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Review paper

Exosomal circRNAs: Deciphering the novel drug resistance roles in cancer therapy

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ABSTRACT

Exosomal circular RNA (circRNAs) are pivotal in cancer biology, and tumor pathophysiology. These stable, non-coding RNAs encapsulated in exosomes participated in cancer progression, tumor growth, metastasis, drug sensitivity and the tumor microenvironment (TME). Their presence in bodily fluids positions them as potential non-invasive biomarkers, revealing the molecular dynamics of cancers. Research in exosomal circRNAs is reshaping our understanding of neoplastic intercellular communication. Exploiting the natural properties of exosomes for targeted drug delivery and disrupting circRNA-mediated protumorigenic signaling can develop new treatment modalities. Therefore, ongoing exploration of exosomal circRNAs in cancer research is poised to revolutionize clinical management of cancer. This emerging field offers hope for significant breakthroughs in cancer care. This review underscores the critical role of exosomal circRNAs in cancer biology and drug resistance, highlighting their potential as non-invasive biomarkers and therapeutic targets that could transform the clinical management of cancer.

1. Introduction

Cancer continues to be a significant global health challenge, with its impact varying widely based on the type of cancer, geographic region, and socioeconomic status [1–7]. In 2020, cancer, the world's second leading cause of death, caused around 10 million deaths and 23.6 million new cases, a 26.3% rise in incidence since 2010 [8,9]. The global incidence and mortality rates of cancer differ by region and socioeconomic factors, with lung cancer remaining the most prevalent in areas with high tobacco use [10]. By 2040, it is estimated that there will be 3.2 million new cases of colorectal cancer and 1.6 million deaths, with elevated rates in Australia/New Zealand and Europe [11]. The rise in gastrointestinal cancers in East Asia is attributed to population growth, aging, and changing lifestyle habits [12]. The incidence of neurological, hematological, and urological cancers is increasing. For example, in 2020, multiple myeloma accounted for 14% of leukemia, lymphoma, and myeloma cases [13]. Gynecological cancers like cervical cancer are challenging in low- and middle-income countries due to disparities in access to human papilloma virus (HPV) vaccination and screening [14]. Novel diagnostic and therapeutic approaches are urgently required to enhance the outlook for cancer patients globally. Cancer pathogenesis involves genetic mutations that disrupt normal cell regulation, promoting unchecked growth and division. Key factors include mutations, environmental exposure, and lifestyle choices that activate oncogenes or deactivate tumor suppressor genes, leading to malignant tumors. Immune evasion is crucial in cancer progression as tumors avoid immune detection by upregulating checkpoint proteins such as programmed cell death-ligand 1 (PD-L1), highlighting the need for immunotherapies to counteract these mechanisms [15]. Enhancing our understanding of these complex interactions will support the development of more effective diagnostic and therapeutic strategies.

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Diagnosing cancer is challenging due to overlapping symptoms with other diseases, often resulting in misdiagnoses or late detections. Cancer treatments like chemotherapy, radiotherapy, and immunotherapy are hindered by high costs, limited availability in resource-poor areas, and significant side effects impacting patient quality of life [16,17]. The diagnosis of these cancers is challenging due to the absence of uniform screening guidelines and the complex nature of these conditions. Despite significant advancements in treatment modalities including chemotherapy, radiotherapy, and immunotherapy, issues with diagnostic accuracy and treatment accessibility persist [14]. Investigating the etiological mechanisms of cancer is crucial for enhancing diagnostic and therapeutic strategies, with the ultimate goal of reducing the global impact of this widespread disease.

Exosomes are lipid bilayer vesicles, 30–150 nm in size, released by various cells, including cancer cells, and present in bodily fluids like blood and urine [18]. Transporting a variety of substances such as proteins, fats, and various types of nucleic acids, including circular RNAs (circRNAs) [19], microRNAs (miRNAs) [20], long non-coding RNAs (lncRNAs) [21], and mRNA, these vesicles re essential for cell-to-cell communication. Their ability to transfer genetic information and influence the recipient cells' behavior makes them critical players in cancer progression, metastasis, and therapy resistance. Exosomes are a promising drug delivery platform in cancer therapy, capable of encapsulating and protecting RNA molecules like small interfering RNA (siRNA) or clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) components. This method targets specific pathways involved in tumor growth and resistance, potentially revolutionizing cancer treatment [22].

circRNAs are non-coding RNAs with a closed loop structure that enhances their stability. They are involved in cancer progression by promoting tumor growth, angiogenesis, and metastasis, and altering the tumor microenvironment (TME). In the realm of tumorigenesis, exosomal circRNAs influence various cellular processes, such as proliferation and angiogenesis. Yi et al. [23] and Wang et al. [24] has shown that specific circRNAs, when enriched in exosomes, can regulate gene expression in recipient cells, thus promoting cancer development and altering the TME. circRNAs contribute to cancer by modulating signaling pathways and interacting with RNA-binding proteins, thereby supporting tumor growth and its microenvironment. The complex interplay between circRNAs and miRNAs, and their presence in exosomes, highlights their significance in regulating cancer-related pathways [25]. Additionally, exosomes and their circRNA components are emerging as promising non-invasive biomarkers for cancer detection and prognosis due to their durability and presence in bodily fluids [26]. The distinct characteristics found in blood or urine samples of cancer patients provide hopeful opportunities for early cancer detection and tracking its progression and response to treatment (Table 1) [24,27–32].

This study reviews the role of exosomal circRNAs in cancer progression, highlighting their influence on the tumor microenvironment and intercellular communication. These molecules could contribute to treatment resistance. The review underscores their potential as oncological biomarkers and therapeutic targets, suggesting that future research could lead to novel diagnostic and treatment strategies, potentially revolutionizing cancer care.

2. Exosomes in cancer progression

Exosomes are small vesicles released from cells through exocytosis, typically ranging in diameter from 30 to 150 nm. These vesicles play crucial roles in various biological processes, particularly in cell communication. The production of exosomes involves the fusion of endosomes, formed through endocytosis, with the cell membrane. The molecules contained within exosomes can reflect the nature and state of their cells of origin. Consequently, exosomes are often regarded as vital mediators of intercellular communication, capable of transmitting signals and substances within and beyond the bodily environment.

2.1. Composition and biogenesis of exosomes

The composition of exosomes is considerably complex, encompassing proteins, RNA, DNA, and various bioactive molecules. The specific constituents can vary depending on the type of source cells and their physiological or pathological state. At the protein level, exosomes commonly contain cytoskeletal proteins, multiple enzymes, signaling molecules, and membrane proteins. The RNA components primarily include various non-coding RNAs, such as miRNAs and lncRNAs, which play crucial roles in regulating gene expression and cellular functions [33,34]. By analyzing these biomolecules in exosomes, scientists can gain a deeper understanding of the mechanisms of intercellular communication.

The biogenesis of exosomes involves the cellular mechanisms of endocytosis and secretion. In the early stages of biogenesis, cells form endosomes through endocytosis. Subsequently, these endosomes internally develop into multivesicular bodies, which are aggregates of small vesicles formed by the invagination of the endosomal membrane. Ultimately, the multivesicular bodies fuse with the plasma membrane, releasing the contained vesicles—known as exosomes—into the extracellular space [35]. This process not only involves complex regulation of membrane transport and fusion but also reflects the cell's capacity to respond to environmental signals.

2.2. Exosomes and cancer

Exosomes play a crucial role in the onset and progression of tumors. Research indicates that exosomes produced by tumor cells can influence the tumor microenvironment, promoting tumor

Table 1
Exosome in cancer.

Source cell	Cancer type	Exosome function	Refs.
Prostate cancer cells	Prostate cancer	KLB promoted tumor progression by regulating exosome secretion through a Rab8a-dependent mechanism.	[24]
NSCLC cells: A549 and H1299 cells	NSCLC	Promoted the tumorigenesis, angiogenesis and metastasis of A549 cells.	[27]
Breast cancer cells	Breast cancer	Facilitated cancer cachexia-related fat loss.	[28]
Cancer-associated fibroblasts	Colorectal cancer	Drived colorectal cancer stemness and chemo-resistance.	[29]
Gastric cancer cells	Gastric cancer	Exo-TTN-AS1 promoted gastric cancer cell growth and migration by promoting CDX2 expression.	[30]
Esophageal squamous cell carcinoma cells	Esophageal squamous cell carcinoma	Exosomal M6PR and EphB4 promoted tumor angiogenesis and malignancy.	[31]
M2 macrophages	Pancreatic cancer	Targeting TRIM62 promoted pancreatic cancer progression and glutamine uptake.	[32]

NSCLC: non-small cell lung cancer; KLB: klotho beta; TTN-AS1: titin antisense RNA 1; TRIM67: /tripartite motif-containing 67.

proliferation, invasion, and metastasis [36]. Zhao et al. [37] reported that tumor-derived exosomal miR-934 induces M2 polarization of macrophages, promoting liver metastasis in colorectal cancer. Furthermore, research by He et al. [38] also indicates that miR-205, originating from cancer cells, regulates tumor angiogenesis through an exosome-dependent mechanism and suggests that exosomal miR-205 could serve as a potential therapeutic target for ovarian cancer. Therefore, understanding the role of exosomes in tumors not only helps us delve deeper into the mechanisms of tumor pathogenesis but also opens possibilities for developing new therapeutic strategies. Through these studies, exosomes have emerged as a highly promising research direction in the field of tumor biology.

3. Characteristics and mechanism types of circRNAs

circRNAs, which have closed loop structures, are a distinct type of non-coding RNAs that set them apart from linear RNAs. These circRNAs are formed through a process known as backsplicing, in which the 5′ and 3′ ends of a single RNA strand are joined together. This circular configuration imparts remarkable stability to circRNAs, protecting them from the exonucleolytic degradation commonly experienced by linear RNAs. A growing body of research has uncovered the multifaceted mechanisms through which circRNAs contribute to tumorigenesis and cancer progression (Fig. 1). One of the most studied mechanisms of circRNA function is their role as miRNA sponges. circRNAs can bind to and sequester miRNAs, thus preventing them from interacting with their target mRNAs. This miRNA sponge mechanism alters gene expression patterns and has been implicated in various aspects of cancer biology, including tumor cell proliferation, invasion, metastasis, and drug resistance. circRNAs are also involved in regulating transcription. By interacting with RNA-binding proteins (RBPs), circRNAs are able to regulate gene expression. This interaction can lead to changes in the protein's nuclear-cytoplasmic distribution or recruitment to chromatin, thereby influencing transcriptional outcomes. Another intriguing aspect of circRNAs involves their role in translation. Some circRNAs can bind to ribosomes and influence protein synthesis, thereby affecting cellular processes relevant to cancer. In addition to these roles, by altering the subcellular localization of proteins, circRNAs can impact various signaling pathways and cellular responses. Furthermore, circRNAs are involved in the modulation of signaling pathways through their interactions with various proteins (Table 2) [39–45]. Building on the roles in cancer, the exploration of circRNAs as potential therapeutic targets and diagnostic markers opens new avenues for advancing cancer treatment strategies.

circRNAs emerge as pivotal regulators in cancer, with diverse mechanisms including acting as miRNA sponges, influencing transcription and translation, modulating protein localization, and interacting with proteins to regulate signaling pathways. Their participation in different areas of cancer biology, including tumor growth and resistance to drugs, highlights their promise as

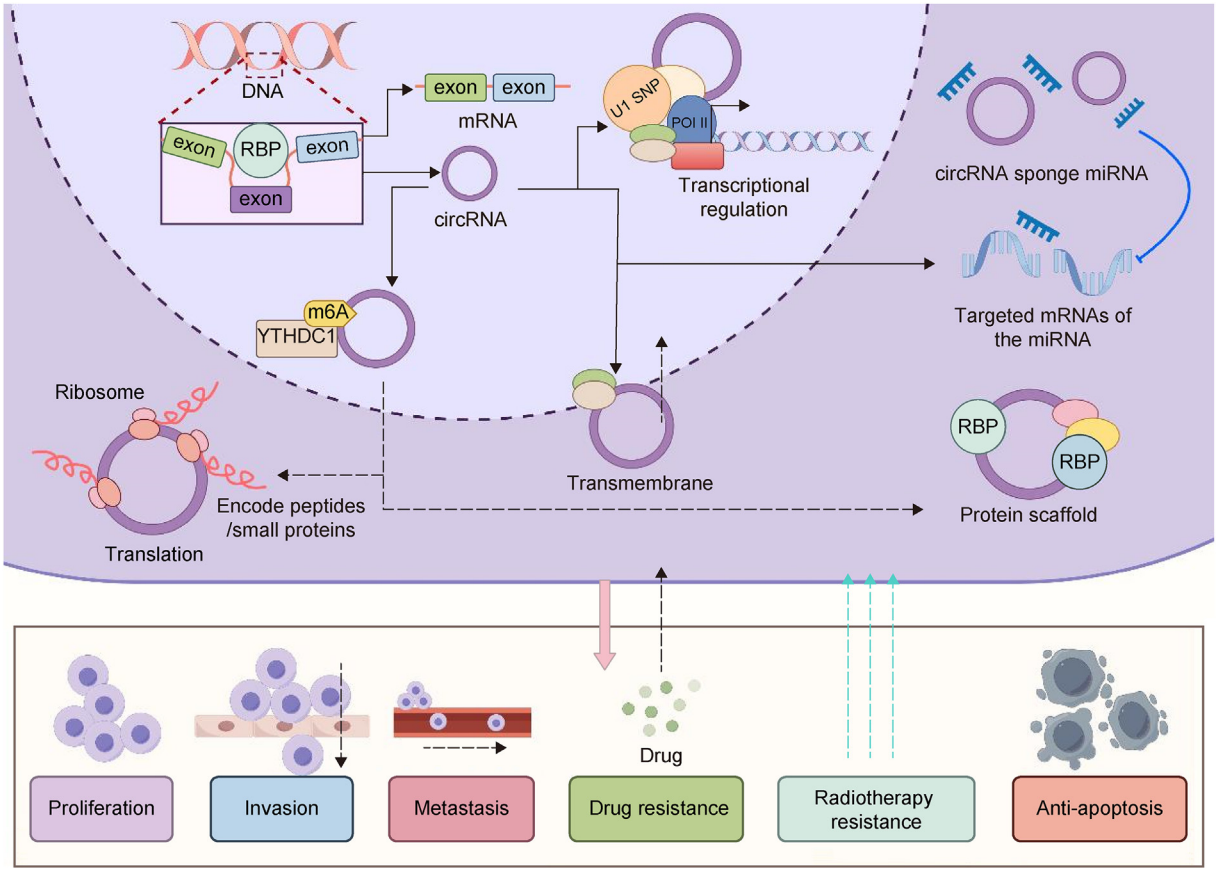

Fig. 1. The multiple molecular mechanisms of circular RNA (circRNA). circRNAs in cancer biology act as miRNA sponges, altering gene expression and influencing cell proliferation, invasion, metastasis, and drug resistance. They regulate transcription by interacting with RNA-binding proteins (RBPs), modify protein synthesis by binding to ribosomes, and can produce peptides affecting cancer cell metabolism and resistance. Additionally, circRNAs impact signaling pathways and cellular responses in cancer by altering protein localization and interactions, thus playing a dual role in promoting or suppressing oncogenesis.

