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REVIEW

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Role of circular RNAs in cancer therapy resistance

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Abstract

Over the past decade, circular RNAs (circRNAs) have gained recognition as a novel class of genetic molecules, many of which are implicated in cancer pathogenesis via different mechanisms, including drug resistance, immune escape, and radio-resistance. ExosomalcircRNAs, in particular, facilitatecommunication between tumour cells and micro-environmental cells, including immune cells, fibroblasts, and other components. Notably, micro-environmental cells can reportedly influence tumour progression and treatment resistance by releasing exosomalcircRNAs. circRNAs often exhibit tissue- and cancer-specific expression patterns, and growing evidence highlights their potential clinical relevance and utility. These molecules show strong promise as potential biomarkers and therapeutic targets for cancer diagnosis and treatment. Therefore, this review aimed to briefly discuss the latest findings on the roles and resistance mechanisms of key circRNAs in the treatment of various malignancies, including lung, breast, liver, colorectal, and gastric cancers, as well as haematological malignancies and neuroblastoma.This review will contribute to the identification of new circRNA biomarkers for the early diagnosis as well as therapeutic targets for the treatment of cancer.

Keywords Circular RNAs, Exosome, Tumour immunity, Drug resistance, Radioresistance

Background

In 2022, nearly 20 million new cancer cases and 9.7 million cancer-related deaths were reported [1, 2]. Lung cancer (LC) remains the most prevalent, with approximately 2.5 million new diagnoses, accounting for one in eight (12.4%) cancer cases worldwide [1], followed by female breast (11.6%), colorectal (9.6%), prostate (7.3%), and gastric cancers (4.9%) [1]. LC was also the leading cause of cancer-related mortality, accounting for approximately 1.8 million deaths (18.7%), followed by colorectal (9.3%), liver (7.8%), female breast (6.9%), and gastric cancers (6.8%) [1]. The common methods of cancer treatment include surgery, chemotherapy, radiotherapy, immunotherapy, and combination therapy [3–5]. However, currently, many cancer cases cannot be diagnosed effectively at the early stages [6]due to the limited availability and low specificity of serum tumour biomarkers.Thus, most cancers are diagnosed only at the advanced stages. This, together with cancer-related drug resistance, renders cancer treatments that target invasive and metastatic tumoursineffective [5, 7, 8]. This underscores the urgent

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need to discover new biomarkers and therapeutic targets, which are more effective than the existing ones, for early cancer diagnosis, treatment, and prognosis.

Data from human genome sequencing indicate that > 98% of the human genome consists of non-coding genes [9]. The transcripts of these genes lack the capacity to encode proteins and are considered non-coding RNAs (ncRNAs) [9, 10]. With the advances in high-throughput sequencing technology, an increasing number of circular RNAs (circRNAs) have been identified since Memczak et al. first reported their role as post-transcriptional regulators in 2013 and found them to exhibit tissue-specific expression patterns [11, 12]. circRNAs, a type of single-stranded, covalently closed ncRNA lacking a 5′ cap or 3′ poly(A) tail, are produced through the non-canonical splicing of pre-mRNA and are widely expressed in many species [12–14]. circRNAs mainly serve as competing endogenous RNAs (ceRNAs) that regulate the expression of target genes [15]. Despite their prevalence, only a limited number of them have been functionally annotated, and various methods have been developed to explore their expression, distribution, and function [8, 16]. Recent studies employing bioinformatics and high-throughput methods have found that dysregulated circRNA profiles are extensively involved in the mechanisms of tumorigenesis, including cell proliferation, migration, invasion, epithelial-mesenchymal transition (EMT), and antitumour drug resistance [6, 17, 18]. These characteristics, along with their readily available presence in bodily fluids, including saliva, blood, and urine, indicate that circRNAs have the potential to serve as promising targets and biomarkers for the diagnosis and treatment of malignancies [3, 19, 20]. Therefore, we herein aimed to review the roles and resistance mechanisms of key circRNAs in the treatment of lung, breast, liver, colorectal, and gastric cancers, as well as haematological malignancies and neuroblastoma.

Biogenesis, biology, and characterisation of circRNAs

For a long time, circRNAs were mainly regarded as "junk" resulting from aberrant splicing events [21]. In fact, only the testis-specific circRNA from the sex-determining region Y (Sry) was considered functional (in mouse testes) [22, 23]. However, in recent years, the adoption of high-throughput RNA sequencing (RNA-seq) and circRNA-specific bioinformatics algorithms has enabled the identification of thousands of circRNAs in eukaryotes, including fungi, protists, plants, worms, fish, insects, and mammals, that play biological roles [24–26]. Some experiments have demonstrated that circRNA biogenesis is dependent onalternative back-splicing (ABS),regulated by trans-acting proteins and cis-regulatory elements [27]. ABSof circRNA is divided into four types:(1) direct back-splicing. When pre-mRNA processing events slow down, nascent RNA can be directed to promote back-splicing [27]. The loss of splicing factors can increase circRNA levels [21, 27, 28]. The predominant mechanism of back-splicing involves the circularisation of intronic sequences flanking the downstream splice-donor (SD) site and upstream splice-acceptor (SA) site, bringing these sites into close proximity [29, 30]. During back-splicing, an upstream branch point (BP) attacks a downstream SD site, which in turn attacks the upstream SA site, thereby forming exonic-intronic circRNAs (EIcircRNAs) or exonic circRNAs (that is, circRNAs with internal introns excised) [28]. (2) Canonical linear splicing is blocked by adenosine deaminase (ADAR1) [30] and ATP-dependent RNA helicase A (also known as DHX9) [31]. These RNA binding proteins (RBPs) disrupt the base-pairing among inverted repeats, which emables the splicing machinery to produce linear mRNA [23]. (3) Conventional splicing. The conventional splicing process involves the formation of intronic lariats, escaping debranching and ligation, resulting in the creation of intronic circRNAs. (4) CircRNA can also be derived from splicing intermediates, resulting from exon skipping events that occur during linear splicing or intron lariats that escape the debranching step in canonical splicing [27].ABS is widespread in eukaryotic cells and plays roles in various biological processes such as gene regulation, RNA metabolism, and disease development [32]. Recently, with the development of RNA sequencing technology and corresponding bioinformatics tools, increasing evidence has supported the notion that alternative splicing (AS) is involved in the mechanism of drug resistance. Cancer cells often use circRNAs formed by ABS to overcome the cytotoxicity of chemotherapy drugs, thus leading to drug resistance [33].

Existing methods for the detection and quantification of circRNAs have their pros and cons (Fig. 1). Most publicly available RNA-seq datasets offer relatively high analytical sensitivity, quantitative capabilities, and large sample sizes [9, 34]. These are primarily employed in the discovery of new circRNAs. However, they are also costly and require adequate computational power and bioinformatics expertise for analysis. Genome-wide and locus-specific circRNA detection methods facilitate the simultaneous analysis of circRNAs in large quantities; however, these methods do not provide information on their linear counterparts [19, 35]. CircRNA detection by Northern blotting involves relatively high labour costs [36, 37]. Reverse transcription polymerase chain reaction and quantitative PCR have relatively small sample sizes; however, they can serve as qualitative and quantitative supplements to RNA-seq and microarray screening results [38]. Although droplet digital PCR and the

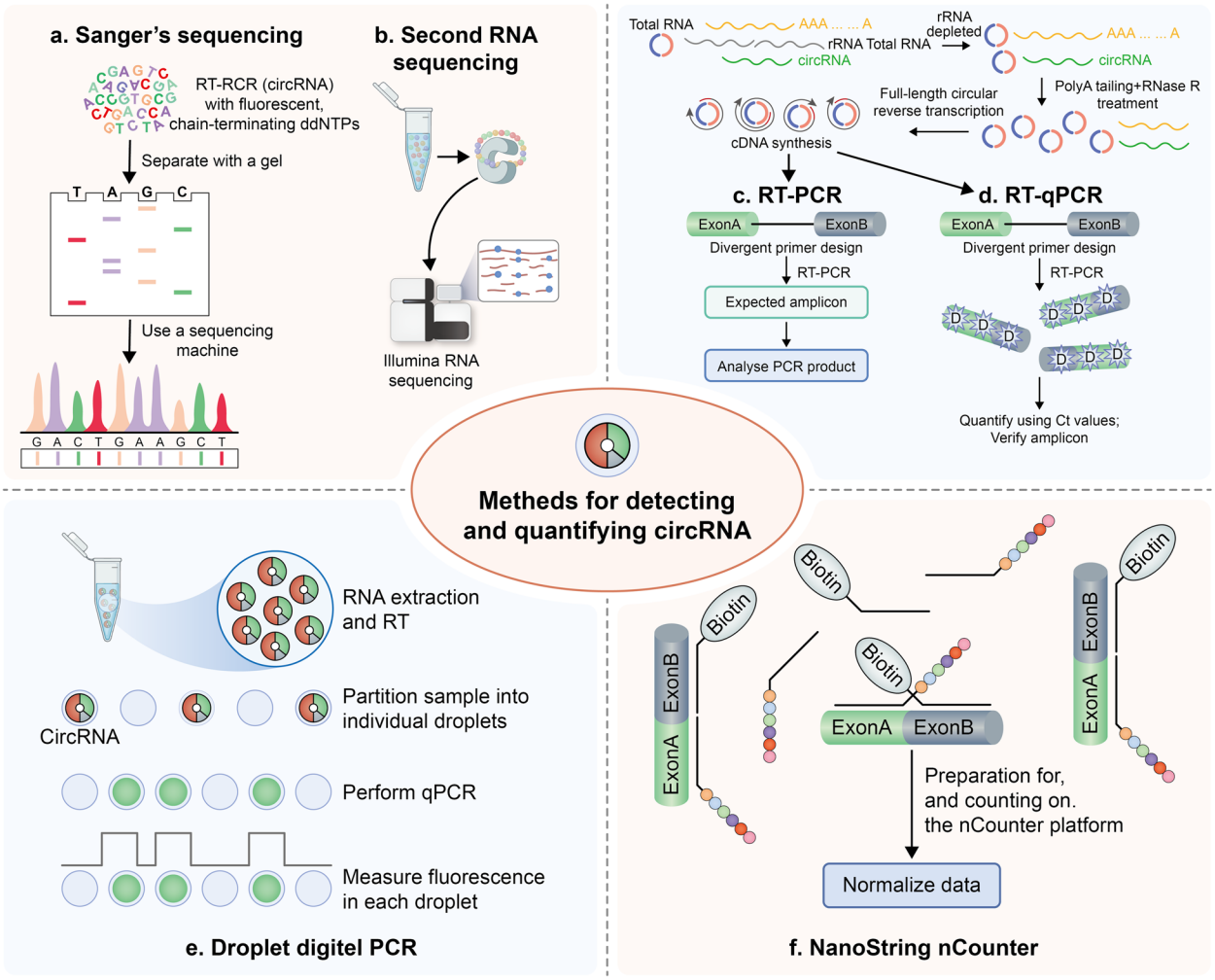

Fig. 1 Methodologies used to detect and quantify the expression of circRNAs. **a** Sanger' sequencing. DNA strands are separated based on size, which is defined by where into the chain a ddNTP is incorporated. This reveals the identity of the nucleobase at any position, as incorporation of a ddNTP terminates the growing chain at that position. **b** Transcriptome sequencing technology is to use high-throughput sequencing technology for sequencing analysis, reflecting the expression level of mRNA, small RNA, noncoding RNA, etc., or circRNA. **c** To detect circRNA, reverse transcription (RT)-PCR utilizes a divergent primer pair, which only amplifies the circRNA during PCR. The PCR product is analysed by gel electrophoresis and/or sequencing. **d** RT and quantitative PCR (RT-qPCR) also utilizes a divergent primer pair to quantify circRNAs. Detection can be based on double-stranded DNA intercalating fluorescent dyes (**d**). In both cases, circRNA levels are quantified using cycle quantification (Ct) values, which represent the PCR cycle number at which the sample's reaction curve intersects the threshold line. When using intercalating dyes, the identity of the amplicon should be confirmed by melting analysis or gel electrophoresis. **e** Droplet digital PCR can be used for the absolute quantification of circRNAs and is based on the qPCR of single molecules in droplets, which are subsequently analysed and scored as positive or negative based on the fluorescent signal. **f** In the NanoString Technologies nCounter assay multiple circRNAs can be quantified simultaneously based on their hybridization with biotinylated capture probes and reporter probes that carry a unique fluorescent barcode for each circRNA. Probes span the unique backsplice junction (BSJ) of the circRNAs and do not generate a signal when bound to a corresponding linear transcript in the reverse orientation. Overnight hybridization is followed by washing, immobilizing biotinylated capture probes using a streptavidin-coated surface, aligning probe–target complexes and counting circRNAs that were hybridized to the probes on the nCounter platform

NanoString Technologies nCounter facilitate the digital detection and quantification of circRNAs, they require specialised equipment [39, 40].Artificial intelligence (AI)-based analysis of routine clinical data also holds promise for personalized medicine [41]. Advancing precision oncology will require the development of a larger number of more accurate biomarkers for predicting treatment response, the identification of new drug gable targets in cancer cells and an accelerated drug development platform to simplify matching targets with drugs [42]. Here, AI could uncover hidden patterns in molecular profiling to advance this [42].Using computational

algorithms for the prediction of circRNA–disease associations has become increasingly prominent in disease diagnosis and treatment due to their efficiency [43]. Generally, circRNA features are used as machine learning inputs to build more reliable classification models. There are three common machine learning algorithms: PredcircRNA, which aims to distinguish circRNAs from other long non-coding RNAs (lncRNAs) based on multicore learning algorithms [43]. Web circRNAs are trained on stem cell datasets to further predict stem-cell specific circRNAs. PredicircRNATool uses the conformation and thermodynamic properties of flanking regions to predict circRNA [43]. Another machine learning model is DeepCirCode, which is used to predict human circRNAs [43]. Nevertheless, we still lack known circRNA associated with diseases, which results in data sparsity and limits model accuracy. Hence, the collection and accumulation of experimentally validated circRNA biological data is an urgent task.

In this review, we found that tumour-derived extracellular circRNAs associated with drug resistance played a double-edge "pro- and anti-oncogenic" role in the advancement of cancer treatment through various mechanisms, such as acting as miRNA sponges, that circRNAs can function as microRNA (miRNA) sponges or decoys to protect target mRNAs from miRNA-dependent degradation. This enables target mRNAs to more actively undergo translation and bind with ribosomes [29, 34, 44, 45]. In addition, circRNA containing RBP-binding motifs can also act as sponges or decoys for RBPs, thereby indirectly regulating their function, act as scaffolds to mediate complex formation between specific enzymes and substrates and recruit proteins to specific locations. Third, circRNAs can also recruit specific proteins to certain sites or subcellular compartments, as demonstrated here by the interleukin enhancer-binding factor 3 (FLI1) exonic circRNA [46], which recruits the methylcytosine dioxygenase TET1 to the promoter region of its host gene [47]. Fourth, circRNAs may interact with, and enhance the function of, particular proteins, as illustrated for the RNA polymerase II (Pol II) complex containing the U1 small nuclear ribonucleoprotein (snRNP) and other proteins. Fifth, circRNAs with internal ribosome entry site (IRES) elements and AUG sites may be translated under certain circumstances, giving rise to unique peptides. Adapted from REF. Finally, circRNAs containing internal ribosome entry site elements and AUG codes may be translated under specific circumstances to produce unique peptides [34].In addition, the mechanisms of therapy resistance and proposed biological functions of key circRNAs are listed and discussed below (Tables 1, 2 and 3).

Role of circRNAs in LC

LC is the leading cause of cancer-related deaths, accounting for 18.7% of all cancer-related deaths, with an incidence of 12.4% in both men and women, ahead of all other cancers [1]. In 2022, an estimated 2.5 million new cases of LC were diagnosed worldwide, and 1.8 million deaths were reported [1]. Pathologically, LC can be classified into small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) [52]. NSCLC is further classified into lung squamous cell carcinoma (LSCC), lung adenocarcinoma (LAD), and large cell carcinoma (LCC) [52, 211]. Although considerable advances have been made in LC treatment, including surgical resection and chemotherapy, over the past few decades, its 5-year survival rate remains at 4–17% owing to factors, such as late diagnosis, metastasis, poor response to chemotherapy, and recurrence [211]. Therefore, exploring novel targets and biomarkers is important for early diagnosis and development of more effective treatments [52, 212]. Notably, some circRNAs have already been shown to serve as potential novel biomarkers and targets for LC diagnosis and treatment.

circRNA circ_0010235

Hsa_circ_0010235 (*circ_0010235*) is a circRNA derived from the exonic back-splicing of aldehyde dehydrogenase 4 family members A1 [56, 58, 95]. *circ_0010235*expression in human NSCLC tissues was higher than that in paracancerous lung tissues [48, 58]. Li et al. reported that high expression of circ_0010235 can increased the resistance of NSCLC to paclitaxel (PTX) family by sponging miR-512-5p [53]. FAM83F (family with sequence similarity 83 member F) served as a target of miR-512-5p in NSCLC cells. Circ_0010235 regulated FAM83F expression by interacting with miR-512-5p.Silencing circ_0010235 transfection evidently increased the protein level of Bax, decreased the protein level of Bcl-2 and P-gp in A549/PTX and H1299/PTX cells, whereas the influence was ameliorated by anti-miR-512-5p transfection.Others have reported that circ_0010235 can promote cisplatin (CDDP) resistance in LC cells by modulating the miR-379-5p/E2F7 (E2F transcription factor 7) axis [49].

