Zhao X, Liu X. Exosomal circCOL1A2 from cancer cells accelerates colorectal cancer progression via regulating miR-665/LASP1 signal axis. *Eur J Pharmacol.* 2023;950:175722.
723. Li Y, Li C, Xu R, Wang Y, Li D, Zhang B. A novel circFMN2 promotes tumor proliferation in CRC by regulating the miR-1182/hTERT signaling pathways. *Clin Sci (Lond).* 2019;133(24):2463-2479.
724. Li Y, Hu J, Wang M, et al. Exosomal circPABPC1 promotes colorectal cancer liver metastases by regulating HMGA2 in the nucleus and BMP4/ADAM19 in the cytoplasm. *Cell Death Discov.* 2022;8(1):335.
725. Jiang Z, Hu H, Hu W, et al. Circ-RNF121 regulates tumor progression and glucose metabolism by miR-1224-5p/FOXO1 axis in colorectal cancer. *Cancer Cell Int.* 2021;21(1):596.
726. He J, Zhao H, Liu X, et al. Sevoflurane suppresses cell viability and invasion and promotes cell apoptosis in colon cancer by modulating exosome-mediated circ-HMGCS1 via the miR-34a-5p/SGPPI1 axis. *Oncol Rep.* 2020;44(6):2429-2442.
727. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin.* 2021;71(1):7-33.

728. Hidalgo M. Pancreatic cancer. *N Engl J Med*. 2010;362(17):1605-1617.
729. Khan MA, Zubair H, Srivastava SK, Singh S, Singh AP. Insights into the role of microRNAs in pancreatic cancer pathogenesis: potential for diagnosis, prognosis, and therapy. *Adv Exp Med Biol*. 2015;889:71-87.
730. Ye ZM, Li LJ, Luo MB, et al. A systematic review and network meta-analysis of single nucleotide polymorphisms associated with pancreatic cancer risk. *Aging (Albany NY)*. 2020;12(24):25256-25274.
731. Park W, Chawla A, O'Reilly EM. Pancreatic Cancer: A Review. *JAMA*. 2021;326(9):851-862.
732. Lin J, Wang X, Zhai S, et al. Hypoxia-induced exosomal circPDK1 promotes pancreatic cancer glycolysis via c-myc activation by modulating miR-628-3p/BPTF axis and degrading BIN1. *J Hematol Oncol*. 2022;15(1):128.
733. Ye Z, Zhu Z, Xie J, et al. Hsa_circ_0000069 knockdown inhibits tumorigenesis and exosomes with downregulated hsa_circ_0000069 suppress malignant transformation via inhibition of STIL in pancreatic cancer. *Int J Nanomedicine*. 2020;15:9859-9873.
734. Zeng Z, Zhao Y, Chen Q, et al. Hypoxic exosomal HIF-1 α -stabilizing circZNF91 promotes chemoresistance of normoxic pancreatic cancer cells via enhancing glycolysis. *Oncogene*. 2021;40(36):5505-5517.
735. Gao G, Wang L, Li C. Circ_0006790 carried by bone marrow mesenchymal stem cell-derived exosomes regulates S100A11 DNA methylation through binding to CBX7 in pancreatic ductal adenocarcinoma. *Am J Cancer Res*. 2022;12(5):1934-1959.
736. Yao X, Mao Y, Wu D, et al. Exosomal circ_0030167 derived from BM-MSCs inhibits the invasion, migration, proliferation and stemness of pancreatic cancer cells by sponging miR-338-5p and targeting the Wif1/Wnt8/ β -catenin axis. *Cancer Lett*. 2021;512:38-50.
737. Wang L, Wu X, Ruan Y, Zhang X, Zhou X. Exosome-transmitted hsa_circ_0012634 suppresses pancreatic ductal adenocarcinoma progression through regulating miR-147b/HIPK2 axis. *Cancer Biol Ther*. 2023;24(1):2218514.
738. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer*. 2013;132(5):1133-1145.
739. Wang SC, Chan L, Hsieh TY, Wang CH, Chen SL, Sung WW. Limited improvement in prostate cancer mortality-to-incidence ratios in countries with high health care expenditures. *Aging (Albany NY)*. 2020;12(21):21308-21315.
740. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69-90.
741. Attard G, Parker C, Eeles RA, et al. Prostate cancer. *Lancet*. 2016;387(10013):70-82.
742. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7-30.
743. Gao F, Xu Q, Tang Z, et al. Exosomes derived from myeloid-derived suppressor cells facilitate castration-resistant prostate cancer progression via S100A9/circMID1/miR-506-3p/MID1. *J Transl Med*. 2022;20(1):346.
744. Li T, Sun X, Chen L. Exosome circ_0044516 promotes prostate cancer cell proliferation and metastasis as a potential biomarker. *J Cell Biochem*. 2020;121(3):2118-2126.
745. Zhang H, Li M, Zhang J, Shen Y, Gui Q. Exosomal Circ-XIAP promotes docetaxel resistance in prostate cancer by regulating miR-1182/TPD52 axis. *Drug Des Devel Ther*. 2021;15:1835-1849.