Table 2
circular RNA (circRNA) and cancer.

circRNA	Cancer type	circRNA function	Refs.
circPDIA4	Gastric cancer	circPDIA4 upregulated in malignant tissues and associated with poor survival outcomes in patients with gastric cancer.	[39]
circPDIA4	Gastric cancer	Upregulated circRNA_102231 promotes gastric cancer progression and its clinical significance.	[40]
circRERE	Colorectal cancer	circRERE lowly expressed in colorectal cancer.	[41]
circRBM33	Prostate cancer	Upregulation of circRBM33 enhanced tumor growth and invasion, respectively.	[42]
circGLIS3	Thyroid cancer	circGLIS3 down regulates in thyroid cancer.	[43]
circLOC729852	Bladder cancer	Elevated expression of circLOC729852 in BLCA tissues is associated with enhanced proliferation, migration, and EMT in bladder cancer cells.	[44]
hsa_circ_0067842	Breast cancer	Elevated expression of hsa_circ_0067842 in breast cancer tissues and cells, associated with poor prognosis.	[45]

BLCA: bladder cancer; EMT: epithelial-mesenchymal transition.

biomarkers and targets for treatment. Future research in this field holds promise for the development of novel diagnostic tools and more effective treatments for cancer, leveraging the unique properties of circRNAs.

3.1. Exosomal circRNAs in non-small cell lung cancer (NSCLC)/ lung adenocarcinoma (LUAD)

Recent cancer research has focused on the significant impact of exosomal circRNAs in the development and advancement of NSCLC. A collection of studies provides compelling evidence of the diverse functions and mechanisms of various exosomal circRNAs, emphasizing their potential as diagnostic biomarkers and their involvement in NSCLC progression, metastasis, and treatment resistance (Fig. S1, and Table 3) [46–63]. Upon the foundational roles of exosomal circRNAs, we now explore specific mechanisms by which these entities contribute to NSCLC pathogenesis.

3.1.1. Mechanisms of exosomal circRNAs in NSCLC

Hong et al. [47] explored exosomal circ-CPA4 in NSCLC, uncovering its high expression in cancer tissues. circ-CPA4 acts as a sponge for the let-7 miRNA, which enhances PD-L1 expression and thus contributes to tumor growth, drug resistance, and immune evasion. Liu et al. [48] found that exosomal circ_0048856, derived from NSCLC, promotes aggressive cancer progression by downregulating miR-1287-5p. This rule promotes the growth, movement, and penetration of NSCLC cells, emphasizing the impact of circRNAs on cancer aggressiveness. Ning et al. [49] and Wang et al. [50] further demonstrated how exosomal circRNAs can enhance NSCLC cell proliferation and stemness. Ning et al. [49] identified the miR-1253/FAM83A axis as a target of circ_0007385, while Wang et al. [50] revealed that circ_0008717 sponges miR-1287-5p to elevate PAK2, impacting NSCLC cell behavior and tumorigenicity. This ceRNA network highlights a novel aspect of circRNA functionality in cancer biology. Xiong et al. [51] demonstrated that exosomal circRACGAP1 boosts the characteristics of stem cells and the spread of cancer by recruiting RNA-binding protein polypyrimidine tract-binding protein 1 (PTBP1) to encourage sirtuin-3 (SIRT3) mediated deacetylation of replication timing regulatory factor 1 (RIF1). The intricate molecular process indicates how circRNA influences the Wnt/β-catenin pathway, ultimately affecting tumor growth and metastasis. This study underscores the potential of targeting exosomal circRNAs to modulate epigenetic regulators in cancer therapy. Having detailed the mechanisms, we shift focus to the diagnostic potential of exosomal circRNAs, highlighting their utility in distinguishing NSCLC from non-cancerous conditions.

3.1.2. Exosomal circRNAs as biomarkers of NSCLC

A groundbreaking study by Xian et al. [52] identified circ_0047921, circ_0056285, and circ_0007761 in serum exosomes as important biomarkers for NSCLC. These exosomal circRNAs

Table 3
Exosomal circRNAs in non-small cell lung cancer/lung adenocarcinoma (NSCLC/LUAD).

Parent cell	Target cell	Mechanism signal axis	Cell function	Refs.
NSCLC	Tumor cells	circ-MEMO1/miR-101-3p/KRAS axis	Tumor growth, glycolysis, cell cycle progression, and inhibits apoptosis	[46]
NSCLC	Tumor cells	circ-CPA4/let-7 miRNA/PD-L1 axis	Tumor growth, drug resistance, and immune evasion	[47]
NSCLC	Tumor cells	circ_0048856/miR-1287-5p/	Increases proliferation, migration, and invasion	[48]
NSCLC	Tumor cells	circ_0007385/miR-1253/FAM83A axis	Cell proliferation, stemness	[49]
NSCLC	Tumor cells	circ_0008717/miR-1287-5p/PAK2	Tumor cell behavior, and tumorigenicity	[50]
NSCLC	Tumor cells	circRACGAP1/PTBP1/SIRT3/RIF1/Wnt/β-catenin	Stemness, and metastasis	[51]
NSCLC (Serum exosomes)	Diagnostic use	Not specified	Biomarkers for NSCLC diagnosis	[52]
LUSC	Diagnostic use	Not specified	Potential biomarkers and therapeutic targets	[53]
LUAD (Plasma exosomes)	Diagnostic use	Not specified	Biomarkers for early-stage LUAD diagnosis	[54]
LUAD (Serum and serum exosomes)	Diagnostic use	Not specified	Upregulated in LUAD, higher diagnostic sensitivity and specificity than serum circRNAs alone	[55]
NSCLC	Tumor cells	circ_PIP5K1A/miR-101/ABCC1 axis	Affects cell proliferation, migration, invasion, apoptosis, drug sensitivity	[56]
NSCLC	Tumor cells	hsa_circ_0002130/miR-498/GLUT1/HK2/LDHA axis	Glycolysis, resistance to osimertinib	[57]
NSCLC	Tumor cells	hsa_circ_0014235/miR-520a-5p/CDK4	DDP chemoresistance	[58]
NSCLC	Tumor cells	circ_0008928/miR-488/HK2	Cisplatin resistance	[59]
NSCLC	Tumor cells	circ_0076305/miR-186-5p/ABCC1	Cisplatin resistance	[60]
NSCLC	Tumor cells	circ_0000519/miR-1258/RHOV	Regulate cellular proliferation	[61]
NSCLC	Tumor cells	circERBB2IP/miR-5195-3p/PSAT1	Influences cancer development	[62]
LUAD	M2 macrophages	circ-ADRM1/miR-1287-5p/USP12/MMP14 mRNA	Induce M2 macrophage polarization	[63]

LUSC: lung squamous cell carcinoma; DDP: cisplatin.

demonstrated high diagnostic accuracy in distinguishing NSCLC from healthy controls and other lung conditions, thereby indicating their potential in noninvasive cancer diagnosis. In plasma exosomes from lung squamous cell carcinoma (LUSC) patients, 252 circRNAs were differentially expressed, with 133 being upregulated and 119 downregulated [53]. They highlighted the capabilities of hsa_circ_0014235 and hsa_circ_0025580 as biomarkers for LUSC. Chen et al. [54] and Kang et al. [55] investigated circRNAs in LUAD. Chen et al. [54] discovered various circRNAs that were expressed differently in plasma exosomes of early-stage LUAD patients, showing 182 circRNAs (105 increased and 78 decreased) in comparison to the control group. They emphasized the possible use of circRNAs, such as circ_0001492, circ_0001346, circ_0000690, and circ_0001439, as indicators for LUAD. Kang et al. [55] further substantiated this by showing that levels of hsa_circ_0001492, hsa_circ_0001439, and hsa_circ_0000896 in both serum and exosomes were notably higher in LUAD patients, thus providing greater diagnostic accuracy compared to using serum circRNAs alone. In NSCLC patients, lower overall survival rates were linked to elevated levels of serum exosomal circRACGAP1, as reported by Xiong et al. [51]. Exosomal circRNAs in the field of NSCLC have shown promise as diagnostic biomarkers, with the potential to greatly improve early detection and monitoring of this common form of cancer. With their diagnostic capabilities established, we next examine how exosomal circRNAs are intricately linked to drug resistance in NSCLC, underscoring their therapeutic relevance.

3.1.3. Exosomal circRNAs and drug resistance in NSCLC

The role of exosomal circ_PIP5K1A in controlling NSCLC advancement and response to cisplatin was investigated by Shao et al. [56]. The circRNA regulates the interaction between miR-101 and ABCC1, impacting the cell growth, movement, and invasion, while also playing roles in apoptosis and drug responsiveness. Ma et al. [57] emphasized the significance of hsa_circ_0002130 in NSCLC that is resistant to osimertinib. They observed that this exosomal circRNA sponges miR-498, thereby regulating key metabolic enzymes such as glucose transporter 1 (GLUT1), hexokinase 2 (HK2), and lactate dehydrogenase A (LDHA), which promotes glycolysis and confers resistance to osimertinib. This finding underscores the potential of exosomal circRNAs in mediating drug resistance mechanisms. Xu et al. [58] added to this narrative by identifying hsa_circ_0014235 as a circRNA that enhances cisplatin (DDP) chemoresistance. This exosomal circRNA modulates the miR-520a-5p/CDK4 pathway, affecting the aggressive traits of NSCLC and offering a new insight into the mechanisms of drug resistance in cancer therapy. Shi et al. [59] investigated the impact of circ_0008928 in cisplatin-resistant NSCLC. They found that this circRNA was upregulated in serum exosomes of resistant patients, playing a crucial role in enhancing cisplatin resistance. circ_0008928 acts as a sponge for miR-488, which targets HK2, a key enzyme in glycolysis. This interaction underscores the complexity of circRNA-mediated drug resistance in NSCLC. Wang et al. [60] focused on circ_0076305, which is associated with DDP resistance in NSCLC. The researchers discovered that circ_0076305 enhances the levels of ATP-binding cassette subfamily C member 1 (ABCC1) by acting as a sponge for miR-186-5p, ultimately leading to resistance to DDP. This study suggests a new circRNA-targeted therapeutic approach for overcoming chemoresistance in NSCLC. Beyond drug resistance, exosomal circRNAs also play pivotal roles in the tumor microenvironment and metastasis, as we will discuss in the following section.

3.1.4. Roles in tumor microenvironment and metastasis

Wang et al. [61] and Peng et al. [62] explored the roles of exosomal circ_0000519 and circERBB2IP in NSCLC. circ_0000519 was found to regulate cellular proliferation and spread by modulating the miR-1258/RHOV pathway, while circERBB2IP influenced cancer development by elevating phosphoserine aminotransferase 1 (PSAT1) levels through the miR-5195-3p pathway. These studies highlight the complex interactions within the tumor microenvironment mediated by circRNAs. Qian et al. [63] observed that circADRM1 in exosomes from LUAD induces M2 macrophage polarization, altering matrix metalloproteinase 14 (MMP14) mRNA and protein levels. This study provides insight into the complex interplay between circRNAs, tumor cells, and the tumor microenvironment.

These studies collectively illustrate the diverse and complex roles of exosomal circRNAs in NSCLC. From their contribution to tumor progression, drug resistance, and metastasis, to their potential as diagnostic biomarkers and therapeutic targets, circRNAs have emerged as crucial players in the NSCLC landscape. Understanding these multifarious roles opens new avenues for research and clinical application, potentially leading to more effective diagnostic and therapeutic strategies in the battle against NSCLC.

3.2. Hepatocellular carcinoma (HCC)

Recent studies investigating exosomal circRNAs have greatly progressed the field of HCC research. The growing investigation of exosomal circRNAs in HCC reveals their significant influence on the advancement of tumors, detection, and possible treatment options. These studies have uncovered their multifaceted roles in HCC progression, diagnosis, and therapeutic targeting, offering new insights into the complex biology of this malignancy (Fig. 2, and Table 4) [64–78]. Based on these foundational insights into the roles of exosomal circRNAs, we now turn to explore their specific applications in the diagnosis and prognosis of HCC.

3.2.1. Exosomal circRNAs in HCC diagnosis and prognosis

Significant attention has been given to the diagnostic capabilities of exosomal circRNAs. Sun et al. [64] identified a three-circRNA signature (hsa_circ_0004001, hsa_circ_0004123, hsa_circ_0075792) with high sensitivity and specificity for HCC detection. Similarly, Lyu et al. [65] showed that exosomal circ_0070396, significantly elevated in HCC patients, effectively distinguishes HCC from other liver conditions. A study by Wang et al. [66] found that serum exosomal hsa_circ_0028861 served as a new diagnostic indicator for HBV-related HCC, offering higher precision than conventional markers such as alpha-fetoprotein (AFP). Guo et al. [67] investigated exo_circ_0006602 as a potential non-invasive biomarker for HCC. They found it markedly upregulated in HCC patients, correlating with clinical features like HBsAg and liver cirrhosis. Interestingly, when combined with the traditional tumor marker AFP, exo_circ_0006602 significantly improved diagnostic accuracy, presenting a promising tool for early HCC detection. Zhu et al. [68] used machine learning to establish an exosomal 3-RNA detection panel for liver cancer, which is particularly beneficial in detecting AFP-negative and early-stage liver cancer. Wu et al. [69] conducted a comprehensive bioinformatics analysis, revealing a distinctive exosome transcriptome in HCC. Their study identified unique signatures of mRNAs, lncRNAs, and circRNAs, which illuminated potential biomarkers and key pathways involved in HCC, such as the mitogen-activated protein kinase (MAPK) signaling network. This research highlighted the significant diagnostic and therapeutic potential of exosomal biomarkers in HCC. These studies collectively improve our comprehension of exosomal circRNAs in HCC, providing fresh insights into early detection and targeted treatment approaches. They emphasize the diagnostic value and therapeutic implications of circRNAs, paving the way for improved management of HCC. After exploring the diagnostic potential of