Zhu et al. found that circ_0010235 can regulate homeobox A10 (HOXA10) expression by sponging miR-588, thereby increasing NSCLC radioresistance [71]. With regard to its mechanisms, circ_0010235 can accelerate the immune escape of LC cells by suppressing miR-636 and upregulating programmed death-ligand 1 (PD-L1) expression [189]. Silencing circ_0010235 increased the expression levels of interferon γ and tumour necrosis factor α, as well as cytokine-induced killer cells, thereby enhancing the anti-NSCLC tumour immune response

Table 1 Specific circRNAs regulating drug resistance of cancer cells

Cancer types	CircRNA	Expression	Functions	Signaling pathway	Clinical feature	References
NSCLC	circ_0010235	Up	Associated with CDDP and PTX resistance in lung cancer, promoted NSCLC growth, proliferation, migration and invasion by activating EMT transcription factors	miR-379-5p/E2F7; miR-512-5p/FAM83F; miR-1249-3p/HOXA13; miR-338-3p/ KIF2A; miR-34a-5p/NFAT5	TNM grade, Lymph node metastasis, Tumor size	(Liu and Fu, 2022 [48]; Wang et al. 2023 [49–51]; Li et al. 2022 [52–55]; Zhang et al. 2023 [56, 57]; Zhu et al. 2021 [58, 59])
LADC	circCCDC66	Up	Associated with gefitinib resistance, and promoted LC migration and invasion by activating EMT transcription factors	HGF/c-Met, SAE2; miR-211/SRCIN1; miR-33a-5p/KPNA4		(Joseph et al. 2018 [60]; Hong et al. 2020 [61–63]; Wang et al. 2020 [64–67])
LUAD	circFBXW7	Down	Associated with osimertinib sensitivity, and inhibit the renewal of cancer stem cells	YTHDF3, Wnt/β-catenin signaling pathway; miR-492; miR-942-5p/BARX2		(Li et al. 2023 [68–70]; Zhu et al. 2022 [71, 72])
NSCLC	circPTK2	Up	Associated with CDDP resistance, and TGF-β-induced EMT and NSCLC cell invasion	miR-942/TRIM16, miR-429/miR-200b-3p		(Wang et al. 2018 [73]; Wang et al. 2022 [74–78])
Lung cancer	circPVT1	Up	Associated with CDDP and pemetrexed resistance, and promoted cell metastasis and autophagy	miR-145-5p/ABCC1; miR-181a-5p/NEK7; miR-429/FOXK1	TNM stage, OS, prognostic biomarker	(Zheng and Xu, 2020 [79]; Lu et al. 2021 [80]; Cao et al. 2021 [81])
Lung cancer	circABCA10	Up	Associated with CDDP resistance, and promoted cell proliferation, migration and invasion	miR-556-3p/AK4; miR-1252/FOXR2; miRNA-217; miR-584-5p/ E2F5; KISS1	OS, prognostic biomarker	(Ma et al. 2020 [82]; Hu et al. 2020 [83]; Tian et al. 2019 [84]; Wu et al. 2020 [85])
NSCLC	circPRMT5	Up	Associated with CDDP resistance, and promoted cell proliferation	miR-4458/REV3L; miR-377/382/498/ EZH2		(Pang et al. 2020 [86]; Wang et al. 2019 [87–90])
NSCLC	circSETD3	Up	Associated with gefitinib resistance, and promoted cell proliferation	miR-520 h/ABCG2, SRSF1		(Wen et al. 2023; Huang et al. 2020 [91, [92])
NSCLC	circ_0004015	Up	Associated with CDDP and gefitinib resistance, and enhanced proliferation, migration and invasion	miR-198/KLF8, miR-1183/PDPK1	Differentiation grade, invasion, TNM stage	(Li et al. 2022 [52–55]; Zhou et al. 2019 [93])
NSCLC	circRBM33	Up	Associated with osimertinib resistance, and promoted proliferation, migration and invasion	DNMT1, IL6		(Pan et al. 2023 [94])
Breast cancer	circHIPK3	Up	Associated with trastuzumab and PTX resistance, and promoted proliferation, migration and invasion	miR-582-3p/ RNF11, miR-124-3p/MTDH, miR-326, miR-193a/HMGB1/PI3K/AKT, miR-1286/ HK2		(Zhang et al. 2021 [95–98]; Ni et al. 2021; Qi et al. 2021; Shi et al. 2022; Lian et al. 2023; Chen et al. 2020 [99–101])

Table 1 (continued)

Cancer types	CircRNA	Expression	Functions	Signaling pathway	Clinical feature	References
Breast cancer	circABCA10	Up	Associated with PTX resistance, and promoted breast cancer proliferation and progression	Let-7a-5p/DUSP7, miR-1271	OS, prognostic biomarker	(Liang et al. 2017 [44, 102]; Yang et al. 2020 [103])
Breast cancer	circBACH1	Up	Associated with PTX resistance, and promoted the cell viability, stemness, migration, and angiogenesis	miR-217/G3BP2		(Xia et al. 2023 [100])
Breast cancer	circ_0069094	Up	Regulated malignant phenotype and paclitaxel resistance	miR-136-5p/YWHAZ		(Kong et al. 2023 [104])
Breast cancer	circABCB1	Up	Contributed to cell viability, docetaxel resistance and migration/invasion	miR-153-3p	lymph node metastasis	(Liu et al. 2023 [105])
Breast cancer	circRNF111	Up	Associated with paclitaxel resistance, and enhanced cell viability, invasion and glycolysis	miR-140-5p/ E2F3		(Zang et al. 2020 [106])
Breast cancer	circFBXL5	Up	Promoted the 5-FU resistance, and enhanced cell viability, invasion	miR-216b/HMGA2	Tumor size, TNM stage	(Zhu et al. 2021 [58, 59])
Breast cancer	circCDR1as	Up	Increased 5-FU resistant, and inhibit apoptosis	miR-7/CCNE1		(Yang et al. 2019 [107, 108])
Triple-Negative Breast Cancer	circWAC	Up	Promoted the PTX resistance, and affect the proliferation, invasion and metastasis	miR-142/WWP1, PI3K/AKT pathway		(Wang et al. 2021 [109, 110])
Triple-Negative Breast Cancer	circCREIT	Down	Enhanced the doxorubicin sensitivity	PKR, RACK1/MTK1 apoptosis signaling pathway	grade, lymphatic metastasis, tumor size	(Wang et al. 2022 [74–78])
Triple-Negative Breast Cancer	circUBE2D2	Up	Promoted cell proliferation, metastasis and doxorubicin resistance	miR-512-3p/CDCA3	TNM stage, lymph node metastasis and prognostic biomarker	(Du et al. 2020 [111])
HER2-positive breast cancer	circCDYL2	Up	Associated with trastuzumab resistance, and Promoted proliferation, migration, metabolism	circCDYL2/GRB7/FAK, HER2 signaling	DFS, OS	(Ling et al. 2022 [112])
HER2-positive breast cancer	circ-β-TrCP	Up	Confered trastuzumab resistance	β-TrCP-343aa/NRF2/GSK3		(Wang et al. 2023 [49–51])
HER2-positive breast cancer	circ_0001598	Up	Promoted BC cell growth, trastuzumab-resistance, PD-L1 expression, and immune escape	miR-1184/ PD-L1		(Huang et al. 2021 [113, 114])

Table 1 (continued)

Cancer types	CircRNA	Expression	Functions	Signaling pathway	Clinical feature	References
HER2-positive breast cancer	circBGN	Up	Induced ferroptosis and trastuzumab resistance	OTUB1, SLC7A11		(Wang et al. 2022 [74–78])
HER2-positive breast cancer	circKDM4B	Down	Suppressed tumor growth and metastasis	miR-675/NEDD4L, PI3KCA, PI3K/AKT signaling and VEGFA expression		(Guo et al. 2022 [115, 116])
HER2-positive breast cancer	circPPID	Down	Inhibited trastuzumab resistance	NAT10, XPO4		(Wang et al. 2024 [5, 117–119])
ER^+ breast cancer	circPVT1	Up	Associated with tamoxifen resistance, and is required for ERα-positive breast cancer cell growth and tumorigenesis	miR-181a-2-3p/ ESR1, IFN signaling pathway		(Yi et al. 2023 [120])
ER^+ breast cancer	circSFMBT2	Up	Promoted cell growth and tamoxifen resistance	ERα signaling pathway, RNF181	Tumor size	(Li et al. 2023 [68–70])
ER^+ breast cancer	circMET	Up	Associated with tamoxifen resistance, and induced the cell viability and proliferation	miR-204/AHR		(Liu et al. 2022 [48, 121–123])
ER^+ breast cancer	circ_0097922	Up	Promoted tamoxifen resistance and cell malignant	miR-876-3p/ ACTN4	TNM stage	(Liang et al. 2022 [124])
ER^+ breast cancer	circTRIM28	Up	Enhanced tamoxifen resistance, and promoted cell proliferation, cell migration and invasion	miR-409-3p/HMGA2		(Yang et al. 2022 [125, 126])
ER^+ breast cancer	circ_0025202	Down	Suppressed cell tumorigenesis and tamoxifen resistance	miR-182-5p/FOXO3a, miR-197-3p/HIPK3	TNM, Lymph node metastasis	(Li et al. 2021 [127, 128])
colorectal cancer	circCCDC66	Up	Associated with oxaliplatin resistance, promoted CRC proliferation, migration, and invasion	miR-370/MDM4, DHX9		(Lin et al. 2020 [129]; Mo et al. 2022 [130])
colorectal cancer	circFBXW7	Down	Enhanced oxaliplatin sensitivity and suppressed tumor growth and metastasis	miR-18b-5p, NEK2, mTOR, and PTEN	TNM stage, lymph node metastasis, tumor recurrence	(Lu et al. 2019 [131]; Xu et al. 2021 [132])
colorectal cancer	circHIPK3	Up	Promoted oxaliplatin-resistance and cell autophagy, cells proliferation and metastasis	miR-637/STAT3, Bcl-2; miR-1207-5p/FMNL2		(Yan et al. 2020 [133]; Zhang et al. 2019 [134])
colorectal cancer	circPRKDC	Up	Enhanced 5-FU resistance, cell colony formation and invasion	miR-375/ FOXM1, wnt/β-catenin	TNM stage, lymph node metastasis, tumor size	(Chen et al. 2020 [99–101])
colorectal cancer	circ_0000338	Up	Via exosomes enhanced 5-FU resistance	miR-217 and miR-485-3p		(Zhao et al. 2021 [135, 136])

Table 1 (continued)

Cancer types	CircRNA	Expression	Functions	Signaling pathway	Clinical feature	References
colorectal cancer	circPDIA3	Up	Promoted oxaliplatin resistance, and regulated cell pyroptosis	miR-449a/XBP1		(Lin et al. 2024 [137])
colorectal cancer	circZEB1	Up	Regulated EMT and oxaliplatin resistance	miR-200c-5p		(Chen et al. 2023 [138–140])
colorectal cancer	circATG4B	Up	Induced oxaliplatin resistance and promoted Autophagy	circATG4B /ATG4B		(Pan et al. 2022 [141])
colorectal cancer	ciRS-122	Up	Promoted glycolysis to induced oxaliplatin resistance by exosomal transferring	miR-122/PKM2		(Wang et al. 2020 [64–67])
colorectal cancer	circ_0004085	Up	Associated with oxaliplatin/5-FU resistance	RRBP1		(Hui et al. 2024 [142])
colorectal cancer	circCSPP1	Up	Promoted doxorubicin resistance and tumor progression	miR-944/FZD7		(Wang et al. 2022 [74–78])
colorectal cancer	circ_0006174	Up	Promoted doxorubicin resistance by exosomal transferring	miR-1205/CCND2		(Zhang et al. 2022 [17, 143–147])
colorectal cancer	circIFNGR2	Up	Enhanced proliferation and migration and induced cetuximab resistance	miR-30b/KRAS		(Zhang et al. 2023 [56, 57])
colorectal cancer	circHIF1A	Up	Induced cetuximab resistance and glycometabolism alteration	miR-361-5p/HIF1A, GLUT1, LDHA		(Geng et al. 2024 [148])
colorectal cancer	circ_0000392	Up	Promoted cetuximab resistance and enhanced the proliferation and invasion	miR-193a-5p/PIK3R3/AKT		(Xu et al. 2020 [149–152])
PI3KCA-Mut CRC	circLHFPL2	Up	MEK inhibitor resistance (AZD6244 or RDEA119)	miR-556-5p/miR-1322/ PTEN, Foxo3a/PI3K/AKT signaling pathway		(Chong et al. 2022 [153])
Hepatocellular cancer	circSORE	Up	Transported by exosomes to spread sorafenib resistance	YBX1; miR-103a-2-5p/ miR-660-3p/Wnt2b	RFS, prognostic biomarker	(Xu et al. 2020 [149–152])
Hepatocellular cancer	circ_101505	Down	Enhanced cisplatin sensitivity and suppressed tumor growth	miR-103/NOR1		(Luo et al. 2019 [154])
Hepatocellular cancer	circHMGCS1	Up	Associated with CDDP resistance, and promoted cell proliferation	miR-338-5p/IL-7		(Zhang et al. 2024 [32, 155–157])
Hepatocellular cancer	circARNT2	Up	Associated with CDDP resistance, and promoted cell proliferation	miR-155-5p/PDK1		(Li et al. 2021 [127, 128])

Table 1 (continued)

Cancer types	CircRNA	Expression	Functions	Signaling pathway	Clinical feature	References
Hepatocellular cancer	circFBXO11	Up	Promoted the HCC proliferation, cycle progress and OXA resistance	miR-605/FOXO3/ABCB1	Tumour size	(Li et al. 2020 [158–160])
Hepatocellular cancer	circ_0003998	Up	Enhanced cell viability, migration, invasion and EMT, promoted doxorubicin resistance	miR-218-5p/EIF5A2 pathway		(Li et al. 2020 [158–160])
Hepatocellular cancer	circ_0000098	Up	Promoted doxorubicin resistance	miR-383/MCUR1, P-gp, MDR1		(Chen et al. 2023 [138–140])
Hepatocellular cancer	circ_0005785	Up	Enhanced proliferation, migration, invasion, angiogenesis; promoted PTX resistance	miR-640/GSK3β		(Yang et al. 2023 [161])
Hepatocellular cancer	circMEMO1	Down	Associated with sorafenib sensitivity	miR-106b-5p/ TET family, TCF21	OS, DFS	(Dong et al. 2021 [162, 163])
Hepatocellular cancer	circUPF2	Up	Exosome-derived circUPF2 enhanced sorafenib resistance by redeploying ferroptosis sensitivity	IGF2BP2/SLC7A11	Child–Pugh stage	(Dong et al. 2024 [164])
Hepatocellular cancer	circ_0000615	Up	Associated with sorafenib resistance		TNM stage, Lymph node metastasis, prognostic biomarker	(Zhang et al. 2022 [17, 143–147])
Hepatocellular cancer	circKCNN2	Down	Associated with lenvatinib sensitivity	miR-520c-3p/MBD2	OS, RFS	(Liu et al. 2022 [48, 121–123])
Hepatocellular cancer	circMED27	Up	Promoted lenvatinib resistance	miR-655-3p/ USP28	TNM stages, Tumor size, AFP	(Zhang et al. 2022 [17, 143–147])
Hepatocellular cancer	circDCAF8	Up	Induced angiogenesis and regorafenib resistance via exosome mediated transfer	miR-217/NAP1L1	TNM stages, Tumor size	(Gong et al. 2024 [165])
prostate cancer	circ_0004870	Down	Associated with enzalutamide sensitivity	RBM39		(Chen et al. 2022 [166–168])
prostate cancer	circRNA17 (0001427)	Down	Suppressed the enzalutamide-resistant	miR-181c-5p /ARv7		(Wu et al. 2019 [169])
castration-resistant prostate cancer	circBCL2	Up	Associated with enzalutamide-resistant and cell growth via inducing the autophagic cell death	miRNA-198/AMBRA1		(Chen et al. 2022 [166–168])
prostate cancer	circROBO1	Up	Promoted cell growth and enzalutamide resistance via accelerating glycolysis	miR-556-5p/PGK1		(Zhou et al. 2023 [170])
castration-resistant prostate cancer	circMID1(0007718)	Up	Associated with enzalutamide resistance and cell proliferation, migration, and invasion	MDSC-Exo S100A9, miR-506-3p/MID1		(Gao et al. 2022 [18, 171])

Table 1 (continued)

Cancer types	CircRNA	Expression	Functions	Signaling pathway	Clinical feature	References
prostate cancer	circ_0004087	Up	Promoted docetaxel resistance and modulated the error mitosis correction mechanism	SND1/MYB/BUB1		(Chen et al. 2022 [166–168])
prostate cancer	circCYP24A	Up	Promoted docetaxel resistance	miR-1301-3p/ PI3K/AKT/mTOR, ALDH1A3		(Yin et al. 2022 [172])
prostate cancer	circARHGAP29	Up	Promoted aerobic glycolysis and docetaxel resistance	IGF2BP2/c-Myc/LDHA, EIF4A3		(Jiang et al. 2022 [173])
prostate cancer	circFoxo3	Down	Inhibited prostate cancer cell survival, migration, invasion and chemoresistance to docetaxel	Foxo3/EMT, miR-29a-3p/ SLC25A15		(Kong et al. 2020; Shen et al. 2020 [174])
prostate cancer	circSFMBT2	Up	Enhanced the DTX resistance	miR-136-5p/TRIB1		(Tan et al. 2022 [175])
gastric cancer	circCUL2	Down	Inhibited malignant transformation and cisplatin resistance	miR-142-3p/ ROCK2	TNM stage, Lymph node metastasis	(Peng et al. 2020 [176])
gastric cancer	circCCDC66	Up	Regulated cisplatin resistance and associated with malignancy	miR-618/BCL2	TNM stage	(Zhang et al. 2020 [177, 178])
gastric cancer	0091741	Up	Promoted gastric cancer cell autophagy and OXA resistance by exosomal transferring	miR-330-3p/TRIM14/Dvl2/ Wnt/β-catenin		(Chen et al. 2023 [138–140])
gastric cancer	circPVT1	Up	Regulated autophagy, invasion, apoptosis and cisplatin resistance by exosomal transferring, and also participated in PTX resistance	miR-30a-5p/YAP1, miR-124-3p	TNM stages, Tumor size, Lymph node metastasis	(Yao et al. 2021 [179]; Liu et al. 2019 [180])
gastric cancer	circUGGT2(0030632)	Up	Enhanced gastric cancer progression and cisplatin resistance	METTL14, miR-186–3p/ MAP3K9	TNM stages, Tumor size	(Chen et al. 2024 [181])
gastric cancer	circCPM	Up	Modulated autophagy and 5-FU resistance	miR-21-3p/ PRKAA2		(Fang et al. 2022 [182])
gastric cancer	circNRIP1	Up	Enhanced hypoxia-induced resistance to 5-FU and promoted tumour metastasis by exosomal transferring	miR-138-5p/HIF-1α, miR-149-5p, AKT1/mTOR pathway		(Xu et al. 2020 [149–152]; Zhang et al. 2019 [134])
gastric cancer	hsa_circ_0000520	Up	Reversed the Herceptin resistance	PI3K-Akt signaling pathway		(Lv et al. 2020 [183])
glioblastoma	circASAP1	Up	Associated with temozolomide resistance	miR-502-5p/NRAS, MEK1/ ERK1/2		(Wei et al. 2021 [184])