746. Ding L, Zheng Q, Lin Y, et al. Exosome-derived circTFDP2 promotes prostate cancer progression by preventing PARP1 from caspase-3-dependent cleavage. *Clin Transl Med*. 2023;13(1):e1156.
747. Chen Y, Li C, Tan C, Liu X. Circular RNAs: a new frontier in the study of human diseases. *J Med Genet*. 2016;53(6):359-365.
748. Loganathan T, Doss CG. Non-coding RNAs in human health and disease: potential function as biomarkers and therapeutic targets. *Funct Integr Genomics*. 2023;23(1):33.
749. Dawoud A, Ihab Zakaria Z, Hisham Rashwan H, Braoudaki M, Youness RA. Circular RNAs: new layer of complexity evading breast cancer heterogeneity. *Noncoding RNA Res*. 2023;8(1):60-74.
750. Li J, Yang J, Zhou P, et al. Circular RNAs in cancer: novel insights into origins, properties, functions and implications. *Am J Cancer Res*. 2015;5(2):472-480.
751. Chen N, Zhao G, Yan X, et al. A novel FLI1 exonic circular RNA promotes metastasis in breast cancer by coordinately regulating TET1 and DNMT1. *Genome Biol*. 2018;19(1):218.
752. Zhao CH, Qu L, Zhang H, Qu R. Identification of breast cancer-related circRNAs by analysis of microarray and RNA-sequencing data: An observational study. *Medicine (Baltimore)*. 2019;98(46):e18042.
753. Xu JZ, Shao CC, Wang XJ, et al. circTADA2As suppress breast cancer progression and metastasis via targeting miR-203a-3p/SOCS3 axis. *Cell Death Dis*. 2019;10(3):175.
754. Wang H, Xiao Y, Wu L, Ma D. Comprehensive circular RNA profiling reveals the regulatory role of the circRNA-000911/miR-449a pathway in breast carcinogenesis. *Int J Oncol*. 2018;52(3):743-754.
755. Chen B, Wei W, Huang X, et al. circEPSTI1 as a prognostic marker and mediator of triple-negative breast cancer progression. *Theranostics*. 2018;8(14):4003-4015.
756. Nair AA, Niu N, Tang X, et al. Circular RNAs and their associations with breast cancer subtypes. *Oncotarget*. 2016;7(49):80967-80979.
757. Lin L, Cai GX, Zhai XM, et al. Plasma-derived extracellular vesicles circular RNAs serve as biomarkers for breast cancer diagnosis. *Front Oncol*. 2021;11:752651.
758. Wang J, Zhang Q, Zhou S, et al. Circular RNA expression in exosomes derived from breast cancer cells and patients. *Epigenomics*. 2019;11(4):411-421.
759. Zhang H, Yan C, Wang Y. Exosome-mediated transfer of circHIPK3 promotes trastuzumab chemoresistance in breast cancer. *J Drug Target*. 2021;29(9):1004-1015.
760. Nie W, Wu G, Zhang J, et al. Responsive Exosome nanobioconjugates for synergistic cancer therapy. *Angew Chem Int Ed Engl*. 2020;59(5):2018-2022.
761. Wang Y, Li Z, Xu S, Guo J. Novel potential tumor biomarkers: Circular RNAs and exosomal circular RNAs in gastrointestinal malignancies. *J Clin Lab Anal*. 2020;34(7):e23359.
762. Yan Y, Fu G, Ye Y, Ming L. Exosomes participate in the carcinogenesis and the malignant behavior of gastric cancer. *Scand J Gastroenterol*. 2017;52(5):499-504.
763. Shi H, Huang S, Qin M, et al. Exosomal circ_0088300 derived from cancer-associated fibroblasts acts as a miR-1305 sponge

- and promotes gastric carcinoma cell tumorigenesis. *Front Cell Dev Biol.* 2021;9:676319.
764. Li S, Li J, Zhang H, et al. Gastric cancer derived exosomes mediate the delivery of circRNA to promote angiogenesis by targeting miR-29a/VEGF axis in endothelial cells. *Biochem Biophys Res Commun.* 2021;560:37-44.
 765. Hui C, Tian L, He X. Circular RNA circNHS1 contributes to gastric cancer progression through the miR-149-5p/YWHAZ axis. *Cancer Manag Res.* 2020;12:7117-7130.
 766. Yu L, Xie J, Liu X, Yu Y, Wang S. Plasma exosomal CircNEK9 accelerates the progression of gastric cancer via miR-409-3p/MAP7 axis. *Dig Dis Sci.* 2021;66(12):4274-4289.
 767. Ba L, Xue C, Li X, et al. Gastric cancer cell-derived exosomes can regulate the biological functions of mesenchymal stem cells by inducing the expression of circular RNA circ_0004303. *Stem Cells Dev.* 2021;30(16):830-842.
 768. Wang Y, Wang H, Zheng R, et al. Circular RNA ITCH suppresses metastasis of gastric cancer via regulating miR-199a-5p/Klotho axis. *Cell Cycle.* 2021;20(5-6):522-536.