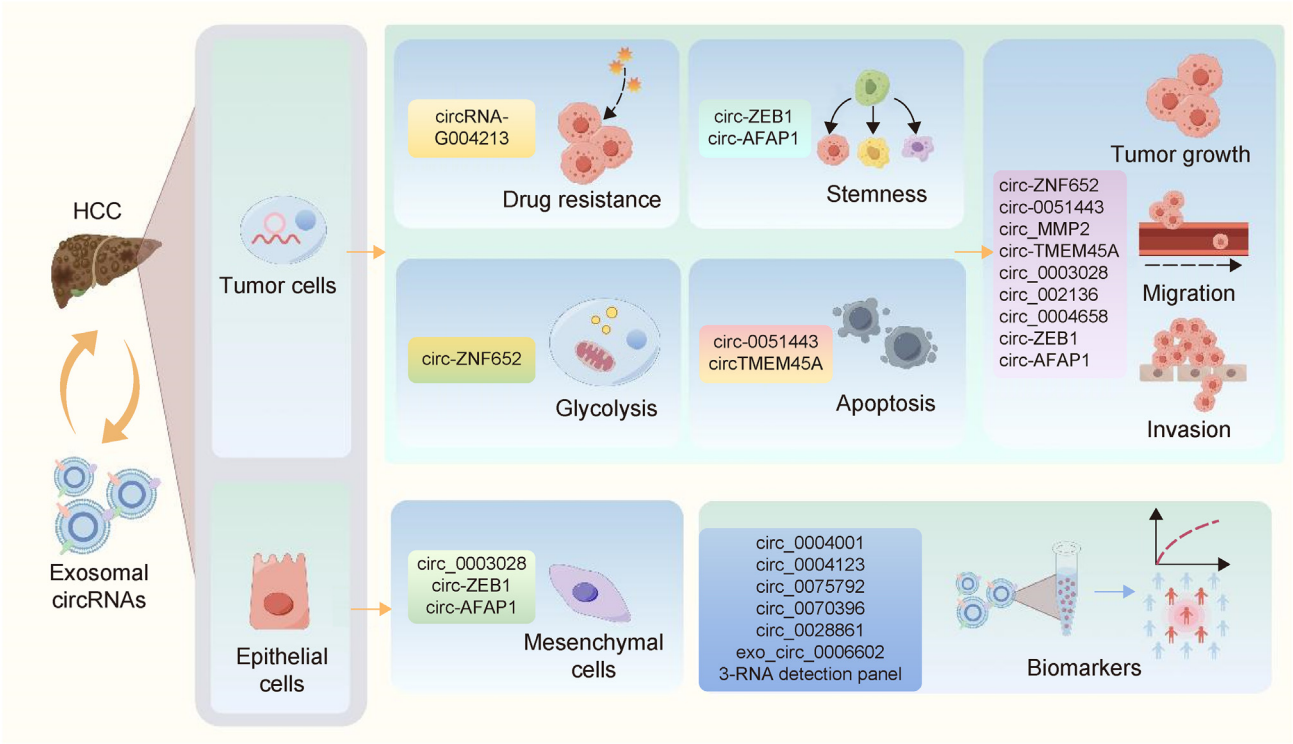

Fig. 2. The functions and mechanisms of exosomal circular RNAs (circRNAs) in hepatocellular carcinoma. The burgeoning research into exosomal circRNAs in hepatocellular carcinoma (HCC) unveils their profound impact on tumor progression, diagnosis, and potential therapeutic avenues. These studies have uncovered their multifaceted roles in HCC progression, diagnosis, and therapeutic targeting, offering new insights into the complex biology of this malignancy. Various types of circRNA exosomes have been identified that act on HCC tumor cells and epithelial cells, thereby affecting drug resistance, stemness, glycolysis, apoptosis, cell proliferation, invasiveness, and migratory abilities of HCC tumor cells; epithelial-to-mesenchymal transition occurs in HCC epithelial cells. circRNA exosomes influence the progression of HCC tumors through multiple mechanisms.

Table 4
Exosomal circular RNAs (circRNAs) in hepatocellular carcinoma.

Exosomal circRNAs name	Parent cell	Target cell	Mechanism signal axis	Cell function	Refs.
hsa_circ_0004001, hsa_circ_0004123, hsa_circ_0075792	HCC (serum exosomes)	Diagnostic use	Not specified	Biomarkers for HCC detection	[64]
circ_0070396	HCC (serum exosomes)	Diagnostic use	Not specified	Differentiates HCC from other liver conditions	[65]
hsa_circ_0028861	HCC (serum exosomes)	Diagnostic use	Not specified	Novel diagnostic biomarker for HBV-derived HCC	[66]
exo_circ_0006602	HCC (serum exosomes)	Diagnostic use	Not specified	Upregulates in HCC, correlates with clinical features	[67]
3-RNA detection panel	HCC (serum exosomes)	Diagnostic use	Not specified	Biomarkers for AFP-negative and early-stage liver cancer	[68]
MARCH8, SH3PXD2A, has-circ-0014088, hsa-miR-186-5p, hsa-miR-613	HCC (serum exosomes)	Diagnostic use	Not specified	Biomarkers and key pathways involved in HCC, such as the MAPK signaling network	[69]
circ-ZNF652	HCC (exosomes)	HCC cells	circ-ZNF652/miR-29a-3p/GUCD1	Enhances HCC cell proliferation, migration, invasion, and glycolysis	[70]
circ-0051443	HCC (exosomes)	HCC cells	circ-0051443/BAK1/miR-331-3p	Suppresses tumor progression, and induces apoptosis and cell cycle arrest	[71]
circ_MMP2	HCC (exosomes)	HCC cells	circ_MMP2/miR-136-5p/MMP2	Promotes HCC metastasis	[72]
circTMEM45A	HCC (exosomes)	HCC cells	circTMEM45A/miR-665/IGF2	Upregulated in HCC, and promotes tumor progression	[73]
circ_0003028	HCC (exosomes)	HCC cells	circ_0003028/miR-498/ODC1	Facilitates tumor progression, proliferation, metastasis, and EMT	[74]
hsa-circRNA-G004213	HCC (exosomes)	HCC cells	Hsa-circRNA-G004213/miR-513b-5p/PRPF39	Enhances cisplatin sensitivity in HCC	[75]
circ_002136	HCC (exosomes)	HCC cells	circ_002136/miR-19a-3p/RAB1A	Promotes HCC progression	[76]
hsa_circ_0004658	Macrophages (Exosomes)	HCC cells	hsa_circ_0004658/miR-499b-5p/JAM3	Inhibits HCC progression	[77]
circ-ZEB1, circ-AFAP1	Liver cancer stem cell exosomes	HCC cells	circ-ZEB1/circ-AFAP1/EMT	Regulates EMT, and influences liver cancer stemness	[78]

HCC: hepatocellular carcinoma; EMT: epithelial–mesenchymal transition; AFP: alpha-fetoprotein; MAPK: mitogen-activated protein kinase.

exosomal circRNAs, our focus now shifts to their impact on the progression and metastasis of HCC.

3.2.2. Exosomal circRNAs in HCC progression and metastasis

Multiple studies have demonstrated how exosomal circRNAs can either facilitate or impede the advancement of HCC. A study by Li et al. [70] showed that exosomal circ-ZNF652 enhanced the growth, motility, invasiveness, and glucose metabolism of HCC cells through the miR-29a-3p/guanylyl cyclase domain containing 1 (GUCD1) pathway. Conversely, Chen et al. [71] discovered that circ-0051443 suppresses tumor progression by inducing apoptosis and cell cycle arrest via the Bcl-2 antagonist killer 1 (BAK1) and miR-331-3p pathways. Liu et al. [72] identified circ_MMP2 as a promoter of HCC metastasis, enhancing MMP2 expression via miR-136-5p sponging. Zhang et al. [73] reported that circ-TMEM45A, upregulated in HCC, acts as a miR-665 sponge, thereby influencing insulin-like growth factor 2 (IGF2) expression and promoting tumor progression. Zhang et al. [74] discovered that circ_0003028 facilitates tumor progression by modulating the miR-498/ornithine decarboxylase 1 (ODC1) axis. circ_0003028 is upregulated in HCC, promoting cell proliferation, metastasis, and triggering the epithelial−mesenchymal transition (EMT) by its exosome pathway. Transitioning from their role in HCC progression, we explore the therapeutic potential of exosomal circRNAs and the mechanistic insights they offer.

3.2.3. Therapeutic potential and mechanistic insights

The therapeutic potential of exosomal circRNAs in HCC has been a key area of investigation. Qin et al. [75] found that hsa-circRNA-G004213 enhanced cisplatin sensitivity in HCC via the miR-513b-5p/PRPF39 axis, suggesting its role in improving chemotherapy efficacy. The study by Yuan et al. [76] showed that circ_002136 enhanced the advancement of HCC by activating the miR-19a-3p/RAB1A pathway, providing fresh perspectives on HCC advancement and possible treatment targets. Zhang et al. [77] found that exosomal hsa_circ_0004658 derived from macrophages inhibited HCC progression through the miR-499b-5p/JAM3 pathway, offering a novel perspective on the interaction between macrophages and HCC cells. Han et al. [78] highlighted the significance of circRNAs in liver cancer stem cell exosomes, particularly circ-ZEB1 and circ-AFAP1, in regulating EMT and influencing liver cancer stemness. These circRNAs are closely associated with liver cancer stemness and poor prognosis, playing a critical role in the EMT process. The study highlights the importance of exosomal circRNAs in tumor progression and intercellular communication within the HCC microenvironment.

In conclusion, the multifaceted roles of circRNAs in HCC, ranging from diagnostic biomarkers to modulators of tumor progression and therapeutic targets, are rapidly being unraveled. Their diverse mechanisms of action and interaction with the tumor microenvironment offer valuable insights for improved management and treatment strategies in HCC.

3.3. Gastrointestinal cancers

3.3.1. Colorectal cancer (CRC)

Recent research has increasingly focused on the role of exosomal circRNAs in CRC, emphasizing their potential as diagnostic indicators, targets for therapy, and important factors in tumor advancement and resistance to treatment (Fig. S2).

Several studies have focused on the diagnostic capabilities of exosomal circRNAs. For example, Xie et al. [79] identified circ-PNN in patient exosomes, identifying it as a potential non-invasive biomarker for CRC with significant diagnostic value . Numerous studies have examined the impact of exosomal circRNAs on the survival, invasion, and apoptosis of colorectal cancer cells. For instance, He et al. [80] demonstrated that sevoflurane, a general anesthetic, suppresses CRC cell viability and invasion while promoting apoptosis by modulating the exosome-mediated circ-HMGCS1/miR-34a-5p/SGPP1 axis. This study suggests a potential therapeutic role for sevoflurane in CRC treatment . Beyond diagnostics, exosomal circRNAs also play a pivotal role in the dynamic processes of tumor progression as demonstrated by various studies.

Multiple research studies offered understanding of the processes involved in the advancement of CRC. Bai et al. [81] reported that circ_0007334 accelerates CRC progression by sequestering miR-577 to derepress KLF12, and Lei et al. [82] performed an integrated analysis of exosome circRNAs in CRC, identifying significant correlations between these molecules and immune cell infiltration. Hu et al. [83] reported that exosomal circCOL1A1 promotes angiogenesis in CRC by activating the Smad2/3 pathway and recruiting EIF4A3 protein. Additionally, Yu et al. 84] highlighted the significance of exosomal circ_FMN2 from serum of patients with CRC in advancing cancer via the miR-338-3p/Musashi-1 signaling (MSI1) pathway. Finally, Yu et al. [84] offered insights into the control of CRC progression, indicating that circ_0005615 regulates this process via the miR-873-5p/FOS-like antigen 2 (FOSL2) signaling pathway. Moreover, exosomal circRNAs not only influence tumor progression but also impact treatment outcomes, particularly in terms of radiosensitivity and drug resistance.

Recent advancements have been propelled by groundbreaking research into exosomal circRNAs, revealing their significant roles in radiosensitivity, drug sensitivity, and resistance. Li et al. [85] reported that exosomal circ_IFT80 enhanced tumorigenesis and reduced radiosensitivity in CRC by controlling the miR-296-5p/MSI1 pathway, enhancing our understanding of radioresistance mechanisms in CRC. The studies by Xu et al. [58] and Zhao et al. [37] emphasized the significance of exosomal circRNAs in chemoresistance. Furthermore, the study by Wang et al. [86] demonstrated that exosome-delivered circRNA enhances glycolysis, thereby promoting chemotherapy resistance in colorectal cancer through the miR-122-PKM2 axis. This finding highlights a novel mechanism behind chemotherapy resistance in CRC. Zhang et al. [87] added to this by illustrating how exosomal transfer of circ_0006174 contributes to doxorubicin chemoresistance in CRC via the miR-1205/CCND2 axis. Cornell et al. [88] examined the impact of exosome-derived circ_0094343 on CRC chemosensitivity, demonstrating its control over glycolysis through the miR-766-5p/tripartite motif-containing 67 (TRIM67) pathway. These findings underscore the critical role of exosomal circRNAs in shaping the clinical landscape of colorectal cancer, from progression to treatment resistance.

Overall, these research findings highlight the significant impact of exosomal circRNAs on the advancement, identification, and resistance to treatment in colorectal cancer. The possibility of using them as biomarkers and targets for therapy creates new opportunities for managing and treating CRC.

3.3.2. Gastric cancer (GC)

Recent studies have identified exosomal circRNAs as promising biomarkers for GC diagnosis and prognosis. Zheng et al. [89] focused on hsa_circ_0015286 and showed its correlation with tumor size, tumor node metastasis (TNM) stage, and lymph node metastasis, with a notable decrease in expression after surgery. Wang et al. [90] identified multiple circRNAs unique to GC, including hsa_circ_0074362, circNRIP1, circAKT3, circ-DONSON, circPSMC3, circ-KIAA1244, circPVRL3, circPVT1, hsa_circ_0000096, ciRS-133, hsa_circ_0001017, and hsa_circ_0061276. These circRNAs, present in exosomes, show potentially high clinical diagnostic values for GC. Huang et al. [91] found hsa_circ_000200

to be overexpressed in GC tissues, serum, and serum exosomes. Notably, hsa_circ_000200 exhibited a remarkable diagnostic ability, surpassing traditional tissue and serum level assessments. Liang et al. [92] and Wang et al. [93] emphasized the potential of circRNAs in the early detection and monitoring of GC. Liang et al. [92] demonstrated that knockdown of circ-LDLRAD3 reduces resistance to cisplatin and hinders GC progression, underscoring its significance in treatment monitoring. Wang et al. [93] identified an exosomal circRNA, circ-RanGAP1, as a key player in GC that regulates the malignant behaviors of the tumor by sponging miR-877-3p. This interaction affects the expression of the host gene and contributes to the proliferation, invasion, migration, and drug resistance of GC cells. The study emphasizes that exosomal circRNAs, such as circ-RanGAP1, can be potential biomarkers for disease diagnosis and effective therapeutic targets in GC. They highlighted the potential of circRNAs, particularly exosomal circRNAs, as novel diagnostic biomarkers for gastrointestinal malignancies, including gastric cancer.