Table 1 (continued)

Cancer types	CircRNA	Expression	Functions	Signaling pathway	Clinical feature	References
glioblastoma	circHIPK3	Up	Associated with temozolomide resistance, and promoted glioma cell migration and invasion	miR-524-5p/KIF2A, PI3K/AKT Pathway		(Yin and Cui, 2021 [185])
glioblastoma	circ_0000936	Up	Associated with temozolomide resistance	miR-1294		(Hua et al., 2020 [186])
acute myeloid leukemia	circPAN3	Up	Associated with doxorubicin resistance	miR-153-5p/miR-183-5p/XIAP		(Shang et al., 2019 [187])
multiple myeloma	circ_0003489	Up	Enhanced cell viability, cell proliferation, and the autophagy, and associated with bortezomib resistance	miR-874-3p/HDAC1		(Tian et al., 2021 [188])
acute myeloid leukemia	circ_0009910	Up	Regulated proliferation, cell cycle and apoptosis, and associated with imatinib resistance	miR-5195-3p/GRB10		(Wang et al., 2021 [109, 110])

Table 2 CircRNAs regulating immune resistance of cancer cells

circRNA	Parent cell	Target cell	Exprssion	Signaling pathway	Fuctions	References
circ_0010235	Lung cancer cells		Up	miR-636/PD-L1	Promoted cell proliferation, invasion and immune escape and inhibited apoptosis	(Zhao et al. 2022 [189])
circHIPK3/circPTK2	Mesenchymal stem cells of lung cancer	$CD163^+$ M2 macrophages	Up		circHIPK3/PTK2 enrichment by exosomal transferring	(Katopodi et al. 2021 [190])
circ_CHST15	Lung cancer cells	$CD8^+$ T cell	Up	miR-155-5p/miR-194-5p/PD-L1	Promoted the PD-L1 mediated immune escape of lung cancer cells	(Yang et al. 2021 [191])
circCPA4	Lung cancer cells	$CD8^+$ T cell	Up	let-7 miRNA/PD-L1	Regulated cell growth, mobility, stemness and drug resistance and inactivated $CD8^+$ T cells via PD-L1-exosomal transferring	(Hong et al. 2020 [61–63])
circCELF1	NSCLC cells	$CD8^+$ T cell	Up	miR-491-5p/EGFR	Affected number of $CD8^+$ T cells, and drive immunosuppression and anti-PD1 therapy resistance	(Ge et al. 2021 [192])
circCRIM1	NSCLC cells	$CD8^+$ T cell	Down	IGF2BP1	Promoted the expressions of Granzyme B, IFN-γ, and TNF-α of $CD8^+$ T and NK cell	(Peng et al. 2023 [176])
circATAD2	Breast cancer cells	$CD8^+$ T cell	Up	IGF2BP3/m6A/PD-L1	Impaired $CD8^+$ T cells-mediated breast cancer immune surveillance	(Zhang et al. 2024 [32, 155–157])
circWWC3	Breast cancer cells	M2 macrophages	Up	IL-4	Promoted M2 macrophage polarization and tumor immune escape	(Zheng et al. 2022 [193])
circCFL1	Triple-negative breast cancer cells	$CD8^+$ T cell	Up	HDAC1/c-Myc/mutp53	Promoted the expression of PD-L1 and suppressed the antitumor immunity of $CD8^+$ T cells	(Wang et al. 2024 [5, 117–119])
circCCDC66	Colorectal cancer cells	M2 macrophages	Up	miR-342-3p/MTDH	Augmented immune evasion and development of colorectal cancer	(Fan et al. 2023 [194])
circRERE	Colorectal cancer cells		Down	EP300/miR-6837-3p/MAVS	Activated type I IFN pathway and antitumor Immunity	(Ding et al. 2023 [195, 196])
circATXN7	CTLs	$KRAS^{MUT}$ colorectal cancer cells	Up	NF-κB	Govern T cell sensitivity to AICD by inactivating NF-κB	(Zhou et al. 2024 [197])

Table 2 (continued)

circRNA	Parent cell	Target cell	Exprssion	Signaling pathway	Fuctions	References
circQSOX1	Colorectal cancer cells	Treg cells	Up	miR-326/miR-330–5p/PGAM1	Promoted CRC immune escape by activating glycolysis and inactivating the anti-CTLA-4 therapy response	(Liu et al. 2022 [48, 121–123])
circUHRF1	Hepatocellular cancer cells	NK cell	Up	miR-449c-5p/ TIM-3	Induced natural killer cell exhaustion and caused resistance to anti-PD1 therapy by exosomal transferring	(Zhang et al. 2020 [177, 178])
CircCCAR1	Hepatocellular cancer cells	$CD8^+$T cells	Up	EP300/ EIF4A3, miR-127-5p/ WTAP	Exosome-derived circCCAR1 promoted $CD8^+$T-cell dysfunction and anti-PD1 resistance	(Hu et al. 2023 [198])
circTMEM181	Hepatocellular cancer cells	$CD39^+$ macrophages	Up	miR-488-3p/CD39, ATP–adenosine pathway	Exosome-derived circCCAR1 contributed to immunosuppression and anti-PD1 resistance	(Chen et al. 2023 [138–140])
circMET	Hepatocellular cancer cells	$CD8^+$T cells	Up	miR-30-5p/snail/DPP4 / CXCL10	Induced EMT of HCC, and enhanced anti-PD1 therapy resistance	(Huang et al. 2020 [91, 92])
circSOD2	Hepatocellular cancer cells	$CD8^+$T cells	Up	miR-497-5p/ANXA11	Promoted tumor progression, immune evasion and anti-PD-1 resistance	(Ye et al. 2023 [199])
circDLG1	Gastric cancer cells	$CD8^+$T cells	Up	miR-141-3p/CXCL12	Promoted the proliferation, migration, invasion, and immune evasion of gastric cancer cells	(Chen et al. 2021 [200])
circSOD2	M1 macrophages	Gastric cancer cells	Up	miR-1296/STAT1	Polarized macrophages towards the M1 phenotype to alleviate cisplatin resistance in gastric cancer cells	(Qu et al. 2023 [201])
circPVT1	Hematological malignancies		Genomic amplification, rearrangements, up	PVT1/circPVT1, MYC	Promoted a more aggressive phenotype of malignant cells and negative regulation of the immune system	(Ghetti et al. 2020 [202])

Table 3 CircRNAs regulating radio resistance of cancer cells

Cancer Type	CircRNA	Physiological functions	Expession	Target gene	Fuctions	Ref
NSCLC	circ_0010235	Radioresistance	Up	miR-588/HOXA10	Enhanced cell proliferation, invasiveness, and migratory ability	(Zhu et al. 2022 [71, 72])
Lung adenocarcinoma	circNEIL3	Radiosensitivity	Down	miR-1184/PIF1	Inhibited radiation-induced cell pyroptosis	(Zhang et al. 2022 [17, 143–147])
NSCLC	circ_0086720	Radioresistance	Up	miR-375/SPIN1	Enhanced cell proliferation	(Jin et al. 2021 [203])
NSCLC	circ_0001287	Radiosensitivity	Down	miR-21/PTEN	Suppressed the multiplication, migration, invasion, and radioresistance	(Zhang et al. 2021 [95–98])
NSCLC	circMTDH.4	Radioresistance and chemoresistance	Up	miR-630/AEG-1	Promoted proliferation, migration, invasion, chemoresistance, and radioresistance	(Li et al. 2020 [158–160])
Breast Cancer	circABCB10	Radioresistance	Up	miR-223-3p/PFN	Promoted cell proliferation, glycolysis, colony formation, and increased IR resistance	(Zhao et al. 2021 [135, 136])
Breast Cancer	circAAGAB	Radiosensitivity	Down	miR-378 h, activating p38 MAPK pathway	Reduced cell colony formation, cell migration and increased radiosensitivity	(Lee et al. 2023 [204])
Breast Cancer	CircABCC1	Radioresistance	Up	miR-627-5p/ABCC1	Increased IR resistance	(Zhang et al. 2022 [17, 143–147])
Colorectal cancer	circCCDC66	Radioresistance	Up	miR-338-3p	Enhanced cell viability, colony formation, and enhanced radioresistance	(Wang et al. 2019 [87–90])
Colorectal cancer	circ_ITGA7	Radiosensitivity	Down	miR-766/SMAD4, miR-3187-3p/ ASXL1, ITGA7	Suppressed CRC growth and enhanced radiosensitivity	(Yang et al. 2019 [107, 108]; Li et al. 2023 [68–70]; Li et al. 2018 [39, 205, 206])
Colorectal cancer	circ_0005615	Radioresistance	Up	miR-665/NOTCH1	Regulated the radioresistance	(Wang et al. 2023 [49–51])
Prostate cancer	circ_CCNB2	Radioresistance	Up	miR-30b-5p/KIF18A	Inhibited cell autophagy	(Cai et al. 2022 [207])
Prostate cancer	circZNF609	Radioresistance	Up	miR-501-3p/HK2	Promoted the progression and glycolytic metabolism	(Du et al. 2020 [111])
Prostate cancer	circABCC4	Radioresistance	Up	miR-1253/SOX4	Enhanced PCa cell viability, proliferation, invasion, and radioresistance and suppressing apoptosis	(Yu et al. 2023 [208])
Prostate cancer	circ_0062020	Radioresistance	Up	miR-615-5p/TRIP13	Promoted the proliferation and metastasis, and inhibited apoptosis	(Li et al. 2020 [158–160, 209])
Prostate cancer	circLPAR3	Radioresistance	Up	miR-513b-5p/JPT1	Promoted PCa cell advancement, glycolysis, and radioresistance	(Chen et al. 2023 [138, 140, 210])

[189]. The function of circ_0010235 is implicated in chemotherapy, radiotherapy, and immunotherapy.In summary, circ_0010235 plays a crucial role in LC progression and tumour resistance to treatment via multiple mechanisms and, hence, can serve as a target for LC treatment. However, further investigations are needed to clarify the role of circ_0010235 in the regulation of tumour EMT and immune escape, especially with respect to the activation mechanism of circ_0010235 in LC tissues.

CircCCDC66 and *CircFBXW7*

CircCCDC66 is derived from exons 8–10 of the coiled-coil domain containing the 66 (*CCDC66*) gene, which is located at 3p14.3 [64]. It is 468 nt in length and produced through the non-linear splicing of the *CCDC66* pre-mRNA [64]. *CircCCDC66* is reportedly involved in the pathogenesis of LC and other human cancers, including colon and gastric cancers, as well as glioblastoma [64]. *CircCCDC66* is mainly distributed in the cytoplasm of NSCLC cells and is highly expressed in NSCLC [61, 64]. *CircCCDC66* acts as a miRNA sponge that can regulate the expression of target proteins, thereby promoting the proliferation, migration, and invasion of NSCLC cells [61, 64]. Sequencing of drug-resistant epidermal growth factor receptor (EGFR)-positive LC cells (H1975) revealed elevated expression of *circCCDC66* [60]. This expression is positively regulated by focal adhesion kinase (FAK) and c-MET, but negatively regulated by nicotine acetylcholine receptor α7 [60]. Elevated *circCCDC66* expression enhanced the phosphorylation of c-MET, SAE2, and EMT in NSCLC cells [60]. Therefore, *circCCDC66* is involved in the feedback mechanism between EGFR and drug resistance-related enzymes.

CircFBXW7 is a tumour suppressor that is produced through the transcription and splicing of the F-box and WD repeat domain containing 7 (*FBXW7*) gene, which harbours seven F-box and WD repeat domains [72]. *CircFBXW7* is reportedly involved in the pathogenesis of LC and other human cancers, including colon and breast cancers, as well as acute lymphoblastic leukaemia [72, 162]. The expression of *circFBXW7* is low in NSCLC cells and tissues, where it can suppress the proliferation and metastasis of LC cells; low circFBXW7 expression has been found to decrease patient survival [72, 162]. Experiments have demonstrated that *circFBXW7* can affect patient prognosis and mitigate the malignant progression of LAD by regulating the miR-942-5p/BARX2 (BARX homeobox 2) axis, which in turn is involved in EMT pathways [162]. *CircFBXW7* expression was found to be significantly reduced in the osimertinib-resistant cell lines, H1975OR and HCC827OR [68]. High *circFBXW7* expression can suppress the proliferation of cancer stem cells, and re-sensitise drug-resistant LAD cells and stem cells to Osimertinib [68]. Mechanistically, circFBXW7 can be translated into a short polypeptide known as circFBXW7-185AA [68]. This polypeptide can interact with β-catenin in an m6A-dependent manner, and these interactions can reduce β-catenin stability by inducing subsequent ubiquitination, thereby inhibiting the activation of canonical Wnt signalling [68]. In addition, the m6A reader, YTH domain family protein 3 (YTHDF3), shares a common binding site with hsa-miRNA-Let-7d-5p [68]. Hence, forced expression of Let-7d can cause post-transcriptional reduction of YTHDF3 expression level. Activation of Wnt signalling can suppress miRNA-Let-7d expression, enabling m6A modification by YTHDF3 and promoting the translation of circFBXW7-185AA [68]. In general, *circCCDC66* activation can promote LC progression, whereas *circFBXW7* activation suppresses it, both of which can serve as serological biomarkers for LC diagnosis. Future studies should focus on their roles in resistance to EGFR-tyrosine kinase inhibitor (TKI) therapy in cancer.

CircPTK2 and *CircHIPK3*

CircPTK2 is a circRNA produced by splicing of the protein tyrosine kinase 2 (*PTK2*) gene (hsa_circ_0008305 in circBase: http://www.circbase.org) [73]. *CircPTK2* is lowly expressed in NSCLC cells and tissues and can suppress the proliferation and metastasis of LC cells [73, 74]. *CircPTK2* has been reported to be involved in the pathogenesis of LC and other human cancers, including breast, colon, bladder, and gastric cancers, as well as haematological malignancies and glioblastoma [74, 195]. In NSCLC cells undergoing EMT induced by transforming growth factor β (TGF-β), *circPTK2* and transcription intermediary factor 1γ (*TIF1γ*) were shown to be significantly downregulated [73]. *CircPTK2* overexpression can enhance TIF1γ expression while also inhibiting TGF-β-induced EMT and NSCLC cell invasion (Fig. 2) [73]. Mechanistically, *circPTK2* acts as a miR-429/miR-200b-3p sponge to inhibit TGF-β-induced EMT and NSCLC cell invasion (Fig. 2) [73]. Furthermore, drug resistance studies have confirmed that *circPTK2*also regulates the miR-942/TRIM16 axis, thereby attenuating CDDP resistance in NSCLC [74].

CircRNA HIPK3 (*circHIPK3*) (CircRNA ID: hsa_circ_0000284) is entirely derived from the large exon 2 of the homeodomain interacting protein kinase 3 (*HIPK3*) gene (1,099 nt), flanked by two long introns [213, 214]. *CircHIPK3* has been reported to be involved in the pathogenesis of LC and other human cancers, including hepatocellular carcinoma (HCC), breast cancer (BC), colorectal cancer, prostate cancer, bladder cancer, and gastric cancer, as well as osteosarcoma, haematological

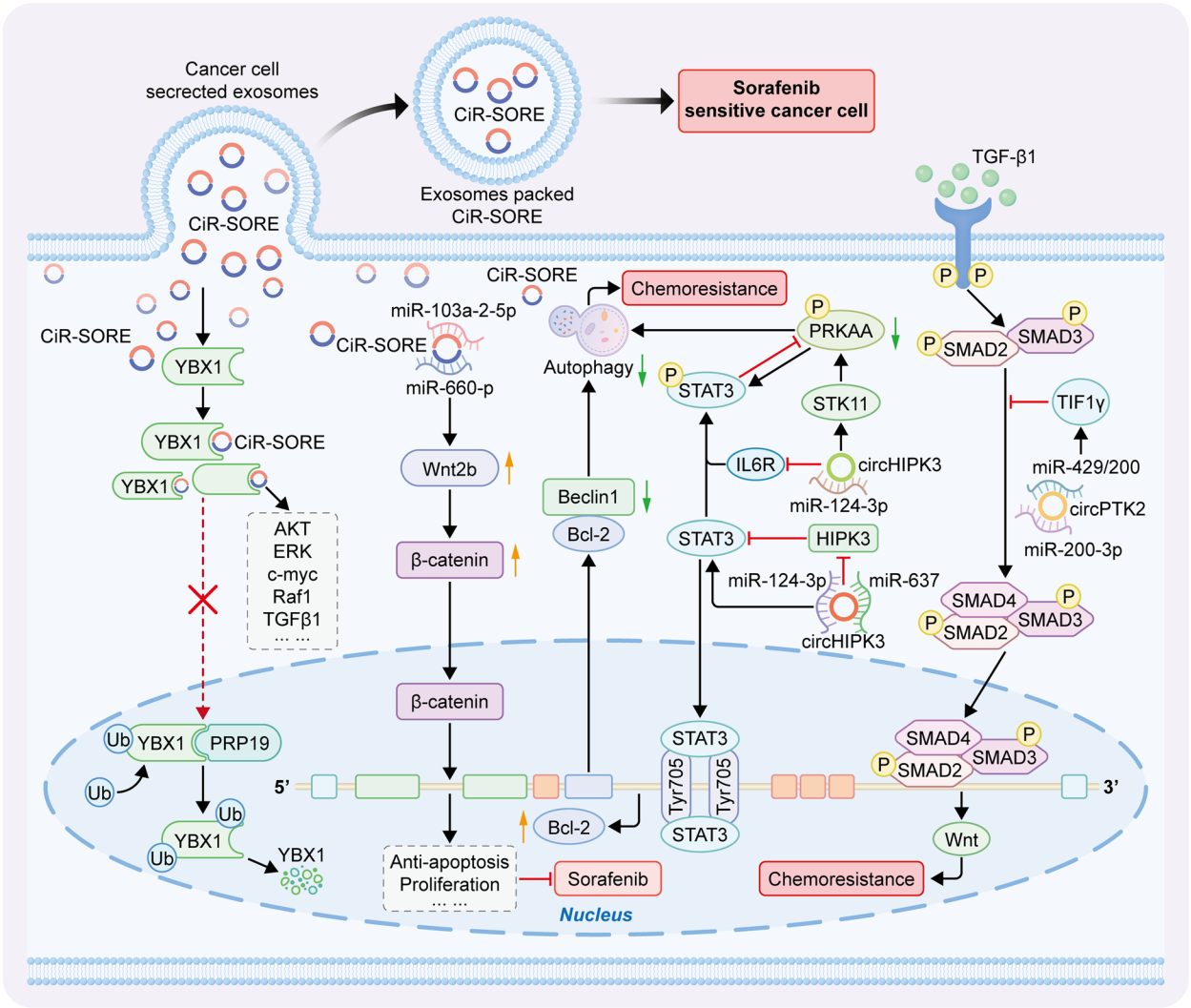

Fig. 2 Mechanisms of action of circRNAs participated in the chemotherapy resistance of cancer. Several circRNAs are involved in cancer chemotherapy resistance by influencing the gene alterations of cellular metabolism, epithelial-mesenchymal transition, apoptosis, autophagy, and exosome through regulating expression of potential target genes and related signalling pathway

malignancies, and glioblastoma [62, 213]. Chen et al. demonstrated that *circHIPK3* inhibits cancer cell proliferation, migration and invasion in vitro. And Chen et al. elevated *circHIPK3* expression can induce autophagy in STK11 mutant lung cancer (Fig. 2) [99]. Silencing *circHIPK3* increased the formation of total autophagosomes and autolysosomes especially in H838 cells. However, knockdown *linHIPK3* in contrast, decreased the autophagic flux in H838 and A549 cells. Furthermore, si-both treatment that silenced both *circHIPK3* and *linHIPK3* reversed the increase in the autophagic flux in both cell lines [99].Moreover, the ratio of *circHIPK3* to linear *HIPK3* (C/L value) reflected the level of cellular autophagy to some extent, with high C/L values (>0.49) indicating poor prognosis, especially among advanced-stage patients [99]. Lu et al. showed that *circHIPK3* can also regulate the proliferation, invasion, and migration of NSCLC cells through miR-149-mediated forkhead box protein M1 expression (FOXM1) [215]. Collectively, Lu also found that *circHIPK3* functions as an autophagy regulator and an oncogene.