 769. Jiang J, Li R, Wang J, Hou J, Qian H, Xu W. Circular RNA CDR1as inhibits the metastasis of gastric cancer through targeting miR-876-5p/GNG7 axis. *Gastroenterol Res Pract.* 2021;2021:5583029.
 770. Yao W, Guo P, Mu Q, Wang Y. Exosome-derived Circ-PVT1 contributes to cisplatin resistance by regulating autophagy, invasion, and apoptosis via miR-30a-5p/YAP1 axis in gastric cancer cells. *Cancer Biother Radiopharm.* 2021;36(4):347-359.
 771. Liu S, Wu M, Peng M. Circ_0000260 regulates the development and deterioration of gastric adenocarcinoma with cisplatin resistance by upregulating MMP11 via targeting MiR-129-5p. *Cancer Manag Res.* 2020;12:10505-10519.
 772. Zhong Y, Wang D, Ding Y, Tian G, Jiang B. Circular RNA circ_0032821 contributes to oxaliplatin (OXA) resistance of gastric cancer cells by regulating SOX9 via miR-515-5p. *Biotechnol Lett.* 2021;43(2):339-351.
 773. Ostrom QT, Bauchet L, Davis FG, et al. The epidemiology of glioma in adults: a “state of the science” review. *Neuro Oncol.* 2014;16(7):896-913.
 774. Mehta S, Lo Cascio C. Developmentally regulated signaling pathways in glioma invasion. *Cell Mol Life Sci.* 2018;75(3):385-402.
 775. Phillips RE, Soshnev AA, Allis CD. Epigenomic reprogramming as a driver of malignant glioma. *Cancer Cell.* 2020;38(5):647-660.
 776. Zhao M, Xu J, Zhong S, et al. Expression profiles and potential functions of circular RNAs in extracellular vesicles isolated from radioresistant glioma cells. *Oncol Rep.* 2019;41(3):1893-1900.
 777. Yin K, Liu X. CircMMP1 promotes the progression of glioma through miR-433/HMGB3 axis in vitro and in vivo. *IUBMB Life.* 2020;72(11):2508-2524.
 778. Han C, Wang S, Wang H, Zhang J. Exosomal circ-HIPK3 facilitates tumor progression and temozolomide resistance by regulating miR-421/ZIC5 axis in glioma. *Cancer Biother Radiopharm.* 2021;36(7):537-548.
 779. Liu Z, Guo S, Sun H, Bai Y, Song Z, Liu X. Circular RNA CircHIPK3 elevates CCND2 expression and promotes cell proliferation and invasion through miR-124 in glioma. *Front Genet.* 2020;11:1013.
 780. Ding C, Wu Z, You H, et al. CircNFIIX promotes progression of glioma through regulating miR-378e/RPN2 axis. *J Exp Clin Cancer Res.* 2019;38(1):506.
 781. Si J, Li W, Li X, Cao L, Chen Z, Jiang Z. Heparanase confers temozolomide resistance by regulation of exosome secretion and circular RNA composition in glioma. *Cancer Sci.* 2021;112(9):3491-3506.
 782. Ding C, Yi X, Chen X, et al. Warburg effect-promoted exosomal circ_0072083 releasing up-regulates NANO expression through multiple pathways and enhances temozolomide resistance in glioma. *J Exp Clin Cancer Res.* 2021;40(1):164.
 783. Friedman HS, Kerby T, Calvert H. Temozolomide and treatment of malignant glioma. *Clin Cancer Res.* 2000;6(7):2585-2597.
 784. Barbagallo D, Caponnetto A, Cirnigliaro M, et al. CircS-MARCA5 inhibits migration of glioblastoma multiforme cells by regulating a molecular axis involving splicing factors SRSF1/SRSF3/PTB. *Int J Mol Sci.* 2018;19(2):480.
 785. Li Y, Chen J, Chen Z, et al. CircGLIS3 promotes high-grade glioma invasion via modulating ezrin phosphorylation. *Front Cell Dev Biol.* 2021;9:663207.
 786. Chen RX, Chen X, Xia LP, et al. N(6)-methyladenosine modification of circNSUN2 facilitates cytoplasmic export and stabilizes HMGA2 to promote colorectal liver metastasis. *Nat Commun.* 2019;10(1):4695.
 787. Du WW, Zhang C, Yang W, Yong T, Awan FM, Yang BB. Identifying and characterizing circRNA-protein interaction. *Theranostics.* 2017;7(17):4183-4191.
 788. McKenzie AJ, Hoshino D, Hong NH, et al. KRAS-MEK signaling controls Ago2 sorting into exosomes. *Cell Rep.* 2016;15(5):978-987.
 789. Pan Z, Zhao R, Li B, et al. EWSR1-induced circNEIL3 promotes glioma progression and exosome-mediated macrophage immunosuppressive polarization via stabilizing IGF2BP3. *Mol Cancer.* 2022;21(1):16.

How to cite this article: Wang Y, Zhang J, Yang Y, et al. Circular RNAs in human diseases. *MedComm.* 2024;5:e699.
<https://doi.org/10.1002/mco2.699>