Exosomal circRNAs play a role in different facets of gastric cancer advancement, such as cellular growth, movement, infiltration, and blood vessel formation. Xie et al. [94] reported that circ-SHKBP1, elevated in GC tissues and blood samples, enhances the growth, movement, invasion, and angiogenesis of cancer cells via the miR-582-3p/HUR/VEGF axis, emphasizing its role in the rapid progression of gastric cancer. Recent studies have explored the role of exosomal circRNAs in enhancing metastasis in GC. Shen et al. [95] explored the role of hsa_circ_0000437 in GC, which is differentially expressed between GC and adjacent non-cancerous tissues. It influences cell proliferation, invasion, migration, and apoptosis. Its presence in GC-secreted exosomes, transferred to human lymphatic endothelial cells (HLECs), promotes lymphangiogenesis and lymph node metastasis through the heat shock protein family A member 2-extracellular signal-regulated kinase (HSPA2-ERK) pathway. This suggests that hsa_circ_0000437 could serve as a biomarker for GC progression and a focal point for therapies targeting metastasis. Finally, they highlighted the role of circ-STAU2, a circRNA that is downregulated in GC. Their findings indicate that its overexpression inhibits GC cell proliferation, invasion, and migration. Intriguingly, when packaged in exosomes and delivered to recipient cells, circ-STAU2 acts as a sponge for miR-589, thereby modulating actin filament capping protein subunit alpha-1 (CAPZA1) expression. This suggests a tumor-suppressive role for exosome-delivered circ-STAU2, opening up a potential therapeutic pathway in GC treatment [96]. While exosomal circRNAs facilitate various aspects of cancer progression, their contribution to chemoresistance highlights another layer of complexity in gastric cancer's treatment challenges.

Exosomal circRNAs are also involved in promoting resistance to chemotherapy in GC. Yao et al. [97] revealed that circ-PVT1 in exosomes leads to cisplatin resistance by regulating autophagy, invasion, and apoptosis via the miR-30a-5p/YAP1 axis in GC cells. Zhong et al. [98] showed that circ_0032821 modulated SRY-box transcription factor 9 (SOX9) expression and enhanced oxaliplatin resistance in GC cells through miR-515-5p, highlighting a potential target for therapy. Continuing the exploration of exosomal circRNAs in GC, Chen et al. [99] highlighted the role of exosomal circ_0091741 in enhancing autophagy and resistance to chemotherapy in GC cells through the miR-330-3p/TRIM14/Dvl2/Wnt/β-catenin pathway. This study provides a deeper understanding of the molecular mechanisms underlying chemoresistance in GC, offering potential avenues for overcoming therapeutic resistance. The studies by Zheng et al. [100] and Song et al. [101] have identified specific exosomal circRNAs as novel therapeutic targets in GC. Zheng et al. [100] 's study on circ_0038138 in GC demonstrated its involvement in promoting glycolysis, proliferation, and spread through the miR-198/EZH2 pathway, indicating its promise as a target for therapy. Song et al. [101] explored the role of exosomal hsa_circ_0017252 in modifying the tumor microenvironment, demonstrating that this circRNA inhibits macrophage M2 polarization, thereby suppressing GC cell invasion and affecting tumor growth *in vivo*. This study adds a new dimension to the understanding of exosomal circRNAs in modulating the tumor microenvironment and highlights potential immunomodulatory strategies in GC treatment.

This section of the review highlights the important influence of exosomal circRNAs in gastric cancer, focusing on their involvement in resistance to treatment, alteration of the tumor environment, potential as targets for therapy and markers for diagnosis, as well as their relevance in early detection and disease monitoring. The intricate interplay between these molecules and various cellular pathways offers a rich landscape for future research, potentially leading to novel therapeutic strategies and improved diagnostic tools in the fight against GC (Fig. 3).

3.3.3. Esophageal squamous cell carcinoma (ESCC)

Several studies have highlighted the importance of exosomal circRNAs in ESCC. Liu et al. [102] identified serum exosomal hsa_circ_0026611 as a potential indicator for lymph node spread and prognosis in ESCC. It was found that increased levels of this circRNA are strongly linked to lymph node spread and unfavorable survival results. The diagnostic value was confirmed through receiver operating characteristic (ROC) analysis. Zang et al. [103] explored the role of exosomal circ_0000337 in cisplatin (CDDP) resistance in ESCC. It was discovered that this circRNA contributes to resistance to cisplatin by modulating Janus kinase 2 (JAK2) via miR-377-3p. This study suggests that targeting exosomal circ_0000337 could be a promising therapeutic approach for treating ESCC. Hu et al. [104] investigated the role of circ_0024108 in the progression of ESCC. They discovered that this circRNA is overexpressed in ESCC and plays a significant role in promoting cell growth, motility, and invasiveness. The research indicates that circ_0024108 could serve as a promising biomarker for diagnosing ESCC (Table 5) [79–110].

3.4. Pancreatic cancer

In pancreatic cancer, exosomal circRNAs have also been identified as key players. Chen et al. [105] examined the impact of exosomal circRNAs on the regeneration of pancreatic cancer cells after exposure to radiation. They identified several circRNAs potentially involved in this process, highlighting them as potential therapeutic targets to prevent tumor recurrence post-radiation therapy. Yao et al. [106] demonstrated that exosomal circ_0030167, originating from bone marrow-mesenchymal stem cells (BM-MSCs), suppresses the invasion, migration, proliferation, and stem cell characteristics of pancreatic cancer cells. This finding opens new avenues for therapeutic interventions targeting this circRNA. Gao et al. [107] studied the role of circ_0006790 in pancreatic ductal adenocarcinoma (PDAC). They found that this circRNA, carried by BM-MSC-derived exosomes, regulates DNA methylation, thereby influencing tumor growth and immune escape. Hong et al. [108] identified exosomal circRNAs hsa_circ_0006220 and hsa_circ_0001666 as potential biomarkers for detecting pancreatic cancer. Their study suggests that these circRNAs could be utilized in strategies for the early detection of pancreatic cancer.

3.5. Cholangiocarcinoma

In cholangiocarcinoma, Xu et al. [109] discovered that cholangiocarcinoma-associated circular RNA 1 (circ-CCAC1) plays a role in promoting tumor progression and stimulating the formation of new blood vessels. This circRNA disrupts vascular endothelial

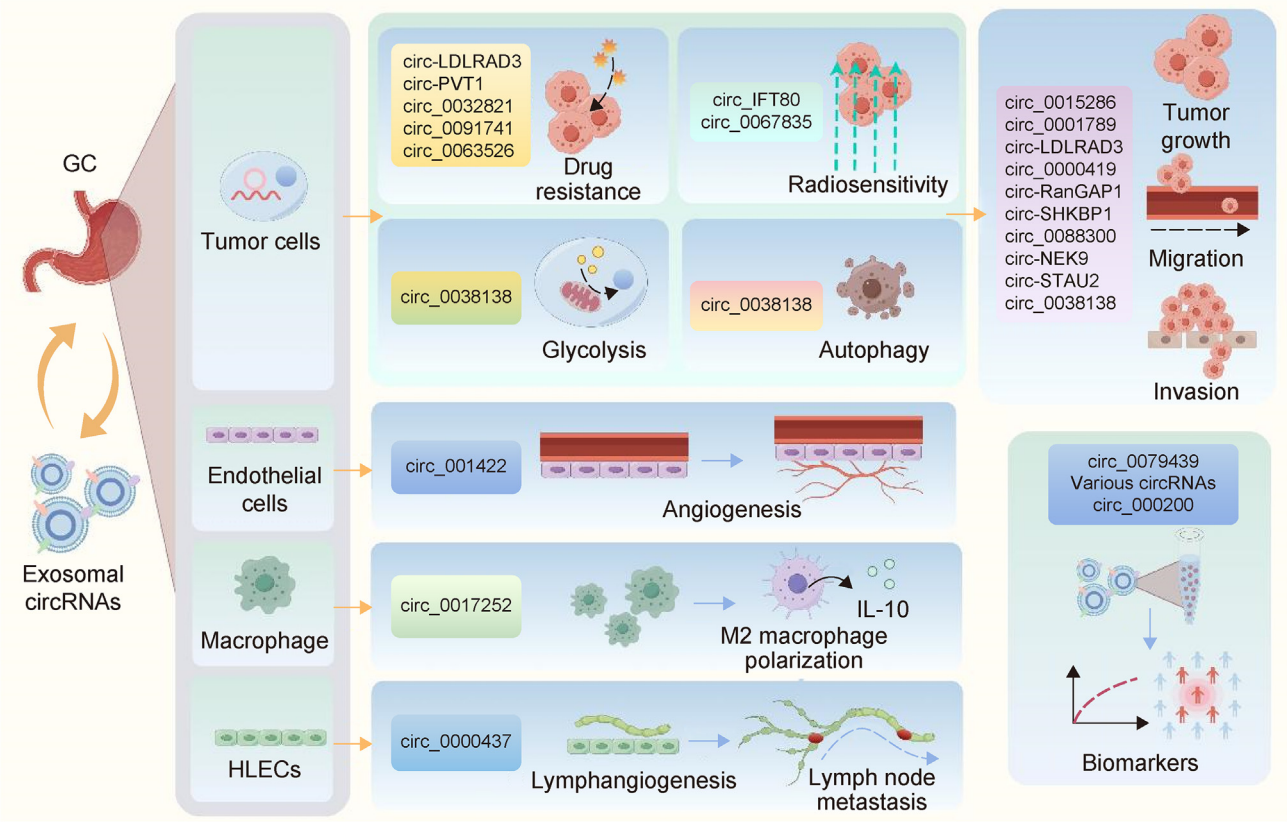

Fig. 3. The functions and mechanisms of exosomal circular RNAs (circRNAs) in gastric cancer. This part emphasizes the significant impact of exosomal circRNAs in gastric cancer (GC), particularly their roles in therapeutic resistance, modulation of the tumor microenvironment, potential as therapeutic targets and biomarkers, and their implications in early detection and monitoring of the disease. circRNA exosomes can act on GC tumor cells, endothelial cells, macrophages, and human lymphatic endothelial cells (HLECs), influencing GC tumor progression in various ways. circRNA exosomes can affect tumor cell drug resistance, radiation sensitivity, glycolysis, and apoptosis levels, as well as the proliferation, migration, and invasiveness of tumor cells. They influence endothelial cell angiogenesis through circ_001422, affect M2 polarization of macrophages through circ_0017252, and impact lymph node metastasis through circ_0000437, among other effects. The intricate interplay between these molecules and various cellular pathways offers a rich landscape for future research, potentially leading to novel therapeutic strategies and improved diagnostic tools in the fight against GC.

barriers, suggesting its potential as a therapeutic target. Chen et al. [110] investigated the role of tumor-associated macrophages (TAMs) in promoting cholangiocarcinoma progression via exosomal circ_0020256. They found that this circRNA enhances the growth, movement, and infiltration of cancer cells, offering valuable information for developing novel treatment approaches.

3.6. Gynecologic tumor

In recent years, significant advancements have been made in understanding the role of circRNAs and exosomes in breast, cervical, ovarian, and endometrial cancers. These findings have opened new avenues in cancer diagnostics and therapeutics (Table 6) [111–119]. Building on these foundational insights, we delve into specific cancer types, starting with breast cancer.

3.6.1. Breast cancer

Breast cancer research has shown a substantial interest in circRNAs and their interactions with miRNAs and exosomes. For example, a crucial investigation demonstrated the role of circ_UBE2D2 in developing tamoxifen resistance in breast cancer cells [111]. This research is particularly significant given the widespread use of tamoxifen in treating estrogen receptor-positive breast cancer. The study revealed that circ_UBE2D2, found in exosomes, binds to miR-200a-3p, thereby influencing drug resistance, a major hurdle in effective breast cancer treatment. This finding underscores the challenge of overcoming tamoxifen resistance. The diagnostic capabilities of serum exosomal hsa_circ_0000615 in breast cancer were investigated in a study by Liu et al. [112]. The discovery of a notable increase in this circRNA among individuals with breast cancer indicates its promise as a non-invasive biomarker for early identification, a crucial element in enhancing the outlook for breast cancer patients. Lu et al. [113] investigated how circ_0001142, released from breast cancer cells under endoplasmic reticulum stress, affects macrophage polarization in the tumor microenvironment. This research sheds light on the complex interactions between cancer cells and the immune system, opening up new avenues for therapeutic interventions. Lastly, Ma et al. [114] focused on triple-negative breast cancer (TNBC), which is known for being a highly aggressive type of breast cancer. circEGFR (hsa_circ_0080220) was discovered to have elevated levels in TNBC cell lines, patient tissues, and plasma exosomes, and these levels were correlated with unfavorable patient outcomes. It plays a crucial role in driving the malignant progression of TNBC and affects the responsiveness of these cancer cells to pirarubicin, a drug used in chemotherapy.

3.6.2. Cervical cancer

In cervical cancer, exosomal circRNAs also play a pivotal role. A recent study showed that circ_PVT1 triggers the EMT, an essential step for the spread of cervical cancer [115]. This finding is significant as it highlights a potential target for preventing the spread of

Table 5
Exosomal circRNAs in gastrointestinal cancers.

Target cell	Mechanism signal axis	Cell function	Refs.
Diagnostic use	Not specified	Biomarker for CRC detection	[79]
CRC cells	circ-HMGCS1/miR-34a-5p/SGPP1	Suppresses CRC cell viability and invasion	[80]
CRC cells	circ_0007334/miR-577/KLF12	Accelerates CRC progression	[81]
CRC cells	Not specified	Significant correlations in immune cell infiltration	[82]
Angiogenesis	circCOL1A1/Smad2/3/EIF4A3	Promotes angiogenesis in CRC	[83]
CRC cells	circ_0005615/miR-873-5p/FOSL2	Regulates CRC progression	[84]
CRC cells	circ_IFT80/miR-296-5p/MSI1	Enhances tumorigenesis, and suppresses radiosensitivity	[85]
CRC cells	circ_0067835/miR-296-5p/IGF1R	Enhances radiosensitivity in CRC	[86]
CRC cells	circ_0006174/miR-1205/CCND2	Contributes to doxorubicin chemoresistance	[87]
CRC cells	circ_0094343/miR-766-5p/TRIM67	Regulates glycolysis and and chemosensitivity	[88]
Diagnostic use	Not specified	Associated with tumor size, TNM stage, and lymph metastasis	[89]
Diagnostic use	Not specified	High clinical diagnostic values for GC	[90]
Diagnostic use	miR-4659a/b-3p/HBEGF axis	Remarkable diagnostic ability for GC	[91]
GC cells	circ-LDLRAD3/miR-588/SOX5	Reduces cisplatin chemoresistance, and inhibits GC	[92]
GC cells	circ-RanGAP1/miR-877-3p	Regulate malignant behavior of GC cells	[93]
GC cells	circSHKBP1/miR-582-3p/HUR/VEGF	Promotes cancer cell proliferation, migration, and invasion	[94]
HLECs	hsa_circ_0000437/HSPA2-ERK	Promotes lymphangiogenesis and lymph node metastasis	[95]
GC cells	circSTAU2/miR-589/CAPZA1	Inhibits GC cell proliferation, invasion, migration	[96]
GC cells	circ-PVT1/miR-30a-5p/YAP1	Leads to cisplatin resistance in GC cells	[97]
GC cells	circ_0032821/miR-515-5p/SOX9	Contributes to oxaliplatin resistance in GC cells	[98]
GC cells	circ_0091741/miR-330-3p/TRIM14/Dvl2/Wnt/β-catenin	Promotes GC cell autophagy and chemoresistance	[99]
GC cells	circ_0038138/miR-198/EZH2	Enhances glycolysis, growth, and metastasis in GC	[100]
Macrophages	hsa_circ_0017252/miR-17-5p	Inhibits macrophage M2 polarization	[101]
Diagnostic use	Not specified	Biomarker for lymph node metastasis and prognosis in ESCC	[102]
ESCC cells	circ_0000337/miR-377-3p/JAK2	Contributes to cisplatin resistance	[103]
ESCC cells	circ_0024108/miR-488-3p/USP14	Promotes cell growth, motility, and invasiveness in ESCC	[104]
Pancreatic cancer	hsa_circ_0002130/hsa_miR_4482-3p/NBN	Potential therapeutic targets to prevent tumor recurrence post-radiation therapy	[105]
Pancreatic cancer cells	circ_0030167/miR-338-5p/Wif1/Wnt8/β-catenin axis	Inhibits invasion, migration, proliferation, and stemness	[106]
PDAC	circ_6790/S100A11/CBX7	Regulate DNA methylation, thereby influencing tumor growth and immune escape	[107]
Diagnostic use	Not specified	Biomarkers for pancreatic cancer diagnosis	[108]
Angiogenesis	circ-CCAC1/Not specified	Induces angiogenesis, and disrupts vascular endothelial barriers	[109]
Cholangiocarcinoma cells	circ_0020256/miR-432-5p/E2F3	Promotes tumor cell proliferation, migration, and invasion	[110]

CRC: colorectal cancer; GC: gastric cancer; ESCC: esophageal squamous cell carcinoma; PDAC: pancreatic ductal adenocarcinoma; HLECs: human lymphatic endothelial cells.