Interestingly, Katopodiet al. reported that intra-epithelial $CD163^{+}/CD206^{+}$ M2 macrophages can drive KRAS immunosuppression through myeloid differentiation to induce chemoresistance in LC cells [190]. In particular, *circHIPK3*/*circPTK2* induced the monocytic MDSC subsets $Gr1^{-}/CD11b^{-}$ and $Gr1^{-}/CD11b^{+}$ to trigger M2-dependent immune responses, thus creating an

immunosuppressive tumour-promoting network [190]. Mechanistically, in a study on C57BL/6 mice, upregulation of exosomal circHIPK3 expression promotes Kras-driven intratumoral heterogeneity, which is necessary for tumour cells to bypass immune surveillance and induce immunosuppression by initiating the infiltration of myeloid-associated tumour macrophages into the lung tumour microenvironment using Kras-driven circRNA signalling. This mechanism leads to immune deregulation and immunosuppression. Moreover, guided lymph node metastasis was observed as a resultof this amplified expression of circHIPK3 [190]. These studies suggest that *circHIPK3*/*circPTK2*are carcinogens in LC, with stable biological properties and are less prone to degradation [190].Receiver operating characteristic (ROC) curve analysis, based on the expression of EVs-circHIPK3, allowed us to distinguish LC from healthy controls (area under the curve, AUC 0.897) [216].Thus, *circHIPK3* can accumulate in cells and maintain its levels and effects over extended periods, meeting essential prerequisites for clinical biomarkers. Therefore, *circHIPK3* may serve as a novel diagnostic or prognostic marker. Notably, combined testing of *circHIPK3* and conventional tumour biomarkers can improve diagnostic specificity and sensitivity.

CircPVT1

CircPVT1 is formed through the circularisation of exon 2 in the plasmacytoma variant translocation 1 (*PVT1*) gene, and the presence of Alu repeats in the flanking introns facilitates this circularisation process [205, 217]. Several lines of evidence demonstrating that two different promoters independently drive the expression of long non-coding PVT1 (lncPVT1) and circPVT1 have been reported [218]. In fact, Verduci et al. analysed the intronic region upstream of exon 2 (which encodes *circPVT1*) and found a TATA box binding site, which indicates a putative promoter region [219]. In LC, *circPVT1* was found to be associated with chemoresistance development, whereas recent evidence has shown that *circPVT1* is also involved in the pathogenesis of oesophageal, colorectal, and liver, epithelial ovarian, breast, and prostate cancers, as well as acute lymphoblastic leukaemia, head and neck squamous cell carcinoma, and oral squamous cell carcinoma [79–81].

CircPVT1 is highly expressed in LAD, and its expression is positively correlated with the stage and insensitivity to chemotherapy (CDDP and pemetrexed) in patients with LAD [79–81]. Silencing *circPVT1* can increase the sensitivity of LAD cell lines to CDDP and pemetrexed [79]. Mechanistically, *circPVT1* participates in CDDP and pemetrexed chemoresistance via the miR-145-5p/ABCC1 axis [79]. Interestingly, patients with NSCLC who received CDDP and gemcitabine showed decreased *circPVT1* expression, whereas patients in the chemoresistance group showed higher expression levels of *circPVT1* [80]. These findings suggest that testing serum circPVT1 expression levels can be used to assess chemotherapy outcomes. A recent study by Huang et al. showed that *circPVT1* was upregulated in cells following irradiation treatment, serving as a sponge for miRNA-1208, whereas its silencing enhanced the radiosensitivity of NSCLC cells [113]. Cao et al. recently demonstrated that *circPVT1* is associated with CDDP resistance in LAD [81]. They found that *circPVT1* can exert oncogenic activity through the sequestration of miR-429, leading to the upregulation of fork head box k1 (FOXK1), which is an important regulator of cell proliferation [81].

CircPVT1 and *lncPVT1* are encoded by the same gene and have similar functions [218]. Surprisingly, *circPVT1* (202 nt in length) can substantially promote tumorigenesis through miRNA sponging alone [218]. Moreover, *circPVT1* is more stable than *lncPVT1* in the blood, which signifies that *circPVT1* can serve as an independent prognostic biomarker for patients with LAD [218]. Currently, only one line of evidence indicating that *circPVT1* may encode a protein containing 104 amino acids has been reported [218]. Although further verification is needed to support these findings, they most certainly add a new level of complexity to the non-coding network induced by aberrant *circPVT1* activity [218]. More research should be conducted to better elucidate the role of *circPVT1* in tumorigenesis, as well as its functional contribution to tumour progression.

circRNAs associated with drug resistance (Table 1)

CircABCB10 is upregulated in NSCLC tissues and cells, prompting the proliferation, migration, invasion, and CDDP resistance [82–84]. Mechanistically, many studies have reported that *circABCB10* can affect mRNA expression by regulating miRNA expression, thereby promoting the proliferation, migration, and CDDP resistance in LC cells [84, 85].*CircPRMT5* expression can inhibit the apoptosis of NSCLC cells and promote their metastasis, causing CDDP resistance in NSCLC cells [86, 87]. Silencing *circPRMT5* reduces the expression of P-glycoprotein (P-gp) and glutathione S-transferase π (GST-π), which can promote the CDDP sensitivity of LC cells [86]. Huang et al. found that high *circSETD3* expression in vitro and in nude mouse xenografts significantly lowered the sensitivity of NSCLC cells to gefitinib [91]. Mechanistic studies suggest that *circSETD3* sponging of miR-520 h can lead to the upregulation of the gefitinib efflux translocation protein, ATP-binding cassette superfamily G member 2 (ABCG2), causing a decrease in intracellular gefitinib concentration, thus inducing

cellular drug resistance [91]. Hsa_circ_0004015 is associated with CDDP chemoresistance in NSCLC; in addition, Zhou et al. demonstrated that it was related to TKI resistance [54, 93]. *Circ_0004015*-mediated enhancement of gefitinib resistance in HCC827 cells is achieved through its sponging of miR-1183, which leads to the upregulation of 3-phosphoinositide dependent protein kinase 1 (PDPK1) expression [93]. Pan et al. found using RNA-seq that *circRBM33*was upregulated in osimertinib-resistant NSCLC cells [94]. Other studies have also shown that *circRBM33* can mediate the osimertinib resistance of H1975 cells by regulating the DNMT1/IL-6 axis [94].

circRNAs and immunotherapeutic resistance in LC (Table 2)

Circ_CHST15 (hsa_circ_0109320) can upregulate PD-L1 expression, thereby promoting PD-L1-mediated LC immune escape and increasing drug resistance to PD-L1 inhibitors [155, 191, 220]. By sponging miR-155-5p and miR-194-5p, *circ_CHST15* upregulates PD-L1 expression, suppresses $CD8^+$ T cell activity, and induces $CD8^+$ T cell apoptosis to promote immune escape [191].*CircCPA4* is an oncogenic factor in LC, mainly exerting its effects by sponging miRNAs [220]. Serving as a sponge for let-7 miRNA, *circRNA-CPA4* can promote EMT of NSCLC cells by upregulating PD-L1 expression [63]. Notably, increased exosomal PD-L1 can enhance CDDPresistance in NSCLC cells. In addition, *circCPA4* can positively regulate exosomal PD-L1, and silencing *circCPA4* in NSCLC cells within a co-culture system reactivates the biological functions of $CD8^+$ T cells [63]. *CircRNA-CPA4* acts by sponging let-7 miRNA to increase PD-L1 expression, inactivating $CD8^+$ T cellsto facilitate immune evasion and inhibit the expression of IFN-γ, IL-4 and IL-10 in $CD8^+$ T cells.High *circ_CELF1* expression promotes NSCLC cell invasion and metastasis while also increasing immunotherapeutic resistance in NSCLC [192]. *Circ_CELF1* acts by sponging miR-491-5p to increase EGFR expression, ultimately promoting NSCLC progression [192]. *CircCRIM1* is a novel tumour suppressor, and its overexpression can suppress immune escape in LAD [96, 221]. By binding competitively with insulin-like growth factor-2 mRNA-binding protein (IGF2BP1), *circCRIM1* decreases the mRNA expression of human leukocyte antigen F (HLA-F) and promote the expressionof granzyme B, IFN-γ, and TNF-α in $CD8^+$ T cells and natural killer (NK) cells, thereby suppressing tumour immune escape [176].

circRNAs and LC radioresistance(Table 3)

Zhang et al. reported that *circNEIL3* was significantly downregulated in irradiated LAD cells, while *circNEIL3* knockdown significantly enhanced radiotherapy efficacy [143]. Through miR-1184 sequestration, *circNEIL3* can promote PIF1 upregulation, inducing significant DNA damage and triggering AIM2 inflammasome activation to induce pyroptosis in LAD cells [143]. This ultimately impacts LC sensitivity to radiotherapy. Silencing *circ_0086720* sensitizes NSCLC cells to radiotherapy, further suppressing tumour cell survival and inducing apoptosis [203]. Silencing *circ_0086720* increases and decreases miR-375 and spindlin 1 expression, respectively, ultimately affecting LC sensitivity to radiotherapy [203]. *Circ_0001287* overexpression has been shown to suppress radioresistance in NSCLC cells [97]. Furthermore, Li et al. reported that the circMTDH.4/miR-630/AEG-1 axis was involved in NSCLC proliferation, migration, invasion, chemoresistance, and radioresistance [158].

Role of circRNAs in BC

Based on Global Cancer Statistics 2022, the BC incidence in both sexes is 11.6%, almost comparable to that of LC [1]. It is estimated that BC is the second leading cause of cancer-related death, with 666,000 deaths reported in 2022 [1]. BC has the highest incidence among females. Based on its histological features, BC can be classified into three subtypes: hormone receptor-positive (HR^+), human epidermal growth factor receptor 2-positive ($HER2^+$), and triple-negative BC (TNBC) [115, 222]. Herceptin, tamoxifen, and trastuzumab have been widely used in the clinical treatment of HR + and HER2 + BC, with good clinical outcomes to some extent [223]. However, owing to drug resistance in BC and the limitations of chemotherapy in TNBC, the mortality rates of BC remain relatively high [223–225]. A large number of circRNAs have been reported to be involved in BC pathogenesis (Tables 1, 2, and 3).

CircHIPK3

CircHIPK3 is highly expressed in BC [226]. Many reports have shown that *circHIPK3* is critical to the onset, development, and metastasis of various cancers [100, 227, 228]. Qi et al. found that *circHIPK3* sponging of miR-326 can enhance the proliferation, migration, and invasion of BC cells [226]. In addition, Chen et al. reported that *circHIPK3* can promote HMGB1 expression by binding to miR-193a and establish a miR-193a/HMGB1/PI3K/AKT signalling axis, thereby promoting the progression of BC [100]. In summary, *circHIPK3* can be useful in the diagnosis, treatment, and prognostic evaluation of cancer. *CircHIPK3* is highly expressed in PTX-resistant BC cells, as well as PTX-resistant BC tissues. Silencing *circHIPK3in vitro* and in vivo can promote the PTX sensitivity of PTX-resistant BC cells [229]. Mechanistically, *circHIPK3* acts by sponging miR-1286, whereas silencing *circHIPK3* releases miR-1286 and downregulates hexokinase

2 (HK2) expression, thus sensitising PTX-resistant BC cells to chemotherapy [229]. BC cells can also transfer *circHIPK3* to surrounding endothelial cells (ECs) via exosomes, thereby promoting angiogenesis and, hence, tumour growth [98, 230]. BC-derived exosomes can promote EC angiogenesis in the microenvironment via the circHIPK3/miR-124-3p/MTDH axis [230]. Zhang et al. reported that exosomes carrying *circHIPK3* were associated with trastuzumab resistance [230]. Exosomes are involved in trastuzumab chemoresistance, and exosomes from trastuzumab-resistant cells can enhance the resistance of trastuzumab-sensitive cells. The enhancement of trastuzumab resistance in BC cells by exosomes carrying *circHIPK3* is achieved via the circHIPK3/miR-582-3p/RNF11 axis [98].

CircABCB10

CircABCB10 is derived from exons 2 and 3 of the ATP binding cassette subfamily B member 10 (*ABCB10*) gene located on chromosome 1 [231]. It is formed through the back-splicing of the 5′ and 3′ ends of the ABCB10 antisense strand, resulting in a circRNA [231]. *CircABCB10* expression is tissue-specific and was first reported in BC [231]. *CircABCB10* promotes the proliferation and migration of BC cells by sponging miR-1271 [102]. *CircABCB10*, also known as *hsa_circ_0008717*, is involved in BC as well as in the pathogenesis of many different tumours, including oesophageal squamous cell carcinoma, glioma, oral squamous cell carcinoma, LC, ovarian cancer, thyroid cancer, and HCC [232]. Furthermore, elevated *circABCB10* expression was found to exhibit a strong correlation with pathological grade and lymph node metastasis stage [231, 232]. Therefore, *circABCB10* is a promising candidate as a diagnostic and prognostic biomarker [231, 232].

Yang et al. found that *circABCB10* was highly expressed in PTX-resistant patients with BC [103]. Silencing *circABCB10* suppressed the invasion and autophagy of BC cells, thus promoting the PTX sensitivity and apoptosis of PTX-resistant BC cells [103].Dual specificity phosphatase 7 (DUSP7) is a direct target of Let-7a-5p [103]. Its accumulation can reverse the promotion of PTX sensitivity and apoptosis induced by LeT7a-5p overexpression [103]. In addition, further experiments suggested that *circABCB10* can mediate PTX resistance, apoptosis, invasion, and autophagy of BC cells via the let-7a-5p/DUSP7 axis [103]. Another study by Zhao et al. revealed another mechanism of *circABCB10* in BC pathogenesis [102, 135]. They reported that *circABCB10* was associated with chemosensitivity in BC; silencing circABCB10 inhibited BC cell colony formation and resistance to irradiation [135]. *CircABCB10* can upregulate profilin 2 expression by acting as a sponge for miR-223-3p [135].

CircRNAs and drug resistance in BC (Table 1)

Chemoresistance

Chemotherapy is an effective strategy for the clinical treatment of BC, mainly involving PTX, doxorubicin (DOX), fluorouracil (5-FU), and oxaliplatin (OXA) [222]. However, chemotherapy drugs may show reduced efficacy in some cases owing to chemoresistance, leading to treatment failure and poor prognosis in patients with BC [115, 222]. For example, challenges remain in PTX therapy. *CircBACH1* showed increased expression in exosomes from PTX-resistant BC cells and BC tissues [233]. Xia et al. reported that upregulation of *circBACH1* expression promoted PTX resistance and angiogenesis in BC cells [233]. *CircBACH1* acts by sponging miR-217 and upregulating Ras GTPase-activating protein-binding protein 2 (G3BP2) expression to promote PTX resistance in BC cells [233]. *Circ_0069094* and *circRNF111* have also been associated with PTX resistance in BC [104, 106].*CircABCB1* diminishes the sensitivity of breast cancer cells to docetaxel by sponging miR-153-3p [105]. *CircFBXL5* and *circCDR1as* have been associated with 5-FU resistance in BC [59, 107]. Silencing *circFBXL5* can enhance BC cell sensitivity to 5-FU [59]. In addition, *circFBXL5* sponging of miR-216b can induce upregulation of high mobility group AT-hook 2, thereby regulating 5-FU resistance in BC [59].

TNBC is the most malignant BC subtype, accounting for 15–20% of all breast tumours. TNBC is an immunohistochemically defined BC subtype that is negative for oestrogen receptor (ER) or progesterone receptor expression and is characterised by HER2 amplification, rapid proliferation, and early metastasis [234, 235]. Owing to the loss of the aforementioned receptors, conventional chemotherapy and radiotherapy combined with endocrine therapy cannot be replaced by endocrine therapy alone [234]. Currently, the main treatment methods for TNBC include surgery, radiotherapy, and chemotherapy [234]. In clinical practice, adjuvant chemotherapy, such as anthracycline and PTX-based regimens, remains the primary treatment method [235]. However, chemoresistance development is still a major cause of clinical treatment failure and poor prognosis in these patients [235]. Notably, the 5-year survival rate of TNBC is significantly lower than that of non-TNBC [235]. Wang et al. discovered a circRNA related to TNBC drug resistance, namely, *circWAC* [109]. Silencing *circWAC* can enhance TNBC cell sensitivity to PTX [109]. *CircWAC* acts as a miR-142 sponge to regulate the expression of WW domain-containing E3 ubiquitin protein ligase 1. Hence, high *circWAC* expression can activate the PI3K/AKT pathway, leading to a poorer prognosis in patients with TNBC [109]. Wang et al. found that *circRNA-CREIT* was associated with DOX resistance in TNBC, and patients with

low *circRNA-CREIT* expression had shorter overall survival (OS) [75]. By employing animal models and patient-derived organoids, Wang et al. verified that *circCREIT* overexpression significantly enhanced DOX sensitivity in TNBC cells [75]. In mouse xenograft models, overexpression circCREIT enhanced TNBC cell doxorubicin sensitivity. Mechanistically, *circCREIT* serves as a scaffold to promote the interaction between protein kinase R and the E3 ligase HACE1 and facilitates the proteasomal degradation of PRK protein via K48-linked polyubiquitination [75]. In addition, *circCREIT* can be packaged into exosomes to induce DOX sensitivity among TNBC cells [75]. Patients with TNBC with high *cirUBE2D2* (*hsa_circ_0005728*) expression had an advanced TNM stage, lymph node metastasis, and poor prognosis [88, 236]. Silencing *cirUBE2D2* decreased the DOX resistance of TNBC cells [236]. *CirUBE2D2* can promote the DOX resistance of TNBC cells by regulating the miR-512-3p/CDCA3 axis [236].

HER2-targeted therapy resistance

Patients with trastuzumab-resistant BC have a poorer prognosis [237, 238]. Hence, it is of great significance to explore molecular markers that can predict trastuzumab efficacy and therapeutic targets in trastuzumab resistance [237, 238]. Deep RNA-seq analysis of circRNAs revealed that *circCDYL2* was overexpressed in patients with trastuzumab resistance [112]. Compared with patients with low circCDYL2 levels, patients with $HER2^+$ BC with high circCDYL2 levels showed rapid recurrence and shorter disease-free survival (DFS) and OS following HER2-targeted therapy [112]. *CircCDYL2* can stabilize the expression of growth factor receptor-bound protein 7 by blocking its ubiquitination and degradation and enhancing its interaction with FAK, thereby activating the downstream AKT and ERK1/2 signalling pathways to trigger BC cell resistance to trastuzumab [112]. Wang et al. reported that the β-transducin repeat-containing protein (β-TrCP) isoform encoded by *circ-β-TrCP* drives resistance to HER2-targeted therapy in an NRF2-dependent manner [50]. The orthotopic transplantation tumor model was established in vivo effect of *circ-β-TrCP* on trastuzumab resistance [50]. The effect of circ-β-TrCP on trastuzumab resistance was investigated in subcutaneous tumor animal model with BT474-TR cells. The tumor decreased significantly after circ-β-TrCP was knocked down. Overexpression of circ-β-TrCP significantly reduced the therapeutic effect of trastuzumab. Furthermore, Huang et al. found that *hsa_circ_0001598* can promote PD-L1-mediated immune escape and trastuzumab resistance in BC cells by sponging miR-1184 [114]. *CircBGN* can also promote trastuzumab resistance in BC cells [76]. By binding directly to OTU deubiquitinase ubiquitin aldehyde binding 1 (OTUB1) and solute carrier family 7 member 11 (SLC7A11), *circBGN* can enhance OTUB1-mediated SLC7A11 de-ubiquitination, thereby inhibiting BC cell ferroptosis [76].

CircKDM4B (*hsa_circ_0002926*) was also identified through transcriptome sequencing; however, its expression was significantly decreased in BC tissues [116]. *CircKDM4B* has been shown to inhibit the migration and tube formation of human umbilical vein endothelial cells in vitro and suppress angiogenesis in vivo [116]. *CircKDM4B* acts by sponging miR-675 to upregulate the expression of NEDD4-like E3 ubiquitin-protein ligase, which catalyses PI3KCA ubiquitination, thereby inhibiting the PI3K/AKT signalling pathway and vascular endothelial growth factor A expression [116]. Similarly, *circPPID* has been shown to be significantly downregulated in trastuzumab-resistant cells and tissues [117]. In vitro and in vivo experiments demonstrated that *circPPID* overexpression significantly enhanced $HER2^+$ BC cell sensitivity to trastuzumab [117]. *CircPPID* binds directly to intranuclear N-acetyltransferase 10 (NAT10), blocking its interaction with HER2 mRNA and reducing the N4-acetylcytidine modification of HER2 exon 25, thereby causing HER2 mRNA decay [117]. Interestingly, *circPPID* exhibited differences in subcellular localisation between trastuzumab-sensitive and -resistant cells. In trastuzumab-resistant cells, *circPPID* was mostly found in the cytoplasm, which was mainly due to exportin 4 upregulation, causing *circPPID* to lose the spatial conditions needed to bind to nuclear NAT10 [117].

Endocrine resistance

The ER^+ BC subtype accounts for about 70% of all BC cases [225, 239]. Treatments that block ER itself, as well as pathways upstream and downstream of ER, are collectively known as endocrine therapy [225]. Thus far, several methods of endocrine therapy have been developed, including selective ER modulators, such as tamoxifen; aromatase inhibitors, such as letrozole, anastrozole, and exemestane; and selective ER down-regulators, such as fulvestrant [225]. Nevertheless, a proportion of patients with ER^+ BC do not benefit from endocrine therapy owing to primary resistance, while patients who benefit initially may also face difficulties with acquired resistance following long-term or multi-line endocrine therapy [225]. A number of recent reports have demonstrated that circRNAs play a key role in endocrine therapy resistance in ER^+ BC [225]. An example is *circPVT1*, which was found to be highly expressed in $ER\alpha^+$ BC cell lines and tumour samples and plays a crucial role in promoting tumorigenesis and endocrine therapy resistance in $ER\alpha^+$ BC [120]. Serving as a sponge for the ceRNA, miR-181a-2-3p, *circPVT1* can promote the expression of

ESR1 and downstream ERα target genes [120]. In addition, *circPVT1* can interact directly with mitochondrial antiviral-signalling (MAVS) proteins to disrupt RIGI-MAVS complex formation, thereby suppressing the type 1 IFN signalling pathway and anti-tumour immunity [120]. Anti-sense oligonucleotide-targeting *circPVT1* can inhibit ERα$^+$ BC cell and tumour growth, thus re-sensitising tamoxifen-resistant ERα + BC cells to tamoxifen therapy [120]. Therefore, *circPVT1* can serve as a diagnostic biomarker and therapeutic target for ERα$^+$ BC in clinical practice [120]. *CircRNA-SFMBT2* can also drive tamoxifen resistance in BC cells [69]. *CircRNA-SFMBT2* was shown to bind to ERα, causing the latter to interact with activation function 2 and DNA-binding domain, thus enforcing ring finger protein 181 (RNF181) recruitment to the AF1 domain of Erα [69]. Furthermore, the circRNA-SFMBT2/RNF181 axis differentially regulated K48-linked and K63-linked ERα ubiquitination to enhance ERα stability, which led to increased expression of ERα target genes and tamoxifen resistance in ERα BC [69]. *CircMET* [121], *Hsa_circ_0097922* [124], and *circTRIM28* [125] have all been shown to promote tamoxifen resistance in ERα$^+$ BC cells. *Hsa_circ_0025202* was lowly expressed in HR$^+$ BC [127]. *CircRNA_0025202* can inhibit BC cell tumorigenesis and tamoxifen resistance by regulating the miR-182-5p/FOXO3a axis or miR-197-3p/HIPK3 axis in BC [127].

CircRNAs and immunotherapeutic resistance in BC (Table 2)

CircATAD2 can undergo m6A modification in BC, and m6A-modified *circATAD2* was found to be upregulated in BC samples and closely associated with poor prognosis [156]. High expression of *circATAD2* was shown to reduce the killing effect of CD8$^+$ T cells and promote the immune escape of BC cells (Fig. 3) [156]. Mechanistically, the m6A modification in the 3′-untranslated region of the PD-L1 mRNA can bind to circATAD2 to recruit the IGF2BP3 protein, which enhances PD-L1 mRNA stability and expression (Fig. 3) [156]. High expression of PD-L1 promotes the immune escape of BC cells [240]. Macrophages are the most abundant immune cells in the tumour microenvironment and are able to differentiate into M2-like tumour-associated macrophages to further promote tumour progression [241]. An analysis of 140 BC tissue specimens revealed that *circWWC3* was highly expressed and was associated with the OS and DFS of patients with BC [193]. Patients with BC with high *circWWC3* expression/high PD-L1 expression in BC cells and high CD1 expression in macrophages showed less favourable OS and DFS [193]. By regulating IL-4 expression and secretion, *circWWC3* can promote M2 macrophage polarisation and tumour immune escape, thereby facilitating BC progression [193]. *CircCFL1* has been found to be highly expressed in TNBC cells and is associated with prognosis [118]. *CircCFL1* can promote the proliferation, metastasis, and stemness of TNBC cells [118]. Mechanistically, *circCFL1* serves as a scaffold to enhance the interaction between histone deacetylase 1 and c-Myc, further promoting c-Myc stability through deacetylation-mediated inhibition of K48-linked ubiquitination (Fig. 3) [118]. In TNBC cells harbouring TP53 mutations, stably expressed c-Myc further enhanced mutp53 expression by binding tothe TP53 promoter, thus promoting TNBC cell stemness by p-AKT/WIP/YAP/TAZ pathway activation (Fig. 3) [118]. Furthermore, *circCFL1* can inhibit the anti-tumour immunity of CD8$^+$ T cells by promoting PD-L1 expression, thereby facilitating the immune escape of TNBC cells (Fig. 3) [118]. In animal experiments, MDA-MB-231 cells overexpressing circCFL1 were implanted subcutaneously into female BALB/c nude mice, and animal models were established together with negative controls. To evaluate the regulatory effect of circCFL1 on the stem-cell character of TNBC cells in vivo, xenotrans plantation experiments were performed using restricted dilution of MDA-MB-231 cells. The results showed that overexpression of circCFL1 significantly increased the incidence of TNBC xenografted tumor in mice. To identify circCFL1 as a potential target for anti-PD-L1 therapy in TP53-mutated TNBC patients. Wang et al. constructed mouse models that reprogrammed components of the human immune system. The results showed that the knockdown of circCFL1 in TP53-mutated TNBC cells promoted the sensitization of TNBC tumors to anti-PD-L1 treatment, which was superior to monotherapy. Together, the findings suggest that circCFL1 may be a potential target to improve the efficacy of anti-PD-L1 therapy in TP53-mutated TNBC patients. In summary, *circCFL1* can serve as a potential diagnostic biomarker and therapeutic target for patients with TNBC carrying TP53 mutations.

CircRNAs and radioresistance in BC (Table 3)

Solid tumours form hypoxic microenvironments over the carcinogenesis course, leading to comparable malignancy and therapeutic resistance levels [242]. *CircAAGAB* is lowly expressed in BC cells and is further downregulated under hypoxic conditions, whereas its high expression can increase MDAMB-231 cell radiosensitivity [204]. Binding toRBPs, FUS can increase *circAAGAB* stability [204]. Furthermore, *circAAGAB* serves as a sponge for miR-378 h, causing upregulation of the miR-378 h target genes, *KIAA1522*, *NKX3-1*, and *JADE3* [204]. *CircABCC1* knockdown was found to inhibit BC cell radioresistance, whereas the inhibitory effect of circABCC1 silencing on BC cell radioresistance could be suppressed

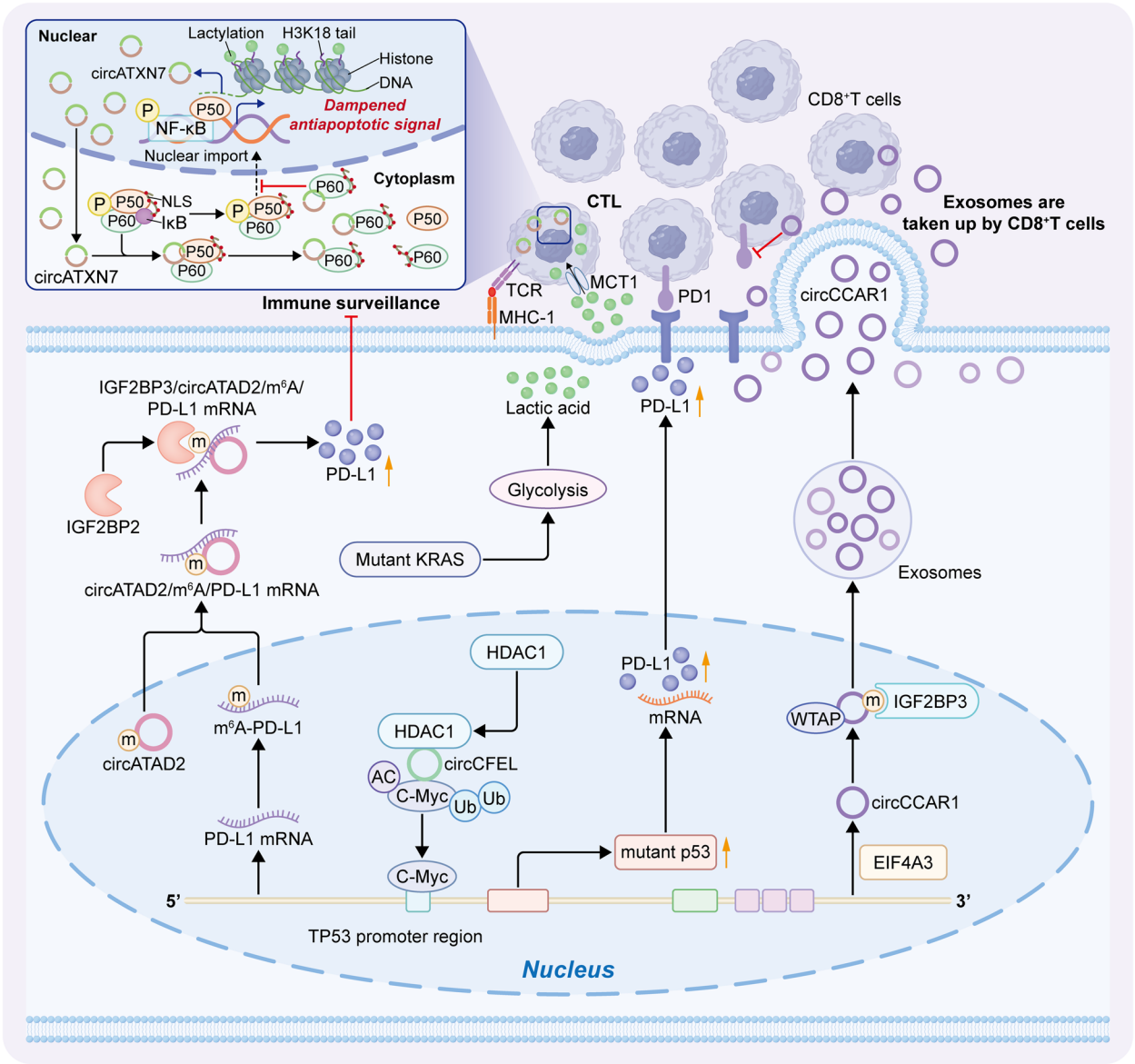

Fig. 3 The role of tumor-derived circRNAs in immune cells, including T cell and macrophage

by miR-627-5p or antagonised by ABBC1 upregulation [144]. These findings demonstrate that circABCC1 can exacerbate BC cell radioresistance by targeting the miR-627-5p/ABCC1 axis.

CircRNAs in colorectal cancer (CRC)

CRC is one of the most common gastrointestinal tumours, with the second highest incidence among women (9.5%) and the third highest among men (10.9%) [1]. In 2022, 1,096,601 new cases and 551,269 CRC-related deaths were reported globally [1]. In some developed countries, many CRC cases were detected at an early stage, and early endoscopic resection was employed to effectively reduce CRC incidence [243, 244]. However, nearly half of new CRC cases were still diagnosed at an advanced stage, and the 5-year survival rate for CRC with distant metastasis was only 11% [243, 244].

circCCDC66

CircCCDC66 has been reported to be involved in gastric and kidney cancers, as well as LAD and abdominal aortic aneurysms, where it primarily functions as a miRNA sponge [245]. CircCCDC66 (hsa_circ_0001313) also exhibits abnormally elevated expression in CRC tissues

[89]. Through competitive binding with miR-370, circCCDC66 can upregulate MDM4, thereby enhancing the metastatic capacity of CRC cells and promoting CRC development [130]. Wang et al. found that circCCDC66 was significantly elevated in CRC cells following radiotherapy, whereas circCCDC66 knockdown decreased cell viability and colony formation and increased caspase-3 activity [89]. CircCCDC66 enhances the radioresistance of CRC cells by sponging the tumour suppressor miR-338-3p [89]. In another study, Lin et al. demonstrated that circCCDC66 expression was increased in oxaliplatin (OXA)-resistant CRC cells [129]. Notably, their study revealed that phosphoinositide 3-kinase-mediated DexH-box helicase 9 (DHX9) phosphorylation promoted the oncogenic circCCDC66 expression and contributed to the development of OXA resistance [129]. Furthermore, circCCDC66 is associated with immune escape in CRC [194]. M2 macrophage-derived extracellular vesicles (M2-EVs) can also enhance immune escape during tumour progression [194]. M2-EVs enhance immune escape and CRC progression by delivering circRNA_CCDC66 [194]. Mechanistically, circRNA_CCDC66 acts by sponging miR-342-3p to upregulate metadherin expression, thereby enhancing immune escape and CRC progression [194].