Table 6
Exosomal circular RNAs (circRNAs) in gynecologic tumor.

Parent cell	Target cell	Mechanism signal axis	Cell function	Refs.
Breast cancer cells	Breast cancer cells	circ_UBE2D2/miR-200a-3p	Contributes to tamoxifen resistance	[111]
Serum (exosomes)	Diagnostic use	Not specified	Biomarker for early detection of breast cancer	[112]
Breast Cancer cells	Macrophages	circ_0001142/circ_0001142/miR-361-3p/PIK3CB	Affects macrophage polarization	[113]
TNBC cell lines, patient tissues	TNBC cells	circEGFR/miR-1299/EGFR	Regulates malignant progression and drug sensitivity	[114]
Cervical cancer cells	Cervical cancer cells	circ_PVT1/miR-1286	Induces EMT	[115]
Cervical cancer cells	Cervical cancer cells	circ_0006646/miR-758-3p/RRM2	Accelerates growth and metastasis	[116]
Serum (exosomes)	Ovarian cancer cells, T cells	circ-0001068/PD1	Biomarker for ovarian cancer, influences PD1 expression	[117]
Ovarian cancer cells	Ovarian cancer cells	circ-PIP5K1A/miR-942-5p/NFIB axis	Contributes to cisplatin resistance	[118]
Tumor-associated macrophages	Endometrial cancer cells	hsa_circ_0001610/miR-139-5p/cyclin B1	Reduces radiosensitivity	[119]

TNBC: triple-negative breast cancer; EMT: epithelial-mesenchymal transition.

cervical cancer. The study by Yu et al. [116] showed that circ_0006646 promotes the growth and spread of cervical cancer by affecting the miR-758-3p/ribonucleotide reductase M2 (RRM2) pathway. Understanding this mechanism opens up new therapeutic possibilities for managing cervical cancer. These studies underscore the importance of exosomal circRNAs in the molecular mechanisms of cervical cancer progression and metastasis.

3.6.3. Ovarian cancer

For ovarian cancer, which often presents late in patients, exosomal circRNAs offer promising biomarkers. Wang et al. [117] identified circ-0001068 in serum exosomes as a novel biomarker for ovarian cancer, potentially offering a method for early detection of the disease. This circRNA also influences programmed death 1 (PD-1) expression in T cells, providing insights into the immune evasion tactics of ovarian cancer cells. Sheng and Wang [118] focused on the role of circ-PIP5K1A in cisplatin resistance in ovarian cancer. Their findings suggest that targeting this exosomal circRNA could enhance the effectiveness of chemotherapy, marking a significant advancement in the treatment of this often drug-resistant cancer.

3.6.4. Endometrial cancer

Endometrial cancer research, particularly concerning radioresistance, has also benefited from circRNA studies. Gu et al. [119] discovered that hsa_circ_0001610, carried in exosomes from tumor-associated macrophages, reduces radiosensitivity in endometrial cancer cells. This discovery is crucial for understanding and

potentially overcoming radioresistance in the treatment of endometrial cancer. After highlighting the impact of exosomal circRNAs in endometrial cancer, it is pivotal to explore their similar roles in other malignancies. Transitioning into nervous system neoplasms, the next section delves into glioma.

3.7. Nervous system neoplasms

The burgeoning research on exosomal circRNAs in glioma offers profound insights into their multifaceted roles in disease progression, resistance to therapy, and potential as diagnostic and prognostic biomarkers. Collectively, these studies paint a comprehensive picture of how exosomal circRNAs influence glioma biology. With the emerging focus on exosomal circRNAs, the field of glioma research has witnessed a significant leap forward, recognizing these molecules as key players in the disease's progression and response to treatment (Table 7) [120–129]. This fundamental understanding sets the stage for exploring specific exosomal circRNAs and their precise roles in glioma progression as seen in recent studies.

Recent progress has significantly enhanced our comprehension of the impact of exosomal circRNAs on promoting glioma advancement. Yin and Liu's study [120] highlighted the role of circ Matrix Metalloproteinase-1(MMP1), encapsulated within exosomes, in promoting glioma through the miR-433/HMGB3 axis. This critical research underlines the intricate and complex interplay between exosomes and circRNAs, synergistically influencing crucial molecular pathways within tumor cells. Furthermore, Han et al. [121] shed light on exosomal circ-HIPK3, identifying it as a vital element in tumor progression and resistance to the chemotherapy drug temozolomide (TMZ), operating through the miR-421/ZIC5 axis. This discovery is crucial for emphasizing the intricate connection between exosomal circRNAs and microRNA networks, significantly impacting the behavior and aggressiveness of tumors. Adding to this, Li and Lan [122] discovered that circ-Serpine2, another exosomal circRNA, significantly contributes to the exacerbation of malignant progression in glioma via the miR-124-3p/kinesin family member 20A (KIF20A) pathway. These collective findings emphasize the critical role of exosomes as not just carriers but active modulators of circRNA activity, which in turn impacts tumor behavior, progression, and the overall cellular environment within gliomas. With the established roles of exosomal circRNAs in tumor progression, their impact extends into the realm of chemotherapy resistance.

Exosomal circRNAs are playing an increasingly important role in glioma treatment, especially in overcoming resistance to TMZ. The study by Ding et al. [123] emphasized the importance of exosomal circ_0072083 in enhancing NANGO expression, leading to heightened resistance to TMZ. This pivotal finding enhances our understanding of how exosomes can actively alter the genetic and molecular landscape of tumor cells, leading to a heightened resistance to chemotherapy drugs. In another critical study, Li et al. [124] elucidated the role of exosomal hsa_circ_0043949 in promoting resistance to TMZ in glioblastoma, specifically through its influence on the ITGA1 axis. Moreover, the research conducted by Si et al. [125] provided profound insights into the role of heparanase in the secretion and function of exosomes, which significantly affects the composition of circRNAs and contributes to chemoresistance in glioma. Expanding on this, the studies by Li and Lan [126] and Li et al. [127] investigated the intricate processes by which exosomal circRNAs like circ-GLIS3 and circ-AHCY bolster resistance to TMZ, revealing the diverse ways in which exosomes and their circRNA contents play a role in emergence of drug resistance in glioma. Beyond their role in treatment resistance, exosomal circRNAs also show promise in the diagnostic and prognostic arenas of glioma management.

The use of exosomal circRNAs for diagnosing and predicting outcomes in glioma is a promising and rapidly advancing field of study. The groundbreaking study by Xia and Gu [128] identified a panel of exosome-derived circRNAs as potential biomarkers for glioblastoma, paving the way for their use in noninvasive diagnostic processes. Similarly, the research by Cao et al. [129] showed the effectiveness of a serum exosome circRNA panel in detecting high-grade astrocytoma, offering a novel, noninvasive approach for early detection and ongoing monitoring of the condition. Overall, these findings suggest that exosomal circRNAs could serve as dependable, easily accessible, and rich sources of information for early detection, accurate diagnosis, and effective monitoring of glioma, thereby providing valuable insights into disease progression and patient response to therapy. These diagnostic advancements highlight the broader implications of exosomal circRNAs in glioma, emphasizing their potential in transforming patient care.

These circRNAs, protected and transported by exosomes, impact glioma pathogenesis, treatment response, and resistance. Their potential as noninvasive biomarkers for diagnosis and prognosis further highlights their clinical significance. Further investigation into exosomal circRNAs may result in the creation of innovative treatment approaches, advancements in diagnostic techniques, and a deeper comprehension of glioma biology, ultimately revolutionizing the care and control of glioma.

3.8. Circulatory system tumors

Recent research has increasingly emphasized the growing importance of exosomal circRNAs in hematological malignancies, including multiple myeloma (MM) and leukemia. These studies

Table 7
Exosomal circRNAs in nervous system neoplasms.

Exosomal circRNAs	Parent cell	Target cell	Mechanism signal axis	Cell function	References
circMMP1	Glioma cells	Glioma cells	circMMP1/miR-433/HMGB3	Promotes glioma progression	[120]
circ-HIPK3	Glioma cells	Glioma cells	circ-HIPK3/miR-421/ZIC5	Influences tumor progression and TMZ resistance	[121]
circ-Serpine2	Glioma cells	Glioma cells	circ-Serpine2/miR-124-3p/KIF20A	Exacerbates malignant progression	[122]
circ_0072083	Glioma cells	Glioma cells	circ_0072083/mir-1252-5p/NANGO	Contributes to resistance to TMZ	[123]
hsa_circ_0043949	Glioma cells	Glioma cells	hsa_circ_0043949/miR-876-3p/ITGA1	Promotes resistance to TMZ in glioblastoma	[124]
Not specified (Study of Heparanase)	Glioma cells	Glioma cells	hsa_circ_0042003/U251	Affects secretion and function of exosomes in chemoresistance	[125]
circ-GLIS3	Glioma cells	Glioma cells	circ-GLIS3/miR-548m/MED31 Axis	Enhances TMZ resistance	[126]
circ-AHCY	Glioma cells	Glioma cells	circ-AHCY/Wnt/β-catenin	Enhances TMZ resistance	[127]
Various (diagnostic panel)	Glioma cells	Diagnostic use	Not specified	Biomarkers for glioblastoma	[128]
Serum exosome circRNA panel	Serum (exosomes)	Diagnostic use	Not specified	Biomarkers for diagnosing high-grade astrocytoma	[129]

Note. TMZ: temozolomide.

Table 8
Exosomal circRNAs in circulatory system tumors.

Tumor type	Exosomal circRNAs	Parent cell	Target cell	Mechanism signal axis	Cell function	References
Multiple myeloma	circ_0007841	Bone Marrow-derived Plasma cells	MM cells	circ_0007841/miR-338-3p/BRD4	Promotes MM progression	[130]
	circ-G042080	MM cells	Myocardial cells (H9C2)	circ-G042080/hsa-miR-4268/TLR4	Involved in MM-related myocardial damage	[131]
	circ-CACNG2	MM cells (U266)	Cardiomyocytes (H9C2)	circ-CACNG2/miR-197-3p/caspase3	Promotes cardiomyocyte apoptosis in MM	[132]
	circ-ATP10A	MM cells	Not Specified	circ-ATP10A/miR-6758-3p/hsa-miR-3977 and others	Biomarker for MM angiogenesis	[133]
Acute myeloid leukemia (AML)	circ_0004136	Not Specified	AML cells	circ_0004136/miR-570-3p/TSPAN3	Enhances AML progression	[134]
Chronic myeloid leukemia (CML)	hsa_circ_0058493	Peripheral Blood Mononuclear cells (PBMCs)	CML cells	hsa_circ_0058493/miR-548b-3p (predicted)	Biomarker for Imatinib-resistant CML	[135]

Note. AML: acute myeloid leukemia; CML: chronic myeloid leukemia; MM: multiple myeloma.

emphasize the pivotal role of these circRNAs not only in the progression of these diseases but also in their potential as therapeutic targets and biomarkers (Table 8) [130–135]. To further illustrate the role of exosomal circRNAs in hematological malignancies, we delve into their specific impacts in MM, firstly.

3.8.1. Exosomal circRNAs in multiple myeloma

Exosomal circRNAs are becoming increasingly important in the study of MM, providing fresh perspectives on the causes of the disease and possible treatment options. Wang et al. [130] made a significant breakthrough by identifying circ_0007841 in bone marrow-derived plasma cells. They revealed that this circRNA accelerates MM progression by engaging the miR-338-3p/BRD4 signaling pathway. This discovery is significant as it unveils the oncogenic properties of circ_0007841, which promotes cell growth and motility while inhibiting apoptosis, thus underscoring its potential as a target for MM treatment. Sun et al. [131] expanded the understanding of exosomal circRNAs in MM by focusing on circ-G042080. Their research established a direct correlation between the abundance of this circRNA in serum exosomes and the severity of MM, as well as MM-related myocardial damage. The findings imply that circ-G042080 impacts the development of MM by affecting the miRNA/TLR4 axis, making it a new potential target for treating heart damage in MM patients. Furthermore, Yu et al. [132] explored the impact of exosomal circ-CACNG2 on MM-related cardiomyocyte apoptosis. Their study highlighted that circ-CACNG2 promotes apoptosis through the miR-197-3p/caspase3 axis, thereby demonstrating the broader systemic effects of MM beyond its hematological manifestations. Additionally, Yu et al. [133] identified exosomal circ-ATP10A as a significant biomarker for MM angiogenesis. This discovery is crucial, as it links circ-ATP10A to the regulation of key angiogenic factors, highlighting its potential utility in prognostic assessments and as a novel therapeutic target to inhibit angiogenesis in MM.

3.8.2. Exosomal circRNAs in leukemia

Exosomal circRNAs have been demonstrated to significantly impact the progression of leukemia, particularly in pediatric cases of acute myeloid leukemia (AML). Bi et al. [134] discovered that exosomal circ_0004136 significantly enhances the progression of AML. This circRNA modulates the miR-570-3p/TSPAN3 axis, impacting vital cellular processes such as viability, migration, invasion, and apoptosis. The research provides important insights into the role of circ_0004136 as a key regulator in AML, influencing the disease's aggressiveness and indicating its potential as a therapeutic target. In chronic myeloid leukemia (CML), exosomal circRNAs have also been identified as key players, particularly in drug resistance scenarios. Zhong et al. [135] identified hsa_circ_0058493, which is highly expressed in the peripheral blood mononuclear cells (PBMCs) and exosomes of CML patients. This circRNA is associated with poor clinical efficacy of imatinib, a frontline drug in treatment of CML. The study positions hsa_circ_0058493 as a promising biomarker for imatinib resistance, offering a potential target for therapeutic intervention to overcome drug resistance in CML.