CircFBXW7

In CRC samples, the expression level of circFBXW7 was significantly lower than that in normal tissues [131]. Silencing circFBXW7 significantly promoted the proliferation, colony formation, migration, and invasion of CRC cells [131]. In contrast, overexpressing circFBXW7 induced tumour suppression by reversing the NIMA-related kinase 2 (NEK2), mammalian target of rapamycin (mTOR), and phosphatase and tensin homolog (PTEN) [131]. In OXA-resistant patients with CRC, circFBXW7 was significantly decreased in tumour tissues and cells. CircFBXW7 can be transported to drug-resistant CRC cells via exosome secretion [132]. Subsequent in vitro and in vivo studies demonstrated that exosomal circFBXW7 sensitised drug-resistant cells to OXA, increased OXA-induced apoptosis, suppressed OXA-induced EMT, and inhibited OXA efflux [132]. Furthermore, rescue experiments showed that exosome-mediated transfer of circFBXW7 enhanced OXA sensitivity by binding to miR-18b-5p [132]. In summary, exosomal delivery of circFBXW7 alleviated OXA chemoresistance in CRC by binding directly to miR-128-3p, offering a promising treatment strategy for OXA-resistant patients with CRC.

CircHIPK3

CircHIPK3 has been shown to be positively correlated with clinical stage and distant metastasis in CRC [133]. Multivariate Cox analysis revealed that elevated circHIPK3 was an independent prognostic factor for poor OS in patients with CRC [133]. CircHIPK3 promotes the growth and metastasis of CRC cells by regulating the miR-1207-5p/FMNL2 axis [133]. Zhang et al. found that circHIPK3 expression was significantly elevated in chemoresistant patients with CRC [134]. CircHIPK3 promotes OXA resistance by inhibiting cellular autophagy. Functionally, circHIPK3 acts as a sponge for miR-637 to promote the expression of the key gene signal transducer and activator of transcription 3 (STAT3), thereby stimulating the downstream Bcl-2/beclin1 pathway (Fig. 2) [134]. CircHIPK3 is a prognostic indicator for patients with CRC, particularly those receiving OXA-based chemotherapy.

CircRNAs and drug resistance in CRC

Chemoresistance

Chemotherapy is an effective strategy for CRC treatment, primarily involving the use of 5-FU, OXA, and DOX [246]. However, chemotherapy drugs may exhibit reduced efficacy in some cases due to chemoresistance, which is associated with treatment failure and poor prognosis in patients with CRC [246]. This section describes several key circRNAs related to CRC chemotherapy and the mechanisms underlying their drug resistance (Table 1) [247, 248]. Upregulated *circPRKDC* expression has been reported in CRC tissues and cells exhibiting 5-FU resistance [65, 101]. *CircPRKDC*sponges miR-375, leading to FOXM1 upregulation and promoting 5-FU resistance in CRC cells [101]. Additionally, *circPRKDC* knockdown impedes the wnt/β-catenin signalling pathway by regulating miR-375 and FOXM1, thereby promoting the 5-FU sensitivity in CRC cells [101]. *Circ_0000338* is another circRNA associated with 5-FU resistance in CRC [136]. Extracellular *circ_0000338* can enter secreted exosomes and be transmitted to 5-FU-sensitive cells, facilitating 5-FU resistance in CRC cells [136]. Moreover, the binding of *circ_0000338* to miR-217 and miR-485-3p has been shown to cause 5-FU resistance in CRC cells [136]. *Circ_0067557* is highly expressed in exosomes derived from cancer-associated fibroblasts (CAFs) [249]. CAF-derived exosomes promote the proliferation, migration, invasion, and 5-FU resistance of CRC cells while suppressing apoptosis [249]. However, further investigation is needed to clarify the relationship between *circ_0067557* and CAF-derived exosomes [249].

CircPDIA3 is associated with OXA resistance and is positively correlated with poor DFS in patients with CRC [137]. *CircPDIA3* overexpression suppresses CRC cell pyroptosis, enhancing their OXA resistance in vitro and in vivo [137]. By inhibiting the palmitoylation of the gasdermin E (GSDME)-C domain, circPDIA3 enhances

the autoinhibitory effect of the GSDME-C domain, thereby suppressing pyroptosis [137]. *Circ-ZEB1* was found to be significantly upregulated in CRC tissues [138]. *CircATG4B* expression is upregulated in OXA-resistant CRC cells and can be transferred via exosomes to surrounding OXA-sensitive cells [141]. The protein encoded by *circATG4B* (circATG4B-222aa) binds competitively with transmembrane p24 trafficking protein 10 (TMED10) to enhance autophagy-related 4B cysteine peptidase (ATG4B) activity, thereby inducing autophagy and contributing to chemoresistance in CRC cells [141]. To explore the effects of exosomal *circATG4B* in vivo, a xenograft mouse model was established by subcutaneous injection of HCT116 cells. Tumor growth rate and tumor weight treated with NC were higher than those treated with silenced exo-*circATG4B*, suggesting that exosome *circATG4B* reduces the sensitivity of CRC patients to oxaliplatin [141]. To further investigate the effect of circATG4B-222aa in vivo, xenograft mouse models were established by subcutaneous injection of HCT116 cells stably transfected with different *circATG4B* vectors. The *circATG4B* and circATG4B-222aa groups had larger growth rates and tumor weights than the vector control and circATG4B-mut groups. In summary, these results suggested that the encoded protein (circATG4B-222aa) but not the circRNA (circATG4B), increases autophagy and induces oxaliplatin resistance in CRC cells.

Exosomes from chemoresistant CRC cells can transfer ciRS-122 between cells, promoting glycolysis and reducing the chemosensitivity of OXA-sensitive cells [66]. Patients with high *hsa_circ_0004085* expression in plasma show poor clinical responses to OXA/5-FU [142]. *Hsa_circ_0004085* binds to RRBP1, enhancing GRP78 mRNA stability, promoting ATF6P50 nuclear translocation, and alleviating endoplasmic reticulum stress [142]. Thus, exosome-packaged *hsa_circ_0004085* confers OXA/5-FU resistance to recipient cells by alleviating endoplasmic reticulum stress [142]. *CircCSPP1* promotes doxorubicin resistance and suppresses tumour progression in CRC via the miR-944/FZD7 axis [67, 77]. Exosomal transfer of *circ_0006174* contributes to doxorubicin resistance of doxorubicin in CRC by modulating the miR-1205/CCND2 axis [145].

EGFR-targeted therapy resistance

Cetuximab has demonstrated good efficacy in CRC treatment and is used in first-line CRC therapy, particularly for metastatic CRC [250, 251]. Although cetuximab provides substantial clinical benefits in promoting progression-free survival (PFS) and OS, improving patient quality of life, and causing minimal side effects, its effectiveness in CRC is limited due to chemoresistance [252]. Kirsten rat sarcoma viral oncogene homolog (KRAS) is a major oncogenic driver contributing to acquired drug resistance in CRC [252]. *CircIFNGR2* is upregulated in CRC tissues and cells and indirectly regulates the target gene KRAS by sponging miR-30b, thereby inducing cetuximab resistance in CRC cells [57]. Suppressing circHIF1A expression increases cetuximab sensitivity [148]. *CircHIF1A* is highly expressed in cetuximab-resistant CRC cells and is a supplementary biomarker for predicting cetuximab efficacy in patients with CRC [148]. *CircHIF1A* promotes glucose metabolism changes mediated by hypoxia-inducible factor subunit α, thereby inducing cetuximab resistance in CRC [148]. Additionally, *circHIF1A* upregulates hypoxia-inducible factor 1A through competitive binding with miR-361-5p, resulting in the overexpression of enzymes, such as glucose transporter 1 and lactate dehydrogenase (LDHA) [148]. *CircRNA_0000392* was upregulated in CRC tissues, where it sponges miR-193a-5p to upregulate PIK3R3 expression and activate the AKT-mTOR pathway, leading to cetuximab resistance in CRC cells [149]. In PIK3CA-mutant CRC, *circLHFPL2* downregulation sustains PI3K/AKT pathway activation through a positive feedback loop [153]. Moreover, *circLHFPL2* downregulation results in resistance to mitogen-activated protein kinase (MEK) inhibitors in CRC cells [153]. Therefore, targeting *circLHFPL2* may provide an effective approach for treating patients with oncogenic PIK3CA mutations [153].

CircRNAs and CRC immunotherapeutic resistance (Table 2)

Immunotherapy benefits only a small percentage (approximately 5%) of patients with advanced CRC [196]. Immune priming may represent a potential approach to enhancing sensitivity to immunotherapy [196]. *CircRERE* is expressed at low levels in CRC, and its overexpression suppresses the malignant behaviour of CRC in vitro and in vivo [196]. *CircRERE* expression is regulated by E1A binding protein p300 (EP300) [196]. Ding et al. demonstrated that the tumour-suppressive molecular axis EP300/*circRERE*/*miR-6837-3p*/MAVS activates the type I IFN pathway, enhancing anti-tumour immunity [196]. Clinically, *circATXN7* expression is significantly elevated in tumour-specific cytolytic T lymphocytes (CTLs) derived from KRASMUT compared to KRASWT CRC tissues, whereas *circATXN7* expression is similar in tumour non-specific CTLs from KRASMUT and KRASWT CRC tissues (Fig. 3) [197]. Compared to tumour-infiltrating CD8 + T cells, only a small amount of *circATXN7* expression is detected in peripheral blood CD8 + T cells [197]. Lactic acid-derived histone lactylation activates *circATXN7* transcription, sensitising T cells to activation-induced cell death (Fig. 3) [197]. *CircATXN7* binds to the nuclear factor (NF)-κB p65 subunit and masks the p65 nuclear localisation signal motif, thereby

sequestering it in the cytoplasm (Fig. 3) [197]. Clinically, *circATXN7* upregulation in tumour-specific CTLs is associated with poor clinical outcomes and immunotherapeutic resistance (Fig. 3) [197]. Silencing *circATXN7* in $CD8^+$ T cells results in mutant-selective tumour suppression and increases the efficacy of anti-programmed cell death protein 1 (PD-1) therapy in female mice with multiple tumour models (Fig. 3) [197]. In CRC cells, high *circQSOX1* expression is associated with carcinogenesis and poor clinical outcomes in patients with CRC [122]. m6A-modified *circQSOX1* mediates phosphoglycerate mutase 1 (PGAM1) expression by sponging miR-326 and miR-330-5p, promoting CRC development [122]. By regulating glycolysis and promoting immune escape in CRC cells, circQSOX1 inhibits the anti-CTL-associated antigen 4 (CTLA-4) therapy response in CRC patients [122]. Therefore, combination therapy with sh-*circQSOX1* and anti-CTLA-4 may overcome Treg cell-mediated CRC immunotherapeutic resistance [122].

CircRNAs and CRC radioresistance(Table 3)

Radioresistance is a major challenge in CRC treatment [18]. CircRNAs play a critical role in CRC pathogenesis [18]. *Circ_ITGA7* expression is lower in CRC tissues and cells than that in normal tissues and cell lines [70, 108]. Furthermore, ectopic *circITGA7* expression in vivo and in vitro suppresses CRC cell growth and metastasis [206]. *CircITGA7* inhibits Ras-responsive element binding protein 1 via the Ras pathway, which upregulates the transcription of integrin subunit alpha 7 (ITGA7) to suppress CRC cell proliferation and metastasis [206]. Others have reported that circ-ITGA7 upregulates ASXL1 through miR-3187-3p to inhibit CRC proliferation [108]. *Circ_ITGA7* overexpression suppresses CRC cell growth and enhances radiosensitivity [70]. *Circ_ITGA7* also targets miR-766 to prevent the degradation of its target gene, mothers against decapentaplegic homolog 4 (SMAD4), while miR-766 inhibition reduces CRC cell growth and increases cellular radiosensitivity [70]. These effects mediated by miR-766 inhibitors are restored through SMAD4 silencing [70]. *Circ_0005615* and NOTCH1 are upregulated in CRC tissues and cells, whereas *miR-665* is downregulated [51]. Radiotherapy increases *circ_0005615* and NOTCH1 levels and decreases *miR-665* levels [51]. *Circ_0005615* knockdown enhances CRC cell radiosensitivity [51]. Furthermore, *circ_0005615* silencing enhances CRC radiosensitivity by regulating the *miR-665*/NOTCH1 axis [51].

CircRNAs in hepatocellular carcinoma (HCC)

Liver cancer is the sixth most common malignancy worldwide, with an alarmingly high mortality rate [1]. In 2022, approximately 782,000 liver cancer-related deaths were reported globally, accounting for 8.2% of all cancer deaths [1]. HCC is the predominant form of primary liver cancer, accounting for 75–85% of all cases [253]. Major risk factors for HCC include hepatitis B virus or hepatitis C virus infection, aflatoxin exposure, smoking, alcohol abuse, obesity, and type 2 diabetes [253]. Although several mechanisms have been proposed for HCC, its early diagnosis remains challenging [254]. In recent years, circRNAs have been proposed as novel biomarkers and therapeutic target for HCC (Tables 1, 2, and 3) [254].

CircRNA-SORE

CircRNA-SORE is derived from the back-splicing of exons 7 and 8 in the transducin-like enhancer protein 4 gene [150, 151]. *CircRNA-SORE* (also known as circRNA_104, 797 and circRNA_0087293) is upregulated in sorafenib-resistant HCC cells, promoting proliferation, invasion and metastasis [150, 151]. Sorafenib is a first-line chemotherapy drug for advanced HCC [255]. However, sorafenib resistance significantly limits its efficacy, and the underlying mechanisms are not fully understood [255]. *CircRNA-SORE* binds to the oncogenic protein Y-box-binding protein 1 (YBX1) in the cytoplasm, preventing its nuclear interaction with the E3 ubiquitin ligase PRP19. This blocks PRP19-mediated YBX1 degradation, thereby affecting the expression of YBX1 target genes, including AKT, Raf1, ERK, c-Myc, and TGF-β1 (Fig. 2) [150]. Both in vitro and in vivo experiments demonstrated that *circRNA-SORE* induces sorafenib resistance in adjacent HCC cells via exosomes [150].To confirm the role of *circRNA-SORE* in in vivo mediating liver cancer resistance to sorafenib, three different mouse models were used in vivo: xenografted tumor (CDX) model derived from sorafenib resistant cell lines in situ, subcutaneous sorafenib resistant CDX model, and xenografted tumor (PDX) model derived from sorafenib resistant patients [150]. In the first mouse model, mice with orthotopic implantation of SKhep1-SR cells expressing *sh-circRNA-SORE* were markedly more sensitive to sorafenib treatment than mice implanted with SKhep1-SR-shNC cells。In the second mouse model, in vivo grade cholesterol-conjugated RIG-I *si-circRNA-SORE* around the LM3-SR cell implantation site in BALB/c nude mice, which significantly increased the sensitivity of mice to sorafenib treatment compared with injection of control siRNA。In the PDX model, local injection of in-vivo cholesterol coupled RIG-I *si-circRNA-SORE* around the site of PDX implantation resulted in significantly increased sensitivity to sorafenib treatment compared to injection control siRNA. Moreover, YBX1 level was reduced by *si-circRNA-SORE* treatment, both in the LM3-SR xenograft and the PDX mode. Overall, these results suggest that in vivo, silencing *circRNA-SORE* enhances the

sensitivity of HCC to sorafenib, further supporting the clinical potential of silencing *circRNA-SORE* to improve the efficacy of sorafenib in HCC patients.Other mechanistic study by the same authors confirmed that *circRNA-SORE* functions as a miRNA sponge, sequestering miR-103a-2-5p and *miR-660-3p*. This, in turn, activates the Wnt/β-catenin pathway to induce sorafenib resistance (Fig. 2) [151]. Further studies revealed that the m6A level of *circRNA-SORE* is high in sorafenib-resistant cells, and inhibiting of its m6A modification reduces *circRNA-SORE* expression [151]. Therefore, m6A modification stabilises *circRNA-SORE* [151]. However, no significant differences were found in the expression levels of m6A-related proteins between sorafenib-resistant and parental cells [151]. Collectively, these findings suggest the potential clinical application of *circRNA-SORE* combined with sorafenib in treating patients with advanced HCC. More clinical samples, particularly blood samples from patients with HCC pre- and post-sorafenib treatment, are needed to validate the clinical value of targeting *circRNA-SORE* to overcome sorafenib resistance in patients with HCC.

CircRNAs and drug resistance in HCC (Table 1)

Chemoresistance

Most patients with HCC develop chemoresistance after prolonged chemotherapy, leading to poor prognosis [256, 257]. Cisplatin (CDDP) is the primary chemotherapeutic agent used to treat HCC, but the biological mechanisms underlying CDDP resistance in these patients remain poorly understood [257]. *CircRNA_101505* expression is significantly reduced in CDDP-resistant HCC tissues and cell lines and is associated with poor survival outcomes [154]. *CircRNA_101505* functions by sponging *miR-103* to upregulate the expression of oxidored-nitro domain-containing protein 1 (NOR1), thereby suppressing tumour growth and sensitising HCC cells to CDDP [154]. *Circ_0072391* (*circ_HMGCS1*) has also been shown to regulate the CDDP resistance in HCC cells [157]. By sponging miR-338-5p, *circ_HMGCS1* promotes CDDP resistance in HCC cells [157]. Similarly, *circARNT2*, an oncogene, sponges *miR-155-5p*, leading to PDK1 upregulation and CDDP resistance in HCC cells [128]. *CircFBXO11* regulates HCC progression and OXA resistance through the *miR-605*/FOXO3/ABCB1 axis [159].

Doxorubicin (DOX) is a first-line chemotherapy strategy for transarterial chemoembolization, which is commonly used in advanced HCC cases [257]. However, DOX resistance eventually develops in many patients with HCC, limiting its efficacy [257]. *Circ_0003998* knockdown suppresses the viability, migration, invasion, and EMT of resistant cells in vitro, promoting DOX sensitivity in HCC and enhancing DOX cytotoxicity in vivo [209]. *Circ_0003998* acts by sponging miR-218-5p to upregulate eukaryotic translation initiation factor 5A2, leading to DOX resistance in HCC cells [209]. Conversely, inhibiting *circ_0000098* reduces DOX resistance in HCC cells by decreasing P-glycoprotein (P-gp, also known as MDR1) expression and intracellular ATP levels [210]. Silencing *circ_0005785* improves paclitaxel (PTX) sensitivity of HCC in vivo [161]. Mechanistically, *circ_0005785* serves as a sponge for miR-640, regulating glycogen synthase kinase 3 β (GSK3β), which alters PTX sensitivity in HCC in vivo [161].

EGFR-targeted therapy resistance

CircMEMO1 regulates the promoter methylation and expression of transcription factor 21 via the miR-106b-5p/TET1/5hmC axis, thereby modulating HCC progression and sorafenib sensitivity [163]. *CircMEMO1* is significantly downregulated in HCC samples, and its expression is closely linked to OS and DFS of patients with HCC [163]. High *circMEMO1* expression can enhance HCC cell sensitivity to sorafenib therapy [163]. Tumour cell-derived exosomes are associated with sorafenib resistance in HCC. Dong et al. reported that exosomes obtained from Huh-7-SR cells increase sorafenib resistance in HCC cells [164]. *CircUPF2* is notably enriched in exosomes derived from sorafenib-resistant cells [164]. Exosomes rich in *circUPF2* enhance sorafenib resistance by promoting SLC7A11 expression and inhibiting ferroptosis in HCC cells [164]. Mechanistically, *circUPF2* serves as a scaffold to form a ternary complex with IGF2BPL2 and SLC7A11, thereby stabilising SLC7A11 mRNA [164]. Therefore, exosomal*circUPF2* promotes SLC7A11 expression, enhances Xc-, and reduces ferroptosis sensitivity, contributing to sorafenib resistance [164].

Zhan et al. identified *hsa_circ_0000615* as a prognostic biomarker for sorafenib resistance in HCC [146]. Their study showed that *hsa_circ_0000615* was significantly upregulated in serum samples from patients with HCC, with higher levels observed in sorafenib-sensitive patients [146]. The area under the receiver operating characteristic curve before serum *has_circ_0000615* was 0.9238 (95% CI, 0.8915–0.956, $p < 0.0001$), confirming its potential as a diagnostic biomarker to distinguish between patients with HCC and healthy controls [146].

Elevated *circKCNN2* levels in HCC tumours correlate longer OS and recurrence-free survival (RFS) in patients [123]. Liu et al. demonstrated that *circKCNN2* expression levels could predict the anti-tumour efficacy of lenvatinib [123]. By acting as a sponge for *miR-520c-3p*, *circKCNN2* upregulates methyl-DNA-binding domain 2 (MBD2) expression to suppress HCC recurrence [123]. Additionally, circKCNN2 inhibits the expression of fibroblast growth factor receptor 4 (FGFR4), thereby enhancing

lenvatinib's anti-tumor effects [123]. These findings suggest that *circKCNN2* could be a predictive biomarker for HCC recurrence treatment [123].

CircMED27 levels are significantly elevated in the serum of patients with HCC, and its upregulation is associated with adverse clinical features and poor prognosis [147]. *CircMED27* overexpression is linked to lenvatinib resistance in HCC [147]. *CircMED27* acts by sponging *miR-655-3p*, leading to increased expression of ubiquitin-specific peptidase 28 (USP28), thereby promoting lenvatinib resistance in HCC cells [147].

Furthermore, exosomal*circDCAF8* promotes angiogenesis in HUVECs [165]. Exosomes from regorafenib-resistant HCC cells transfer *circDCAF8* to sensitive cells, conferring a resistant phenotype [165]. Mechanistically, *circDCAF8* sponges *miR-217*, leading to increased expression of nucleosome assembly protein 1-like 1 (NAP1L1), which contributes to regorafenib resistance in HCC cells [165].

CircRNAs and HCC immunotherapeutic resistance (Table 2)

By measuring circRNA concentration in tumour tissues, tumour-derived exosomes, and cell lines, Zhang et al. found that *circUHRF1* was significantly upregulated in human HCC tissues compared with matched paracancerous tissues [177].Elevated *circUHRF1* levels were associated with poor clinical prognosis [177]. *CircUHRF1* was also found in exosomes from patient plasma samples and correlated with reduced NK cell infiltration [177]. Mechanistically, *circUHRF1* acts by sponge for miR-449-5p, inhibiting IFN-γ and TNF-α secretion by NK cells [177]. Thus, *circUHRF1* may serve as a potential therapeutic target in HCC: inhibiting its function or targeting T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) could promote NK and CD8 + T cell-mediated immunity against tumour cells [177].

EV-*circCCAR1* has been shown to promote resistance to anti-PD1 immunotherapy (Fig. 3) [198]. *CircCCAR1* levels were elevated in the plasma of patients with HCC, culture supernatant of HCC cells, tumour tissues, and exosomes [198]. *CircCCAR1* secretion occurs in a heterogenous nuclear ribonucleoprotein A2/B1-dependent manner [198]. Additionally, Wilms tumour 1-associated protein (WTAP)-mediated m6A modification enhances *circCCAR1* stability by binding with IGF2BP3 (Fig. 3) [198]. Exosomal*circCCAR1* enters CD8 + T cells, leading to their dysfunction by upregulating the PD-1 protein expression (Fig. 3) [198].

CircTMEM181 is upregulated in patients with HCC, correlating with poor response to anti-PD1 therapy and unfavourable postoperative prognosis [139].HCC-derived EV-*circTMEM181* contributes to immune suppression and resistance to anti-PD1 therapy by increasing CD39 expression. Suppressing the ATP-adenosine pathway via CD39 targeting on macrophages can rescue anti-PD1 therapy resistance in HCC [139]. Overexpression of *circMET* (hsa_circ_0082002) promotes HCC progression by inducing EMT and enhancing the immunosuppressive TME [92]. Mechanistically, *circMET* drives TME formation through the miR-30-5p/Snail/DPP4/CXCL10 axis [92]. *CircSOD2* induces annexin A11 (ANXA11) upregulation by interacting with miR-497-5p [199]. The promotion of immune escape and resistance to anti-PD1 therapy by *circSOD2* has been linked to the miR-497-5p/ANXA11 axis [199].

CircRNAs in prostate cancer (PCa)

As research on PCa advances, there is an increasing recognition of the crucial role that circRNAs play in mediating chemoresistance [258]. Below, we highlight several key circRNAs that are implicated in drug resistance PCa (Tables 1, 2, and 3) [259, 260].

CircRNA and anti-androgen drug resistance

The development of castration-resistant prostate cancer (CRPC) from hormone-sensitive PCa is a significant challenge in the treatment of PCa, with nearly all cases eventually becoming resistant to castration therapy [261]. One major mechanism driving this resistance is the substitution of androgen receptors (ARs) by AR splice variants (AR-VS) [262]. Among these variants, ARv7 is particularly important, as its elevated expression in clinical specimens is associated with shorter survival in patients with CRPC and resistance to drugs like abiraterone and enzalutamide [262].

CircRNAs have emerged as critical players in this process, as they can be found in abundance in CRPC clinical samples, suggesting their involvement in resistance mechanisms [262]. For example, *hsa_circ_0004870* downregulation has been shown to enhance Arv7 expression and promote CRPC progression by altering the expression of its host gene RNA binding motif protein 39 [262]. In Enz-resistant (EnzR)-C4-2 cells, *hsa_circ_0001427* expression was found to be lower than that in Enz-sensitive cells [169], and its downregulation promoted Enz resistance by modulating *miR-181c-5p* expression [169]. Additionally, *circRNA-BCL2* expression plays a role in regulating autophagy and EnzR CRPC progression by altering miRNA-198 expression and AMBRA1 expression, with high-dose DHT inhibiting circRNA-BCL2/*miRNA-198*/*AMBRA1* pathway, leading to cell death and suppression of EnzR cell growth [166].

Moreover, *circROBO1* has been identified as a key player in promoting PCa growth and Enz resistance through accelerating glycolysis [170]. Myeloid-derived suppressor cells (MDSCs) also play a role in castration

resistance [171]. Studies showing that exosomes can mediate communication between cells [171]. For example, *circMID1* (*hsa_circ_0007718*) was found to be highly expressed in PCa tissues and in MDSC-exosome treated PC3 cells, enhancing proliferation, migration, and invasion in CRPC [171]. Inhibition of *circMID1* expression was shown to suppress MDSC-Exo-induced CRPC progression, both in vitro and in vivo [171].

CircRNA and resistance to taxane

Circ_0004087 have increasingly been recognized as key players in the development of chemoresistance in PCa. Several circRNAs have been identified to contribute to docetaxel (DTX) resistance, a critical challenge in treating advanced PCa [167].

For example, *circ_0004087* has been shown to enhance DTX resistance in PCa cells by binding to the transcriptional co-activator SND1. This interaction stimulates MYB transactivation and promotes the expression of BUB1, a downstream target, thereby increasing the resistance to DTX [167]. Similarly, *circCYP24A1* has been implicated in DTX resistance, with its expression serving as a potential therapeutic target for overcoming chemoresistance in patients with PCa [172].

Another important circRNA in DTX resistance is *circARHGAP29*. Overexpression of *circARHGAP29* in PCa cells induces DTX resistance and promotes aerobic glycolysis [173]. *CircARHGAP29* stabilises its own expression through EIF4A3 binding, while also interacting with IGF2BP2 to stabilise LDHA mRNA, a key enzyme in glycolytic metabolism [173]. Furthermore, *circARHGAP29* can enhance c-Myc expression, leading to increased LDHA levels and further promoting glycolysis [173].

CircFoxo3, in contrast, acts as a suppressor of DTX chemoresistance. By inhibiting Foxo3 expression, circFoxo3 reduces the survival, migration, invasion, and DTX resistance of PCa cells [174, 263]. Exosomal*circSFMBT2* has been shown to enhance DTX resistance in PCa cells [175]. circSFMBT2 enhances DTX resistance via the *miR-136-5p*/TRIB1 axis and is also found at high levels in the serum of patients with DTX-resistant PCa [175].

CircRNAs in radioresistance

In a study of 25 patients with PCa, including 13 with radiosensitive tumors, circ_CCNB2 expression was found to be significantly higher in radioresistant tissues than that in radiosensitive tissues [207]. Knocking down *circ_CCNB2* enhanced the sensitivity of radioresistant cells to radiotherapy. Autophagy has been shown to play a critical role in the radioresistance of many tumours [207]. Further investigation revealed that upregulation of *circ_CCNB2* inhibited cellular autophagy through the *miR-30b-5p*/KIF18A pathway, contributing to radioresistance [207]. Additionally, glycolysis is another mechanism underlying radioresistance in cancer [207]. *Circ-ZNF609* was found to be abnormally upregulated in PCa tissues, with radioresistance in PCa cells enhanced via the *circZNF609*/*miR-501-3P*/HK2 axis [111]. Circ-ABCC4 contributes to PCaradioresistance by sponging miR-1253 and upregulating the SRY-box transcription factor 4 [208]. Moreover, silencing *circ_0062020* was shown to increase the radiosensitivity of PCa cells [160]. Lastly, *circRNA LPAR3* functions as a sponge for *miR-513b-5p*, promoting the expression of Jupiter microtubule-associated homolog 1 (JPT1) and activating glycolysis, which in turn enhances radioresistance in PCa [168].

CircRNAs in gastric cancer (GC)

Chemotherapy and radiotherapy are considered the most effective and widely used treatments for GC following surgery [264]. However, their clinical effectiveness is often limited by both intrinsic and acquired resistance, which can lead to distant metastases in patients with GC [78]. In addition to these treatments, targeted therapies and immune checkpoint inhibitors have emerged as promising options for GC [265]. Compelling evidence has also shown that various circRNAs play a significant role in modulating resistance to treatment in GC (Tables 1 and 2).

CircRNAs and resistance to platinum drugs

CircCUL2 (circbase ID: hsa_circ_0000234) is derived from the back-splicing of CUL2 mRNA (from exon 2 to exon 4) and is 339 nt in length [266]. It inhibits GC cell proliferation, migration, and invasion. CircCUL2 expression is downregulated in CDDP-resistant GC cell lines, and it plays a regulatory role in CDDP sensitivity [266]. By sponging *miR-142-3p*, *circCUL2* regulates rho-associated coiled-coil containing protein kinase 2-mediated autophagy activation of GC cells, contributing to tumour suppression and enhancing CDDP sensitivity [266]. *CircCCDC66* is also implicated in CDDP resistance in GC [178]. By targeting *miR-618* and upregulating B-cell lymphoma-2 (BCL2) expression, circCCDC66 inhibits apoptosis and promotes drug resistance in GC cells [178].

Exosomes released by cancer cells plays a critical role in chemoresistance, and this is also true in GC. Upregulated expression of *circ_009147* has been detected in GC cells and their exosomes [140]. *Circ_0091741*, transmitted by GC cell-derived exosomes, induces autophagy and OXA resistance in GC cells [140]. *Circ_0091741* blocks the binding of *miR-330-3p* to tripartite motif-containing 14 (TRIM14), which increases TRIM14 expression [140]. TRIM14 may activate the Wnt/β-catenin signalling pathway by stabilising

dishevelled segment polarity protein 2 (Dvl2), thereby enhancing autophagy and OXA resistance in GC cells [140].

Exosomal *circPVT1* has been associated with chemoresistance in various cancers [179]. *CircPVT1* sponges miR-30a-5p to promote GC cell autophagy, leading to CDDP resistance [179]. Additionally, macrophage polarisation plays a key role in chemoresistance [179]. *CircSOD2* is highly expressed in M1-derived macrophages [201]. Overexpression of *circSOD2* in macrophages enhances the effect of CDDP on GC cells [201]. As a sponge for *miR-1296*, *circSOD2* modulates the upregulation of its target gene STAT1 and promotes the polarisation of M1 macrophages, thereby enhancing the CDDP effect on GC [201].

Furthermore, m6A-modified circRNAs can contribute to CDDP resistance in GC. *Hsa_circ_0030632* (*circUGGT2*) is a major m6A target of methyltransferase 14 (METTL14), and METTL14 knockdown reduces *circUGGT2* m6A levels but increases its mRNA levels [181]. The METTL14-dependent m6A modification of *circUGGT2* inhibits GC progression and CDDP resistance by regulating the miR-186-3p/MAP3K9 axis [181].

CircRNAs and other resistance in GC

PTX is another effective first-line chemotherapeutic agent in gastric cancer treatment. *CircPVT1* acts by sponging *miR-124-3p* to regulate the key transcriptional repressor of E-cadherin, ZEB1, thereby contributing to PTX resistance and promoting GC cell invasion [180]. 5-FU is also a first-line drug for the clinical treatment of GC, and *circCPM* is upregulated in 5-FU-resistant GC cell lines and tissues [182]. Moreover, high circCPM expression is positively correlated with survival rate [182]. *CircCPM*binds to miR-21-3p, which increases PRKAA2 expression, thus promoting autophagy and 5-FU resistance in GC cells [182]. *CircNRIP1* can promote hypoxia-induced 5-FU resistance by regulating the *miR-138-5p*/HIF-1 axis in GC [152].

Anti-PD-1 monoclonal antibody are a commonly used immune checkpoint inhibitors in GC immunotherapy. *CircDLG1* promotes GC progression and anti-PD-1 resistance through miR-141-3p-mediated CXCL12 regulation [200]. Herceptin is a humanized monoclonal antibody used in targeted therapy that specifically binds to HER2 and exerts anti-tumour effects in GC [267]. CircRNA *hsa_circ_0000520* has been found to be significantly reduced in GC and can reverse the Herceptin resistance of GC cells by inhibiting the PI3K/AKT signalling pathway [183].

CircRNAs in other cancer

Wei et al. examined the role of *circASAP1* in the chemoresistance of neuroblastoma (NB) cells [184]. Their results indicated that circASAP1 promoted the proliferation, invasion, and resistance of sensitive NB cells by regulating *miR-502-5p*/NRAS axis [184]. Yin et al. reported that *circHIPK3* is involved in NB chemoresistance [185]. *CircHIPK3* regulates proliferation, metastasis and apoptosis through the PI3K/AKT pathway, mediated by the *miR-524-5p*/KIF2A, thereby promoting TMZ resistance in gliomas [185]. Downregulation of *hsa_circ_0000936* sensitized TMZ-resistant glioma cells to TMZ by sponging miR-1294 [186].

CircANXA2 is associated with cytarabine and daunorubicin resistance in patients with acute myeloid leukaemia (AML) [268]. Similarly, circPAN3 acts by sponging *miR-153-5p*/*miR-183-5p* to induce DOX resistance in AML [187]. *Hsa_circ_0003489* can upregulate HDAC1 expression by sponging *miR-874-3p*, thereby promoting autophagy in multiple myeloma (MM) and sensitising MM cells to bortezomib [188]. *Circ-0009910* can trigger autophagy activation by sponging miR-34a-5p, thus promoting imatinib resistance in chronic ML (CML) [110].

Through genomic amplifications, rearrangement, and/or increased transcription, PVT1/*circPVT1* is highly expressed in AML, acute promyelocytic leukaemia, Burkitt lymphoma, MM (*linear PVT1),* and acute lymphoblastic leukaemia (*circPVT1*), conferring a proliferative advantage to tumour cells [202]. Additionally, *circPVT1* exhibits immunosuppressive properties in myeloid and lymphocyte subsets [202].

circRNAs-potential clinicalapplication

This review details the progress of endogenous circRNAs in disease occurrence, progression, metastasis, and therapeutic efficacy. As circRNAs are covalently closed structures, with a long-half-life and cell-type specificity, circRNAs have become a promising therapeutic target and biomarker for cancer diagnosis and therapeutic responses [34]. CircRNA can be detected in all body fluids including plasma, urine, cell-free saliva, feces and tissues [269]. CircRNAs have been reported to be overrepresented by twofold in the exosomes derived from cancer cells versus those from non-cancer cell [270]. Moreover, the ratio of circRNAs to their linear counterpart within exosomes was sixfold higher than in the parental cells [270]. Given the potential value of exosome-*circrNA* in tumor diagnosis and prognosis, there have been various clinical trials targeting exosome-CircRNA as a tumor biomarker [270]. Table 4 summarizes the current domestic and international clinical trial data on circRNAs and exosome circRNAs as diagnostic or

Table 4 Clinical trials with circRNAs and exosomal circRNAs as cancer diagnosis or prognosis biomarkers

Registration Number/NCT number	Approved date	Tumor type	Clinical application	Study type	Sample name	Study phase
ChiCTR2400093481	2024	Gastric cancer	early diagnosis and transformation	Diagnostic test	Blood	0
ChiCTR2300069863	2023	Cholangiocarcinoma	circSIAE and circCAPRIN1 in bile and serum as biomarkers	Observational study	Serum	0
ChiCTR1900027419	2019	Lung cancer	early diagnosis of elderly lung cancer with heart failure	Basic science	Blood	0
ChiCTR1900024188	2019	Prostate cancer	exosome circRNA to diagnosis prostate cancer	Diagnostic test	Urine	0
ChiCTR1800019529	2018	Prostate cancer	predicts prognosis of castration-resistant prostate cancer	Diagnostic test	Plasma	Diagnostic New Technique Clincal Study
ChiCTR1800018038	2018	Pancreatic cancer	exosome-derived circRNAs function as molecular phynotype biomarker for the boardline resectable pancreatic cancer	Diagnostic test	Blood	Diagnostic New Technique Clincal Study

prognostic biomarkers for cancer, including lung, breast, and prostate cancers (data from https://www.chictr.org.cn/ and https://clinicaltrials.gov/). In addition, as an emerging clinical biomarker, most clinical trials are currently in phase 0, and some projects have not yet begun to recruit receptors. In order to validate the clinical utility of circRNA biomarkers, more rigorous data and a large number of clinical samples are needed. In addition, due to the lack of highly specific and sensitive biomarkers, combining exosomalcircRNA with conventional biomarkers such as CEA and CA19-9 may yield better diagnostic results [271]. However, we believe that with the support of more and more research data, circRNA will be very promising as a reliable tumor biomarker.