Collectively, these research findings illustrate the complex interactions between circRNAs and cellular signaling pathways, highlighting the potential of exosomal circRNAs to serve as biomarkers for disease severity, progression, and drug resistance. These insights open new avenues for targeted therapies, potentially enhancing our capacity to more effectively combat these challenging diseases.

3.9. Other cancer types

Prostate cancer research has advanced significantly through the identification of various exosomal circRNAs and their roles in disease progression and medication resistance. Li et al. [136] discovered that circ_0044516 is elevated in prostate cancer, promoting cell proliferation and metastasis and establishing its potential as a novel oncogenic biomarker. This circRNA promotes cell proliferation and metastasis, establishing its potential as a novel oncogenic biomarker. This discovery opens new avenues for targeting circ_0044516 in therapeutic strategies. Zhang et al. [137] focused on circ-XIAP in the context of docetaxel resistance in prostate cancer. The results showed that circ-XIAP regulates the miR-1182/TPD52 pathway, thereby contributing to chemotherapy resistance. This study underscores the potential of targeting circ-XIAP to overcome docetaxel resistance in prostate cancer treatment. Zhang et al. [138] identified circ_0081234 as promoting of tumor growth and metastasis via the miR-1/MAP 3K1 axis. This discovery sheds light on the molecular mechanisms underlying prostate cancer progression and suggests new therapeutic avenues. Yang et al. [139] demonstrated that modulating the androgen receptor (AR) in osteoblasts influences the recruitment of prostate cancer cells to the bone microenvironment through the exosomal circ-DHPS/miR-214-3p/CCL5 pathway. This research offers insights into the metastatic process in prostate cancer and identifies potential targets for preventing bone metastasis. Upon the understanding of exosomal circRNAs in prostate cancer, we now explore how exosomal circRNAs influence oral squamous cell carcinoma (OSCC), highlighting their potential as biomarkers and therapeutic targets.

In OSCC, a study discovered that the increased expression of circ_0000199 in exosomes circulating in the body is strongly linked to poorer survival rates [140]. The circRNA, associated with betel quid consumption, tumor size, spread to lymphatic metastasis, and TNM stage, could serve as a promising biomarker and therapeutic target in OSCC. Chen et al. [141] explored the function of circRNA

has_circ_0069313 in OSCC, finding that it promotes immunity escape via the miR-325-3p-Foxp3 axis in both OSCC cells and Treg cells. The study provides a fresh outlook on how OSCC evades the immune system and suggests new possibilities for immunotherapy. Dai et al. [142] highlighted the diagnostic capabilities of exosomal hsa_circ_0082002 and hsa_circ_0003863 in papillary thyroid cancer, showing a strong connection with lymph node metastasis and vascular invasion. These findings open up possibilities for early detection and intervention in papillary thyroid cancer. Wu et al. [143] initially proposed circFNDC3B as a biomarker in papillary thyroid cancer. However, the subsequent retraction of their study underscores the importance of rigorous validation in circRNA research.

In cutaneous squamous cell carcinoma (cSCC), the work of Zhang et al. [144] marks a significant advancement in understanding the disease's molecular underpinnings. They identified circ-CYP24A1 as an upregulated exosomal circRNA that promotes tumor progression. This identification not only presents a potential treatment target but also a non-surgical marker for cSCC, thereby broadening the options available for patient care and therapy. Renal cell carcinoma (RCC) research has also benefited from exosomal circRNA studies. Xiao and Shi [145] investigated the function of circ_400068, discovering its increased expression and inhibition of apoptosis, suggesting it as a candidate therapeutic target. Complementarily, Qian et al. [146] reported that circ-PRKCI, which is highly expressed in RCC tissues and serum exosomes. The circRNA boosts cancer cell growth, movement, and infiltration, thereby solidifying the crucial function of exosomal circRNAs in the advancement of RCC and presenting novel treatment approaches. Ahangar Davoodi et al. [147] reviewed the role of non-coding RNAs, specifically exosomal non-coding RNAs, in the progression of retinoblastoma. The conversation revolved around different non-coding RNAs, like circ-E2F3 and NEAT1, being identified as oncogenes, offering valuable information on possible treatment targets and diagnostic resources for retinoblastoma (Table 9) [136–147].

Therefore, recent research highlights the crucial role of exosomal circRNAs in various cancers, including prostate, oral squamous cell, thyroid, and cutaneous cancers. Studies pinpoint specific circRNAs that contribute to tumor progression, drug resistance, and metastasis, providing insights into molecular mechanisms and potential therapeutic targets. These findings underscore the importance of circRNAs in cancer diagnostics and treatment, emphasizing their potential as biomarkers and targets in personalized medicine.

4. Conclusion and perspectives

Exosomes, the versatile couriers within the TME, play a crucial role in the progression of cancer. They deftly carry genetic messages and proteins between cells, subtly influencing cancer progression and immune system responses. Notorious for aiding tumor growth and metastasis, exosomes facilitate the formation of supportive niches for cancer cells, fostering conditions that enhance tumor survival and expansion. As cancer cells evolve, so does their ability to utilize exosomes in evading immune surveillance, creating a TME that is both resilient to therapy and hostile to immune cells. However, the story of exosomes isn't solely one of villainy. These particles hold a treasure trove of diagnostic and prognostic biomarkers, offering a window into the molecular underpinnings of cancer. Exosomes can reveal the cancer's genetic blueprint and offer clues to its behavior through non-invasive sampling, guiding clinicians in crafting personalized treatment plans. Furthermore, their natural homing abilities present an opportunity for targeted therapy delivery, potentially reducing the side effects of systemic treatments by ensuring that anticancer agents directly reach the tumor site [148].

By disrupting the exosomal communication lines that cancer cells depend on, new therapies may potentially prevent tumor growth and metastasis. Moreover, harnessing exosomes as delivery vehicles for immune-stimulating agents opens a new frontier in cancer immunotherapy, potentially transforming these once subversive elements into allies in the fight against cancer. As we continue to decipher the complexities of exosome signaling and functionality, the prospect of translating these insights into practical clinical applications becomes increasingly feasible, heralding a hopeful horizon in the relentless battle against cancer. Exosomal circRNAs have emerged as crucial mediators in the dynamic interplay within the TME, conducting a symphony of cellular interactions that promote tumor progression and resilience. These circular non-coding RNAs, deftly

Table 9
Exosomal circRNAs in other cancer types.

Tumor type	Exosomal circRNAs	Parent cell	Target cell	Mechanism signal axis	Cell function	References
Prostate cancer	circ_0044516	Prostate cancer cells	Prostate cancer	circ_0044516/miR-29a-3p	Promotes cell proliferation and metastasis	[136]
	circ-XIAP	Prostate cancer cells	Prostate cancer	circ-XIAP/miR-1182/TPD52	Contributes to docetaxel resistance	[137]
	circ_0081234	Prostate cancer cells	Prostate cancer	circ_0081234/miR-1/MAP 3K1	Promotes tumor growth and metastasis	[138]
	circ-DHPS	Prostate cancer cells	Osteoblasts	circ-DHPS/miR-214-3p/ CCL5	Impacts cell recruitment to bone microenvironment	[139]
Oral squamous cell carcinoma	circ_0000199	OSCC cells	OSCC	circ_0000199/miR-145-5p/ miR-29b-3p	Associated with poor survival outcome	[140]
	has_circ_0069313	OSCC cells	OSCC and treg cells	circ_0069313/miR-325-3p-Foxp3	Promotes immunity escape	[141]
Papillary thyroid cancer	hsa_circ_0082002	RCC cells	RCC	Not specified	Enhances tumor proliferation and invasion	[142]
	circFNDC3B	cSCC cells	cSCC	circFNDC3B/miR-1178/ TLR4	Promotes tumor progression	[143]
Cutaneous squamous cell carcinoma	circ-CYP24A1	PTC cells	PTC	circ-CYP24A1/cSCS2/ MAVS/SOGA	Modulates PTC progression	[144]
Renal cell carcinoma	circ_400068	PTC cells	PTC	circular RNA_400068/miR-210-5p/SOCS1 axis	Promotes EMT, invasion, and migration	[145]
	circ-PRKCI	PTC cells	PTC	circ-PRKCI/miR-545-3p/ CCND1 Axis	Diagnostic biomarker, associated with metastasis	[146]
Retinoblastoma	circ-E2F3	RB cells	RB	circ-E2F3/Not specified	Acts as tumor promoter gene	[147]

Note. OSCC: oral squamous cell carcinoma; RCC: renal cell carcinoma; cSCC: cutaneous squamous cell carcinoma; PTC: papillary thyroid carcinoma; RB: retinoblastoma; EMT: epithelial–mesenchymal transition.

encapsulated within exosomes, traverse the intricate battlefield of the TME, influencing the behavior of distant cells and swaying them towards a pro-tumorigenic state. They engage in this molecular dialogue by modulating key signaling pathways and gene expression, thereby aiding cancer cells in evading immune surveillance, enhancing metastatic potential, and fostering angiogenesis [148].

Exosomal circRNAs play a role that goes beyond simple communication. These biomarkers are used to identify cancer types, predict outcomes, and guide treatments. Their stability and abundance in bodily fluids make them prime candidates for non-invasive liquid biopsies, paving the way for a new era in cancer diagnostics and patient monitoring. Furthermore, the potential of exosomal circRNAs to influence the TME holds promise for innovative therapeutic strategies. By unraveling the complex molecular networks these circRNAs engage in, we can develop targeted interventions to disrupt their pro-cancerous missions or even re-engineer them to deliver therapeutic molecules directly to the heart of the tumor.

The clinical significance of exosomes in the TME lies in their dual role as facilitators of tumor progression and as potential therapeutic targets. As carriers of genetic material and proteins, exosomes contribute to the modulation of immune responses and enhancement of tumor growth and metastasis. Research has identified circRNA as a potential prognostic biomarker for HCC patients undergoing curative surgery, emphasizing that hsa_circ_0036683 is the most useful biomarker [149]. Other studies have demonstrated that circRNA is a promising prognostic biomarker in mantle cell lymphoma (MCL). The circSCORE enhances the identification of high-risk MCL in patients receiving cytarabine-based chemoimmunotherapy and autologous stem cell transplantation [150]. These findings open avenues for the development of targeted therapies that disrupt exosomal signaling or utilize these exosomal circRNAs for the precise delivery of therapeutic agents, thereby innovating treatment strategies and improving clinical outcomes.

Looking forward, exploring exosomal circRNAs in the TME represents a promising frontier in cancer research. As our understanding deepens, so does the potential to exploit these molecular messengers for clinical benefit. The development of novel technologies for isolating and characterizing exosomal circRNAs will accelerate their transition from bench to bedside, offering hope for more precise and personalized cancer therapies. Embracing the complexity of these molecular interactions will enable us to better navigate the TME, turning exosomal circRNAs from foes into allies in our ongoing battle against cancer.

CRediT authorship contribution statement

Xi Li: Writing – original draft, Software, Resources, Project administration, Investigation. **Hanzhe Liu:** Investigation, Methodology. **Peixu Xing:** Resources, Software, Writing – original draft. **Tian Li:** Writing – review & editing, Funding acquisition, Conceptualization. **Yi Fang:** Visualization, Writing – original draft. **Shuang Chen:** Writing – review & editing, Validation, Conceptualization. **Siyuan Dong:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

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References

[1] M. Sun, X. Liu, L. Xia, et al., A nine-lncRNA signature predicts distant relapse-free survival of HER2-negative breast cancer patients receiving taxane and anthracycline-based neoadjuvant chemotherapy, Biochem. Pharmacol. 189 (2021), 114285.
[2] Z. Yang, S. Jiang, C. Lu, et al., SOX11: Friend or foe in tumor prevention and carcinogenesis? Ther. Adv. Med. Oncol. 11 (2019), 1758835919853449.
[3] T. Li, T. Qiao, Unraveling tumor microenvironment of small-cell lung cancer: Implications for immunotherapy, Semin. Cancer Biol. 86 (2022) 117–125.
[4] Z. Tang, H. Dong, T. Li, et al., The synergistic reducing drug resistance effect of cisplatin and ursolic acid on osteosarcoma through a multistep mechanism involving ferritinophagy, Oxid. Med. Cell. Longev. 2021 (2021), 5192271.
[5] W. Hu, Y. Yang, C. Fan, et al., Clinical and pathological significance of N-Myc downstream-regulated gene 2 (NDRG2) in diverse human cancers, Apoptosis 21 (2016) 675–682.
[6] Z. Ma, C. Fan, Y. Yang, et al., Thapsigargin sensitizes human esophageal cancer to TRAIL-induced apoptosis *via* AMPK activation, Sci. Rep. 6 (2016), 35196.
[7] W. Guo, T. Qiao, T. Li, The role of stem cells in small-cell lung cancer: Evidence from chemoresistance to immunotherapy, Semin. Cancer Biol. 87 (2022) 160–169.
[8] Global Burden of Disease 2019 Cancer Collaboration, J.M. Kocarnik, K. Compton, et al., Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019: A systematic analysis for the global burden of disease study 2019, JAMA Oncol. 8 (2022) 420–444.
[9] S. Dadhania, M. Williams, What is so special about digital health in cancer? Clin, Oncol. 35 (2023) 147–149.
[10] H. Rumgay, M. Arnold, J. Ferlay, et al., Global burden of primary liver cancer in 2020 and predictions to 2040, J. Hepatol. 77 (2022) 1598–1606.
[11] E. Morgan, M. Arnold, A. Gini, et al., Global burden of colorectal cancer in 2020 and 2040: Incidence and mortality estimates from GLOBOCAN, Gut 72 (2023) 338–344.
[12] J. Huang, D.E. Lucero-Prisno 3rd, L. Zhang, et al., Updated epidemiology of gastrointestinal cancers in east Asia, Nat. Rev. Gastroenterol. Hepatol. 20 (2023) 271–287.
[13] J. Huang, S.C. Chan, V. Lok, et al., The epidemiological landscape of multiple myeloma: A global cancer registry estimate of disease burden, risk factors, and temporal trends, Lancet Haematol 9 (2022) e670–e677.
[14] D. Singh, J. Vignat, V. Lorenzoni, et al., Global estimates of incidence and mortality of cervical cancer in 2020: A baseline analysis of the WHO global cervical cancer elimination initiative, Lancet Global Health 11 (2023) e197–e206.
[15] M. Wang, F. Yu, P. Li, Intratumor microbiota in cancer pathogenesis and immunity: From mechanisms of action to therapeutic opportunities, Front. Immunol. 14 (2023), 1269054.
[16] Z. Gao, Z. Chen, Z. Xiong, et al., Ferroptosis - a new target of osteoporosis, Exp. Gerontol. 165 (2022), 111836.
[17] K. Yeoh, Y. Wu, S. Chakraborty, et al., Global health system resilience during encounters with stressors - lessons learnt from cancer services during the COVID-19 pandemic, Clin. Oncol. 35 (2023) e289–e300.
[18] N. Mu, J. Li, L. Zeng, et al., Plant-derived exosome-like nanovesicles: Current progress and prospects, Int. J. Nanomed. 18 (2023) 4987–5009.
[19] X. Gao, X. Tian, Y. Huang, et al., Role of circular RNA in myocardial ischemia and ageing-related diseases, Cytokine Growth Factor Rev. 65 (2022) 1–11.
[20] R. Zhao, B. Cao, H. Li, et al., Glucose starvation suppresses gastric cancer through targeting miR-216a-5p/Farnesyl-Diphosphate Farnesyltransferase 1 axis, Cancer Cell Int. 21 (2021), 704.
[21] Q. Guo, D. Li, X. Luo, et al., The regulatory network and potential role of LINC00973-miRNA-mRNA *CeRNA* in the progression of non-small-cell lung cancer, Front. Immunol. 12 (2021), 684807.
[22] J. Li, D. He, Y. Bi, et al., The emerging roles of exosomal miRNAs in breast cancer progression and potential clinical applications, Breast Cancer 15 (2023) 825–840.
[23] Q. Yi, J. Yue, Y. Liu, et al., Recent advances of exosomal circRNAs in cancer and their potential clinical applications, J. Transl. Med. 21 (2023), 516.
[24] Y. Wang, R. Jiang, H. Zhao, et al., TTN-AS1 delivered by gastric cancer cell-derived exosome induces gastric cancer progression through *in vivo* and *in vitro* studies, Cell Biol. Toxicol. 39 (2023) 557–571.
[25] Q. He, J. Yang, Z. Pan, et al., Biochanin A protects against iron overload associated knee osteoarthritis *via* regulating iron levels and NRF2/System xc-/GPX4 axis, Biomed. Pharmacother. 157 (2023), 113915.