It is anticipated that more endogenous circRNAs will be discovered in the future, enabling a comprehensive analysis of their role in disease regulation and providing strong targets for disease-specific therapies. In recent years, advances in RNA synthesis techniques, along with the recognition of circRNA's ability to express highly stable target proteins, have enhanced the therapeutic relevance of circRNAs [272]. This includes the use of circRNA-based molecules, such as antisense oligonucleotides or synthetic circRNA mimics for novel targeted therapies (Table 5).

The high stability of CircRNAs allows them to accumulate in cells in a temporarily regulated manner. This high stability is presumably the result of their covalently closed ring structure protecting these molecules from exonuclease-mediated degradation [14]. In contrast to neural tissues, circRNAs are often downregulated in cancer in which cell proliferation rates are high, possibly because they are diluted by proliferation before reaching steadystate levels [273]. To date, circRNA accumulates during the development of cancer cells. The structure and stability of circRNA can significantly improve protein expression, reduce its immunogenicity, improve its stability, and ultimately improve the performance of circRNA therapeutics [272].One of the most prominent examples of circRNA application is in vaccines. The remarkable success of RNA vaccines in fighting the COVID-19 pandemic has paved the way for circRNA vaccine research [274]. In 2022, Li et al. established the LNP-circRNA vaccine platform, wherein circRNAs encoding antigen proteins are coated with nanoparticles and injected into the human body [55]. The circRNA enters cells and expresses the corresponding antigenic proteins, which are then presented to antigen-presenting cells (APCs) to trigger an immune response in vivo [55]. The study demonstrated the effectiveness of the circRNA vaccine in tumour models with a poor tumour immune microenvironment (TME) [55]. Additionally, they found that combining the circRNA vaccine with adoptive cell therapy enhanced the anti-tumoureffect [55]. The researchers developed a late immunity desert in situ model and administered the RNA vaccine, TCR-T treatment, and a combination of both [55]. The results showed that all tumours in the combination group were completely eradicated, suggesting that circRNA vaccine combined with TCR-T treatment is more effective than treatment alone.

In addition to vaccines, synthetic circRNAs may also play a regulatory role in RNA editing and gene regulation. Liu et al. synthesized circRNAs that competitively inhibit *miRNA-21*, thereby reducing the downstream proteins regulated by *miRNA-21* [275]. In this way, circRNAs can act as a protein sponge to regulate gene expression.

Table 5 Comprehensive overview of published circRNA therapeutics in cancers

Registration Number/NCT number	Start date	Tumor type	categorization	Delivery vector	Product	Study phase	Clinical application
NCT06530082	2024	Breast Cancer	Vaccine		CircFam53B-219aa	Phase 1	CircFAM53B-219aa DC vaccine monotherapy and its combination with camrelizumab in the treatment of HER2-negative advanced breast cancer
	2022	Colorectal cancer, melanoma	Vaccine	LNP	ovalbumin	Preclinical	circRNA vaccine combined with TCR-T treatment in colorectal cancer
	2024	Colorectal cancer, breast cancer	Vaccine + CAR-T	LNP	HER2 fusion protein, anti-HER2-CAR	Preclinical	circRNA vaccine combined with CAR-T treatment in cancers
	2018	Gastric cancer	Gene expression modulation	Lipofectamine RNAiMax	miR-21 sponge	Preclinical	inhibiting expression of miRNA-21
	2019	Esophageal carcinoma	Gene expression modulation	Lipofectamine RNAiMax	miR-21 and miR-93 sponges	Preclinical	inhibiting expression of miRNA-21 and miR-93
	2024	Lung cancer	Cytokine	LNP	IL-12	Preclinical	drug candidate encoding IL-12sc for anti-tumor therapeutics
	2024	Solid tumor	Cytokine	LNP	IL-12	Preclinical	drug candidate encoding IL-12sc for anti-tumor therapeutics
	2022	Melanoma	Other	Intratumor injection	Anti-PCNA (proliferating cell nuclear antigen) PROTAC	Preclinical	anti-tumor therapeutics

Similarly, Wang et al. used enzyme-linked methods to construct circRNAs targeting *miRNA-21* and *miRNA-93*, which inhibitedesophageal carcinomacell proliferation and reduced tumor growth in mouse xenograft models [90]. These circRNAs are still in preclinical studies.

In the field of adoptive cell therapy, traditional approaches often require in vitro viral gene editing and transduction to design immune cells that target specific tumor antigens. However, the complex gene-editing process and the personalized nature of therapeutic products limit their widespread clinical use. Therefore, circRNA-based in vivo/in situ adoptive cell therapy has emerged as a promising alternative that offers safer and more effective treatment without the need for cumbersome extraneous preparation. Notably, RNA therapeutics pioneered a groundbreaking synthetic circRNA combined with an immune-friendly lipied nanoparticle (LNP) platform. The chimeric antigen receptor (CAR) was able to efficiently deliver circRNA to immune cells in preclinical models [276, 277]. The circRNA-CAR, encoding the CAR transmembrane protein synthesized by Wang et al., delivered along with immune-promoting LNPs, significantly inhibited tumor growth in mice, improved survival, and induced a pro-inflammatory tumor microenvironment [277]. Importantly, the combination of circRNA-Anti-HER2-CAR with a circRNA-based cancer vaccine encoding the corresponding transmembrane HER2 antigen, called circRNA-HER2, showed synergistically enhanced anti-tumor activity [277].

In other applications, the protein translation capabilities of circRNA can be utilized to precisely and locally express proteins in specific cell compartments or tissues, facilitating targeted regulation of protein function in a spatiotemporal manner. Xu et al. used combinatorial chemistry techniques to synthesize customized LNPs for lung cancer [278]. In the Lewis lung cancer model, respiratory delivery of circRNA encoding interleukin-12 effectively induced a robust immune response, leading to

significant tumor regression. Similarly, Yang et al. [126], Wang et al. explored the use of circRNAs in other cancer models, demonstrating its therapeutic potential.

In summary, compared with mRNA, circRNAs' inherent stability, extended protein expression, and innate adjuvant properties offer significant advantages. Synthetic circRNA therapies hold exciting prospects for RNA-based treatments. By optimizing synthesis methods, enhancing functional properties, and exploring multiple applications, synthetic circRNAs have the potential to revolutionize personalized medicine and address unmet clinical needs. Targeting or exploiting circRNA in cancer could be an effective treatment strategy. Many companies are investing in preclinical studies of circRNA for various diseases, including cancer, with a primary focus on novel peptides encoded by circRNA, and are eagerly awaiting results. Of all the RNA therapies approved by the U.S. Food and Drug Administration (FDA), none have been approved for cancer treatment.Therefore, in order for circRNA therapy to benefit patients, several challenges must be addressed, such as treatment response duration, circRNA packaging and targeted delivery to cancer cells, off-target effects during treatment, the multi-efficacy of circRNA, interactions with other targets, and its impact on the innate immune environment.The rapid expansion of circRNA's functional range now reveals its great potential as the first RNA therapeutic to improve the lives of cancer patients.

Conclusions and perspective

CircRNAs have garnered significance attention for their roles in cancer progression, including immune escape, angiogenesis, metabolism, drug resistance, proliferation, and metastasis. Despite the discovery of over 100,000 unique human circRNAs, they are less studied compared to other transcriptome components. This review emphasizes the dual role of extracellular tumor-derived circRNAsin drug resistanceacting as both pro- and anti-oncogenic molecules through mechanisms like miRNA sponging and interactions with proteins, scaffolds, and peptides (Tables 1, 2 and 3). Through sponging miRNAs, circRNAs can control thepost-transcriptional process, genes involved indrug metabolism, autophagy, and cell survival. For instance,*circHIPK3*plays various roles in different cancers by interacting with specific miRNAsand signalling pathways, impacting tumour growth, metastasis, and drug resistance [62, 99, 190, 213–216]. *CircHIPK3* knockdown was determined to hinder NSCLC cell proliferation,migration, and glycolysis. *CircHIPK3* was also found to sponge miR-381-3p by sponging, which activity is associatedwith the process of reversinganti-PD-L1-based therapy in NSCLC [213]. *MiR-124-3p* was found to promote NSCLC cells' autophagy and apoptosis [99]. Throughectopic overexpression of *miR-124-3p* using *miR-124-3p* mimics, significant inhibition of growth,migration, and invasion of NSCLC cells was observed, mediated through STAT3/IL6R [99]. Theimportance of this process is highlighted by the fact that *circHIPK3* is found to regulate *miR-124-3p* by sponging [99]. Mechanism found that *circHIPK3* can inhibit HIPK3 expression in STK11-mutated lung cancer cells, and sponge *miR-124-3p* [99]. The target gene of STAT3 and IL6R is *miR-124-3p*, and the high expression of HIPK3 inhibits the expression of STAT3 [99]. High expression of *circHIPK3* increased the expression of STAT3 and IL6R, but inhibited the phosphorylation of STAT3 [99]. Decreased phosphorylation of STAT3 leads to increased phosphorylation of PRKAA, which then leads to autophagy (Fig. 2) [99]. Zhanget al. alsoreported that *circHIPK3* promotes oxaliplatin-resistance in colorectal cancer throughautophagy by sponging miR-637/STAT3/Bcl-2/beclin1 [134]. *CircHIPK3* could function via sponging *miR-637*to activate the STAT3 signalling pathway, thus enhancing Bcl-2 expression and blocking beclin1 dissociation [134]. These events finally resulted in reduced autophagic cell death, which contributes to the development of drug resistance. Through enhancer/scaffold, circRNAs can control the post-transcriptional process, genes involved in drug resistance andmetastasis. *CircCREIT* was aberrantly downregulated and acts as a scaffold to facilitate the interaction between PKR and the HACE1, promotingproteasomal degradation of PKR protein, thus providing a short circuitof the cellular response to doxorubicin [75]. *CircPPID* directly binds toNAT10 asRBP spongein the nucleus and blocks the interaction between NAT10 and HER2mRNA, reducing N4-acetylcytidine (ac4C) modification on HER2 exon 25, leading to HER2 mRNA decay [117]. *CircPPID* sensitizes breast cancerto trastuzumab and provides a promising therapeutic direction. *Circ-β-TrCP* was aberrantly downregulatedas translated circRNA peptideand encodes a novel truncated 343-amino acidpeptide located in the nucleus, referred as β-TrCP-343aa, which competitively binds to NRF2, blocks $SCF^{\beta-TrCP}$mediated NRF2 proteasomal degradation, and this protective effect of β-TrCP-343aa on NRF2 protein requiresGSK3 activity [50]. *Circ-β-TrCP*-encoded β-TrCP protein isoform drives HER2-targeted therapy resistance in a NRF2-dependent manner [50].

The review focus of circRNA research in immunotherapy resistance is mainlyon lung cancer and other cancers. Mechanistically, circRNAs modulate immunotherapy resistance by sponging miRNAs or serving as protein scaffolds. CircRNAs may aid in immunotherapy selection by detecting their expression in tumour tissues. The expression of PD-L1, considered a biomarker for

immunotherapy sensitivity, is intricately regulated by circRNAs, as illustrated in Table 2. Many circRNAs function as ceRNAs to act as key factors by regulating the PD-1/PD-L1 pathway to influence the TME in this review. For instance, circRNA *circ-CPA4* functions as an oncogene in NSCLC, and acts as a sponge for *let-7* miRNA, leading to increased PD-L1 expression and immune evasion [63]. Coculture of NSCLC cells and $CD8^+$T cells, silencing *circ-CPA4* reactivated $CD8^+$T cells, suggesting that *circ-CPA4* enhanced PD-L1 expression by sponging *let-7* to regulate cell growth, mobility, stemness and immunotherapy resistance and to inactivate $CD8^+$T cells in NSCLC [63]. Similarly, *circ_CHST15* and *circ_0010235* also regulate PD-L1 expression to govern the progression and immune evasion of cancer by regulating target genes via miRNA sponging [189, 191]. "Role of circular RNAs (such as *circATAD2*) in regulating resistance to cancer immunotherapy" highlights the role of IGF2BP3, which upregulates tumor cell PD-L1 expression, potentially leading to T cell dysfunction-mediated immune escape and immunotherapy resistance [156]. Despite these complexities, circRNAs continue to play a crucial role in tumour diagnosis and treatment.

Exosomal circRNAs have become a key point of research due to their involvement in cancer progression, including immune escape, drug resistance, proliferation and metastasis. Both tumor and non-tumour derived extracellular circRNAs play a double-edged sword or "pro-and anti-cancer" role in cancer progression through mechanisms such as cellular components, indicating that these molecules have been providing insights into cancer pathogenesis and treatment. Cellular components in the tumor microenvironment communicate with tumour cells through exosomes and can impact immunotherapy resistance by releasing exosomal circRNAs (Figs. 2 and 3). Cellular communication can be divided into two types due to different cell secretions: One is the exosome containing circRNA secreted by tumour cells, which transport circRNA into the tumor microenvironment to initiate immune escape (Tables 1 and 2). The most important cells in tumour microenvironment mainly include cancer-associated fibroblasts (CAFs), cancer stem cells (CSCs), tumour microenvironmental immune cells (TMICs), etc. Second, these types of cells use exosomes transporting circRNAs to promote EMT, tumour metastasis and drug resistance through a variety of mechanisms (Tables 1 and 2). In order to distinguish exosomes from microvesicles and ensure their purity and specificity, it is necessary to improve the extraction and purification techniques of exosomes. Innovations in this area, such as leveraging machine learning, microdrop digital PCR, and artificial intelligence, may improve our ability to identify exosomal circular RNAs involved in tumour diagnosis, ultimately leading to better clinical decision making.

In this review, we describe the biogenesis and biological function of circRNA, clinical applications, and factors related to tumour chemotherapy resistance, targeted resistance, immunotherapy resistance, and radiation resistance. We also explore the potential of circRNAs as biomarkers for predicting therapeutic response and clinical therapeutic applications as targets, and summarize their current regulatory mechanisms in the context of different tumor treatment resistance. In current therapeutic resistance studies, circRNAs have primarily promoted or mitigated resistance by acting as miRNA sponges or protein decoys. However, the regulation of therapy resistance by circRNA may involve other mechanisms that are worth exploring. Uncovering additional mechanisms of circRNAs in therapeutic resistance could lead to the identification of new therapeutic targets or biomarkers, enabling precise personalized therapy, and improving overall patient outcomes. The great potential of circRNA in tumour therapy is promising, but translating preclinical research into clinical practice requires careful consideration.

Abbreviations

circRNAs	Circular RNAs
LC	lung cancer
ncRNAs	Non-coding RNAs
circRNAs	Circular RNAs
ceRNAs	Competing endogenous RNAs
EMT	Epithelial-mesenchymal, transition
RNA-seq	RNA sequencing
SD	Splice-donor
SA	Splice-acceptor
RBPs	RNA-binding proteins
miRNA	MicroRNA
SCLC	Small-cell lung cancer
NSCLC	Non-small-cell lung cancer
LSCC	Lung squamous cell carcinoma
LAD	Lung adenocarcinoma
LCC	Large cell carcinoma
PTX	Paclitaxel
CDDP	Cisplatin
HOXA10	Homeobox A10
EGFR	Epidermal growth factor receptor
PTK2	Protein tyrosine kinase 2
TGF-β	Transforming growth factor β
TIF1γ	Transcriptionintermediary factor 1γ
TNBC	Triple-negative BC
DOX	Doxorubicin
5-FU	Fluorouracil
OXA	Oxaliplatin
ER	Oestrogen receptor
OS	Overall survival
MAVS	Mitochondrial antiviral-signalling
DFS	Disease-free survival
BC	Breast cancer
DHX9	DexH-box helicase 9
TMED10	Transmembrane p24 trafficking protein 10
ATG4B	Autophagy-related 4B cysteine peptidase
ITGA7	Integrin subunit alpha 7
PGAM1	Phosphoglycerate mutase 1
YBX1	Y-box-binding protein 1

PD-1	Programmed cell death protein 1
LDHA	Lactate dehydrogenase
ITGA7	Integrin subunit alpha 7
MBD2	Methyl-DNA-binding domain 2
FGFR4	Fibroblast growth factor receptor 4
TIM-3	T cell immunoglobulin and mucin domain-containing protein 3
WTAP	Wilms tumour 1-associated protein
JPT1	Jupiter microtubule-associated homolog 1
TRIM14	Tripartite motif-containing 14
Dvl2	Dishevelled segment polarity protein 2

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Authors' contributions
Wenjuan Liu, Nasha Zhang and Ming Yang contributed to the conception and design of this review. Wenjuan Liu wrote the original draft and created all the Figures and Tables. Niu Jiling was responsible for the summary and editing of the references. Yanfei Huo and Linyu Han revised the figures of the review. Nasha Zhang and Ming Yang conceived and supervised the project. Wenjuan Liu and Jiling Niu contributed equally to this draft. All authors have read and approve the published version of this manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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