[26] X. Guo, C. Gao, D. Yang, et al., Exosomal circular RNAs: A chief culprit in cancer chemotherapy resistance, Drug Resist. Updates 67 (2023), 100937.
[27] T. Wu, Y. Zhang, Q. Han, et al., Klotho-beta attenuates Rab8a-mediated exosome regulation and promotes prostate cancer progression, Oncogene 42 (2023) 2801–2815.
[28] X. Liu, R. Li, X. Chen, et al., SYT7 is a key player in increasing exosome secretion and promoting angiogenesis in non-small-cell lung cancer, Cancer Lett. 577 (2023), 216400.
[29] S. Sun, Z. Wang, F. Yao, et al., Breast cancer cell-derived exosome-delivered microRNA-155 targets UBQLN1 in adipocytes and facilitates cancer *Cachexia*-related fat loss, Hum. Mol. Genet. 32 (2023) 2219–2228.
[30] S. Lin, B. Zhu, Exosome-transmitted FOSL1 from cancer-associated fibroblasts drives colorectal cancer stemness and chemo-resistance through transcriptionally activating ITGB4, Mol. Cell. Biochem. 479 (2024) 665–677.
[31] D. Yan, D. Cui, Y. Zhu, et al., M6PR- and EphB4-rich exosomes secreted by serglycin-overexpressing esophageal cancer cells promote cancer progression, Int. J. Biol. Sci. 19 (2023) 625–640.
[32] K. Zhang, Y. Li, L. Peng, et al., M2 macrophage-derived exosomal miR-193b-3p promotes progression and glutamine uptake of pancreatic cancer by targeting TRIM62, Biol. Direct 18 (2023), 1.
[33] D.M. Pegtel, S.J. Gould, Exosomes, Annu. Rev. Biochem. 88 (2019) 487–514.
[34] Y. Zhang, Y. Liu, H. Liu, et al., Exosomes: Biogenesis, biologic function and clinical potential, Cell Biosci. 9 (2019), 19.
[35] C. He, S. Zheng, Y. Luo, et al., Exosome theranostics: Biology and translational medicine, Theranostics 8 (2018) 237–255.
[36] M.D.A. Paskeh, M. Entezari, S. Mirzaei, et al., Emerging role of exosomes in cancer progression and tumor microenvironment remodeling, J. Hematol. Oncol. 15 (2022), 83.
[37] S. Zhao, Y. Mi, B. Guan, et al., Tumor-derived exosomal miR-934 induces macrophage M2 polarization to promote liver metastasis of colorectal cancer, J. Hematol. Oncol. 13 (2020), 156.
[38] L. He, W. Zhu, Q. Chen, et al., Ovarian cancer cell-secreted exosomal miR-205 promotes metastasis by inducing angiogenesis, Theranostics 9 (2019) 8206–8220.
[39] Y. Shen, N. Zhang, J. Chai, et al., CircPDIA4 induces gastric cancer progression by promoting ERK1/2 activation and enhancing biogenesis of oncogenic circRNAs, Cancer Res. 83 (2023) 538–552.
[40] G. Yuan, W. Ding, B. Sun, et al., Upregulated circRNA_102231 promotes gastric cancer progression and its clinical significance, Bioengineered 12 (2021) 4936–4945.
[41] N. Ding, A. You, H. Yang, et al., A tumor-suppressive molecular axis EP300/circRERE/miR-6837-3p/MAVS activates type I IFN pathway and antitumor immunity to suppress colorectal cancer, Clin. Cancer Res. 29 (2023) 2095–2109.
[42] C. Zhong, Z. Long, T. Yang, et al., M6A-modified circRBM33 promotes prostate cancer progression *via* PDHA1-mediated mitochondrial respiration regulation and presents a potential target for ARSI therapy, Int. J. Biol. Sci. 19 (2023) 1543–1563.
[43] S. Cao, Y. Yin, H. Hu, et al., CircGLIS3 inhibits thyroid cancer invasion and metastasis through miR-146b-3p/AIF1L axis, Cell. Oncol. 46 (2023) 1777–1789.
[44] C. Dong, P. Hui, Z. Wu, et al., CircRNA LOC729852 promotes bladder cancer progression by regulating macrophage polarization and recruitment *via* the miR-769-5p/IL-10 axis, J. Cell Mol. Med. 28 (2024), e18225.
[45] J. Li, X. Dong, X. Kong, et al., Circular RNA hsa_circ_0067842 facilitates tumor metastasis and immune escape in breast cancer through HuR/CMTM6/PD-L1 axis, Biol. Direct 18 (2023), 48.
[46] C. Ding, G. Xi, G. Wang, 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. 11 (2020), 962.
[47] W. Hong, M. Xue, J. Jiang, et al., 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. 39 (2020), 149.
[48] L. Liu, J. Zhang, Y. Cheng, et al., Gut microbiota: A new target for T2DM prevention and treatment, Front. Endocrinol. 13 (2022), 958218.
[49] Z. Ning, Y. Tian, Y. Li, et al., Exosomal circ_0007385 enhances non-small cell lung cancer cell proliferation and stemness *via* regulating miR-1253/FAM83A axis, Anti Cancer Drugs 33 (2022) 61–74.
[50] H. Wang, Z. Tang, J. Duan, et al., 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 13 (2022) 8937–8949.
[51] H. Xiong, B. Liu, X. Liu, 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. 103 (2023), 100010.
[52] J. Xian, W. Su, L. Liu, 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. 22 (2020) 1096–1108.
[53] Y. Wang, H. Zhang, J. Wang, et al., Circular RNA expression profile of lung squamous cell carcinoma: Identification of potential biomarkers and therapeutic targets, Biosci. Rep. 40 (2020), BSR20194512.
[54] F. Chen, C. Huang, Q. Wu, et al., Circular RNAs expression profiles in plasma exosomes from early-stage lung adenocarcinoma and the potential biomarkers, J. Cell. Biochem. 121 (2020) 2525–2533.
[55] Y. Kang, J. You, Y. Gan, et al., Serum and serum exosomal CircRNAs hsa_circ_0001492, hsa_circ_0001439, and hsa_circ_0000896 as diagnostic biomarkers for lung adenocarcinoma, Front. Oncol. 12 (2022), 912246.
[56] N. Shao, L. Song, X. Sun, Exosomal circ_PIP5K1A regulates the progression of non-small cell lung cancer and cisplatin sensitivity by miR-101/ABCC1 axis, Mol. Cell. Biochem. 476 (2021) 2253–2267.
[57] J. Ma, G. Qi, L. Li, 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 13 (2020) 5293–5307.
[58] X. Xu, R. Tao, L. Sun, et al., 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. 20 (2020), 552.
[59] Q. Shi, T. Ji, Z. Ma, et al., Serum exosomes-based biomarker circ_0008928 regulates cisplatin sensitivity, tumor progression, and glycolysis metabolism by miR-488/*HK2* axis in cisplatin-resistant nonsmall cell lung carcinoma, Cancer Biother. Radiopharm. 38 (2023) 558–571.
[60] X. Wang, H. Wang, H. Jiang, et al., Circular RNAcirc_0076305 promotes cisplatin (DDP) resistance of non-small cell lung cancer cells by regulating *ABCC1* through miR-186-5p, Cancer Biother. Radiopharm. 38 (2023) 293–304.
[61] R. Wang, H. Liu, M. Dong, et al., Exosomal hsa_circ_0000519 modulates the NSCLC cell growth and metastasis *via* miR-1258/RHOV axis, Open Med. 17 (2022) 826–840.
[62] X. Peng, L. Zhao, L. Yao, et al., Exosomal ERBB2IP contributes to tumor growth *via* elevating PSAT1 expression in non-small cell lung carcinoma, Thorac. Cancer 14 (2023) 1812–1823.
[63] J. Qian, J. Li, H. Ma, et al., Exosomal circ-ADRM1 promotes lung adenocarcinoma progression and induces macrophage M2 polarization through regulating MMP14 mRNA and protein, Anti Cancer Drugs 34 (2023) 333–343.
[64] X. Sun, Y. Wang, G. Li, et al., Serum-derived three-circRNA signature as a diagnostic biomarker for hepatocellular carcinoma, Cancer Cell Int. 20 (2020), 226.
[65] L. Lyu, W. Yang, J. Yao, et al., The diagnostic value of plasma exosomal *hsa_circ_0070396* for hepatocellular carcinoma, Biomarkers Med. 15 (2021) 359–371.
[66] Y. Wang, L. Pei, Z. Yue, et al., The potential of serum exosomal hsa_circ_0028861 as the novel diagnostic biomarker of HBV-derived hepatocellular cancer, Front. Genet. 12 (2021), 703205.
[67] S. Guo, C. Hu, X. Zhai, et al., Circular RNA 0006602 in plasma exosomes: A new potential diagnostic biomarker for hepatocellular carcinoma, Am. J. Transl. Res. 13 (2021) 6001–6015.
[68] Y. Zhu, S. Wang, X. Xi, et al., Integrative analysis of long extracellular RNAs reveals a detection panel of noncoding RNAs for liver cancer, Theranostics 11 (2021) 181–193.
[69] Z. Wu, C. Li, Y. Zhang, et al., Bioinformatics study revealed significance of exosome transcriptome in hepatocellular carcinoma diagnosis, Front. Cell Dev. Biol. 10 (2022), 813701.
[70] Y. Li, H. Zang, X. Zhang, et al., Exosomal circ-ZNF652 promotes cell proliferation, migration, invasion and glycolysis in hepatocellular carcinoma *via* miR-29a-3p/GUCD1 axis, Cancer Manag. Res. 12 (2020) 7739–7751.
[71] W. Chen, Y. Quan, S. Fan, et al., Exosome-transmitted circular RNA hsa_circ_0051443 suppresses hepatocellular carcinoma progression, Cancer Lett. 475 (2020) 119–128.
[72] D. Liu, H. Kang, M. Gao, et al., Exosome-transmitted circ_MMP2 promotes hepatocellular carcinoma metastasis by upregulating MMP2, Mol. Oncol. 14 (2020) 1365–1380.
[73] T. Zhang, B. Jing, Y. Bai, et al., Circular RNA circTMEM45A acts as the sponge of microRNA-665 to promote hepatocellular carcinoma progression, Mol. Ther. Nucleic Acids 22 (2020) 285–297.
[74] T. Zhang, Q. Sun, C. Shen, et al., Circular RNA circ_0003028 regulates cell development through modulating miR-498/ornithine decarboxylase 1 axis in hepatocellular carcinoma, Anti Cancer Drugs 34 (2023) 507–518.
[75] L. Qin, Z. Zhan, C. Wei, et al., Hsa-circRNA-G004213 promotes cisplatin sensitivity by regulating miR-513b-5p/PRPF$_3$9 in liver cancer, Mol. Med. Rep. 23 (2021), 421.
[76] P. Yuan, J. Song, F. Wang, et al., Exosome-transmitted circ_002136 promotes hepatocellular carcinoma progression by miR-19a-3p/RAB1A pathway, BMC Cancer 22 (2022), 1284.
[77] L. Zhang, J. Zhang, P. Li, et al., Exosomal hsa_circ_0004658 derived from RBPJ overexpressed-macrophages inhibits hepatocellular carcinoma progression *via* miR-499b-5p/JAM3, Cell Death Dis. 13 (2022), 32.
[78] T. Han, L. Chen, K. Li, et al., Significant CircRNAs in liver cancer stem cell exosomes: Mediator of malignant propagation in liver cancer? Mol. Cancer 22 (2023), 197.
[79] Y. Xie, J. Li, P. Li, et al., RNA-seq profiling of serum exosomal circular RNAs reveals circ-PNN as a potential biomarker for human colorectal cancer, Front. Oncol. 10 (2020), 982.
[80] J. He, H. Zhao, X. Liu, 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/SGPP1 axis, Oncol. Rep. 44 (2020) 2429–2442.

[81] L. Bai, Z. Gao, A. Jiang, et al., Circular noncoding RNA circ_0007334 sequestrates miR-577 to derepress KLF12 and accelerate colorectal cancer progression, Anti Cancer Drugs 33 (2022) e409–e422.
[82] T. Lei, Y. Zhang, X. Wang, et al., Integrated analysis of the functions and clinical implications of exosome circRNAs in colorectal cancer, Front. Immunol. 13 (2022), 919014.
[83] G. Hu, C. Lin, K. Gao, et al., Exosomal circCOL1A1 promotes angiogenesis *via* recruiting EIF4A3 protein and activating Smad2/3 pathway in colorectal cancer, Mol. Med. 29 (2023), 155.
[84] L. Yu, F. Zhang, Y. Wang, Circ_0005615 regulates the progression of colorectal cancer through the miR-873-5p/FOSL2 signaling pathway, Biochem. Genet. 61 (2023) 2020–2041.
[85] L. Li, Z. Jiang, X. Zou, et al., Exosomal circ_IFT80 enhances tumorigenesis and suppresses radiosensitivity in colorectal cancer by regulating miR-296-5p/MSI1 axis, Cancer Manag. Res. 13 (2021) 1929–1941.
[86] X. Wang, H. Zhang, H. Yang, et al., Exosome-delivered circRNA promotes glycolysis to induce chemoresistance through the miR-122-PKM2 axis in colorectal cancer, Mol. Oncol. 14 (2020) 539–555.
[87] Y. Zhang, X. Tan, Y. Lu, 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. 78 (2022) 39–50.
[88] J. Cornell, S. Salinas, H. Huang, et al., Microglia regulation of synaptic plasticity and learning and memory, Neural Regen. Res. 17 (2022) 705–716.
[89] P. Zheng, H. Gao, X. Xie, et al., Plasma exosomal hsa_circ_0015286 as a potential diagnostic and prognostic biomarker for gastric cancer, Pathol. Oncol. Res. 28 (2022), 1610446.
[90] Y. Wang, Z. Li, S. Xu, et al., Novel potential tumor biomarkers: Circular RNAs and exosomal circular RNAs in gastrointestinal malignancies, J. Clin. Lab. Anal. 34 (2020), e23359.
[91] X. Huang, Y. Wang, H. Wang, et al., Exosomal hsa_circ_000200 as a potential biomarker and metastasis enhancer of gastric cancer *via* miR-4659a/b-3p/HBEGF axis, Cancer Cell Int. 23 (2023), 151.
[92] Q. Liang, F. Chu, L. Zhang, et al., Circ-LDLRAD3 knockdown reduces cisplatin chemoresistance and inhibits the development of gastric cancer with cisplatin resistance through miR-588 enrichment-mediated SOX5 inhibition, Gut Liver 17 (2023) 389–403.
[93] H. Wang, X. Zeng, Y. Zheng, et al., Exosomal circRNA in digestive system tumors: The main player or coadjuvants? Front. Oncol. 11 (2021), 614462.
[94] M. Xie, T. Yu, X. Jing, et al., Exosomal circSHKBP1 promotes gastric cancer progression *via* regulating the miR-582-3p/HUR/VEGF axis and suppressing HSP90 degradation, Mol. Cancer 19 (2020), 112.
[95] X. Shen, S. Kong, S. Ma, et al., Hsa_circ_0000437 promotes pathogenesis of gastric cancer and lymph node metastasis, Oncogene 41 (2022) 4724–4735.
[96] C. Zhang, G. Wei, X. Zhu, et al., Exosome-delivered circSTAU2 inhibits the progression of gastric cancer by targeting the miR-589/CAPZA1 axis, Int. J. Nanomed. 18 (2023) 127–142.
[97] W. Yao, P. Guo, Q. Mu, et al., 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. 36 (2021) 347–359.
[98] Y. Zhong, D. Wang, Y. Ding, et al., Circular RNA circ_0032821 contributes to oxaliplatin (OXA) resistance of gastric cancer cells by regulating SOX9 *via* miR-515-5p, Biotechnol. Lett. 43 (2021) 339–351.
[99] Y. Chen, H. Liu, J. Zou, et al., Exosomal circ_0091741 promotes gastric cancer cell autophagy and chemoresistance *via* the miR-330-3p/TRIM14/Dvl2/Wnt/β-catenin axis, Hum. Cell 36 (2023) 258–275.
[100] Y. Zheng, P. Li, J. Ma, et al., Cancer-derived exosomal circ_0038138 enhances glycolysis, growth, and metastasis of gastric adenocarcinoma *via* the miR-198/EZH2 axis, Transl. Oncol. 25 (2022), 101479.
[101] J. Song, X. Xu, S. He, et al., Exosomal hsa_circ_0017252 attenuates the development of gastric cancer *via* inhibiting macrophage M2 polarization, Hum. Cell 35 (2022) 1499–1511.
[102] S. Liu, Z. Lin, W. Rao, et al., Upregulated expression of serum exosomal hsa_circ_0026611 is associated with lymph node metastasis and poor prognosis of esophageal squamous cell carcinoma, J. Cancer 12 (2021) 918–926.
[103] R. Zang, X. Qiu, Y. Song, et al., Exosomes mediated transfer of Circ_0000337 contributes to cisplatin (CDDP) resistance of esophageal cancer by regulating JAK2 *via* miR-377-3p, Front. Cell Dev. Biol. 9 (2021), 673237.
[104] T. Hu, H. Peng, F. Yang, et al., Circ_0024108 promotes the progression of esophageal cancer cells, Gen. Thorac, Cardiovasc. Surg. 71 (2023) 418–431.
[105] Y. Chen, M. Jiang, L. Tian, Analysis of exosomal circRNAs upon irradiation in pancreatic cancer cell repopulation, BMC Med. Genomics 13 (2020), 107.
[106] X. Yao, Y. Mao, D. Wu, 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. 512 (2021) 38–50.
[107] G. Gao, L. Wang, C. Li, 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. 12 (2022) 1934–1959.
[108] L. Hong, L. Xu, L. Jin, et al., Exosomal circular RNA hsa_circ_0006220, and hsa_circ_0001666 as biomarkers in the diagnosis of pancreatic cancer, J. Clin. Lab. Anal. 36 (2022), e24447.
[109] Y. Xu, K. Leng, Y. Yao, et al., A circular RNA, cholangiocarcinoma-associated circular RNA 1, contributes to cholangiocarcinoma progression, induces angiogenesis, and disrupts vascular endothelial barriers, Hepatology 73 (2021) 1419–1435.
[110] S. Chen, Z. Chen, Z. Li, et al., Tumor-associated macrophages promote cholangiocarcinoma progression *via* exosomal Circ_0020256, Cell Death Dis. 13 (2022), 94.
[111] K. Hu, X. Liu, Y. Li, et al., Exosomes mediated transfer of Circ_UBE2D2 enhances the resistance of breast cancer to tamoxifen by binding to miR-200a-3p, Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. 26 (2020), e922253.
[112] J. Liu, X. Peng, Y. Liu, et al., The diagnostic value of serum exosomal Has_circ_0000615 for breast cancer patients, Int. J. Gen. Med. 14 (2021) 4545–4554.
[113] C. Lu, W. Shi, W. Hu, et al., Endoplasmic reticulum stress promotes breast cancer cells to release exosomes circ_0001142 and induces M2 polarization of macrophages to regulate tumor progression, Pharmacol. Res. 177 (2022), 106098.
[114] J. Ma, C. Chen, Z. Fan, et al., CircEGFR reduces the sensitivity of pirarubicin and regulates the malignant progression of triple-negative breast cancer *via* the miR-1299/EGFR axis, Int. J. Biol. Macromol. 244 (2023), 125295.
[115] H. Wang, M. Wei, Y. Kang, et al., Circular RNA circ_PVT1 induces epithelial-mesenchymal transition to promote metastasis of cervical cancer, Aging 12 (2020) 20139–20151.
[116] F. Yu, F. Luo, X. Zhang, et al., Circ_0006646 accelerates the growth and metastasis of cervical cancer by elevating RRM2 through miR-758-3p, Biochem. Genet. 61 (2023) 1300–1318.
[117] X. Wang, Y. Yao, M. Jin, Circ-0001068 is a novel biomarker for ovarian cancer and inducer of PD1 expression in T cells, Aging 12 (2020) 19095–19106.
[118] H. Sheng, X. Wang, Knockdown of circ-PIP5K1A overcomes resistance to cisplatin in ovarian cancer by miR-942-5p/NFIB axis, Anti Cancer Drugs 34 (2023) 214–226.
[119] X. Gu, Y. Shi, M. Dong, et al., Exosomal transfer of tumor-associated macrophage-derived hsa_circ_0001610 reduces radiosensitivity in endometrial cancer, Cell Death Dis. 12 (2021), 818.
[120] K. Yin, X. Liu, CircMMP1 promotes the progression of glioma through miR-433/HMGB3 axis *in vitro* and *in vivo*, IUBMB Life 72 (2020) 2508–2524.
[121] C. Han, S. Wang, H. Wang, et al., Exosomal circ-HIPK3 facilitates tumor progression and temozolomide resistance by regulating miR-421/*ZIC5* axis in glioma, Cancer Biother. Radiopharm. 36 (2021) 537–548.
[122] G. Li, Q. Lan, Bioinformatics analysis reveals a stem cell-expressed circ-Serpine2-mediated miRNA-mRNA regulatory subnetwork in the malignant progression of glioma, J. Transl. Med. 19 (2021), 444.
[123] C. Ding, X. Yi, X. Chen, et al., Warburg effect-promoted exosomal circ_0072083 releasing up-regulates NANGO expression through multiple pathways and enhances temozolomide resistance in glioma, J. Exp. Clin. Cancer Res. 40 (2021), 164.
[124] X. Li, N. Wang, H. Leng, et al., Hsa_circ_0043949 reinforces temozolomide resistance *via* upregulating oncogene ITGA1 axis in glioblastoma, Metab. Brain Dis. 37 (2022) 2979–2993.
[125] J. Si, W. Li, X. Li, et al., Heparanase confers temozolomide resistance by regulation of exosome secretion and circular RNA composition in glioma, Cancer Sci. 112 (2021) 3491–3506.
[126] G. Li, Q. Lan, Exosome-mediated transfer of circ- *GLIS3* enhances temozolomide resistance in glioma cells through the miR-548m/MED31 axis, Cancer Biother. Radiopharm. 38 (2023) 62–73.
[127] Y. Li, X. Zheng, J. Wang, et al., Exosomal circ-AHCY promotes glioblastoma cell growth *via* Wnt/β-catenin signaling pathway, Ann. Clin. Transl. Neurol. 10 (2023) 865–878.
[128] D. Xia, X. Gu, Plasmatic exosome-derived circRNAs panel act as fingerprint for glioblastoma, Aging 13 (2021) 19575–19586.
[129] M. Cao, H. Li, D. Sun, et al., Current cancer burden in China: Epidemiology, etiology, and prevention, Cancer Biol. Med. 19 (2022) 1121–1138.
[130] Y. Wang, Q. Lin, C. Song, et al., Circ_0007841 promotes the progression of multiple myeloma through targeting miR-338-3p/BRD4 signaling cascade, Cancer Cell Int. 20 (2020), 383.
[131] R. Sun, W. Liu, Y. Zhao, et al., Exosomal circRNA as a novel potential therapeutic target for multiple myeloma-related myocardial damage, Cancer Cell Int. 21 (2021), 311.
[132] M. Yu, L. Ji, S. Li, et al., Exosomal circ-CACNG2 promotes cardiomyocyte apoptosis in multiple myeloma *via* modulating miR-197-3p/caspase3 axis, Exp. Cell Res. 417 (2022), 113229.
[133] M. Yu, J. Yu, Y. Zhang, et al., A novel circRNA-miRNA-mRNA network revealed exosomal circ-ATP10A as a biomarker for multiple myeloma angiogenesis, Bioengineered 13 (2022) 667–683.
[134] J. Bi, Y. Pu, X. Yu, Exosomal circ_0004136 enhances the progression of pediatric acute myeloid leukemia depending on the regulation of miR-570-3p/TSPAN3 axis, Anti Cancer Drugs 32 (2021) 802–811.
[135] A. Zhong, Y. Yin, B. Tang, et al., CircRNA microarray profiling reveals hsa_circ_0058493 as a novel biomarker for imatinib-resistant CML, Front. Pharmacol. 12 (2021), 728916.
[136] T. Li, X. Sun, L. Chen, Exosome circ_0044516 promotes prostate cancer cell proliferation and metastasis as a potential biomarker, J. Cell. Biochem. 121 (2020) 2118–2126.
[137] H. Zhang, M. Li, J. Zhang, et al., Exosomal circ-XIAP promotes docetaxel resistance in prostate cancer by regulating miR-1182/TPD52 axis, Drug Des. Dev. Ther. 15 (2021) 1835–1849.
[138] G. Zhang, Y. Liu, J. Yang, et al., Inhibition of circ_0081234 reduces prostate cancer tumor growth and metastasis *via* the miR-1/MAP 3 K1 axis, J. Gene Med. 24 (2022), e3376.

[139] Z. Yang, J. Chen, T. Liu, et al., Knocking down AR promotes osteoblasts to recruit prostate cancer cells by altering exosomal circ-DHPS/miR-214-3p/CCL5 pathway, Asian J. Androl. 26 (2024) 195–204.
[140] Y. Luo, F. Liu, J. Guo, et al., Upregulation of circ_0000199 in circulating exosomes is associated with survival outcome in OSCC, Sci. Rep. 10 (2020), 13739.
[141] Y. Chen, Z. Li, J. Liang, et al., CircRNA has_circ_0069313 induced OSCC immunity escape by miR-325-3p-Foxp3 axes in both OSCC cells and Treg cells, Aging 14 (2022) 4376–4389.
[142] L. Dai, W. Hu, H. Jiang, et al., The diagnostic potential of two exosome-derived circRNAs for papillary thyroid cancer, Int. J. Clin. Oncol. 28 (2023) 1461–1474.
[143] G. Wu, W. Zhou, X. Pan, et al., Retraction notice to: Circular RNA profiling reveals exosomal circ_0006156 as a novel biomarker in papillary thyroid cancer, Mol. Ther. Nucleic Acids 28 (2022), 572.
[144] Z. Zhang, H. Guo, W. Yang, et al., Exosomal circular RNA RNA-seq profiling and the carcinogenic role of exosomal circ-CYP24A1 in cutaneous squamous cell carcinoma, Front. Med. 8 (2021), 675842.
[145] H. Xiao, J. Shi, Exosomal circular RNA_400068 promotes the development of renal cell carcinoma *via* the miR-210-5p/SOCS1 axis, Mol. Med. Rep. 22 (2020) 4810–4820.
[146] Y. Qian, Y. Li, L. Xu, et al., Tumor cell-derived exosomal circ-PRKCI promotes proliferation of renal cell carcinoma *via* regulating miR-545-3p/CCND1 axis, Cancers 15 (2022), 123.
[147] N. Ahangar Davoodi, S. Najafi, Z. Naderi Ghale-Noie, et al., Role of non-coding RNAs and exosomal non-coding RNAs in retinoblastoma progression, Front. Cell Dev. Biol. 10 (2022), 1065837.
[148] A. Quesnel, A. Broughton, G.S. Karagiannis, et al., Message in the bottle: Regulation of the tumor microenvironment *via* exosome-driven proteolysis, Cancer Metastasis Rev. 41 (2022) 789–801.
[149] Y. Sunagawa, S. Yamada, F. Sonohara, et al., Genome-wide identification and characterization of circular RNA in resected hepatocellular carcinoma and background liver tissue, Sci. Rep. 11 (2021), 6016.
[150] M. Dahl, S. Husby, C.W. Eskelund, et al., Expression patterns and prognostic potential of circular RNAs in mantle cell lymphoma: A study of younger patients from the MCL2 and MCL3 clinical trials, Leukemia 36 (2022) 177–188.