# Exosomal circRNAs in hepatocellular carcinoma: Implications for the development and therapeutic resistance of hepatocellular carcinoma (Review)

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**Abstract.** Hepatocellular carcinoma (HCC) is the predominant type of primary liver cancer, with high morbidity and mortality rates globally, ranking it among the leading causes of cancer-related death worldwide. Despite notable advancements in HCC treatment in recent years, high rates of recurrence and treatment resistance remain significant clinical challenges. The development of drug resistance undermines the efficacy of current therapies and leads to poor patient outcomes. However, the specific role and detailed delivery mechanism of exosomal circular RNAs (circRNAs) in mediating this treatment resistance are still largely undefined. circRNAs represent a group of non-coding RNAs with various biological roles. An increasing number of circRNAs are abnormally expressed in HCC and participate in the malignant progression of HCC, playing a role in HCC treatment resistance. Furthermore, circRNAs can exert additional effects when packaged into exosomes. Exosomes, as signaling molecules of intercellular communication, are enriched with circRNAs, which can be packaged, secreted and transferred to target recipient tumor cells, thereby regulating the development process and drug resistance of cancer. The present comprehensive review aims to summarize how these exosomal circRNAs regulate key hallmarks of cancer in HCC and critically synthesize the current literature, elucidating how exosomal circRNAs modulate therapeutic resistance in HCC and highlighting their potential as biomarkers and therapeutic targets.

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## Contents



## 1. Introduction

Liver cancer is the sixth most common cancer and the third leading cause of cancer-specific mortality worldwide. In 2022, liver cancer accounted for ~866,136 cases and 758,725 deaths globally, with an estimated 42,240 new cases and 30,090 related deaths expected in the United States in 2025 (1,2). Although the relative survival rate for liver cancer has shown notable improvement over the past 5 years, its prognosis remains the least favorable compared with lung, esophageal and pancreatic cancer. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for 75-85% of primary liver cancer cases (1). However, the pathogenesis of HCC is very insidious and there are often no specific clinical manifestations in the early stages of the disease, which poses a considerable obstacle and difficulty in diagnosis. Therefore, the majority of patients are typically diagnosed only when the disease has progressed to an advanced stage and apparent symptoms such as severe jaundice and ascites have appeared (3). In the later stages of HCC, due to the severity of the condition, the widespread proliferation or metastasis of tumor cells and the limitations of local treatment, conventional treatments such as surgical resection, liver transplantation or local percutaneous

tumor ablation are unable to effectively treat the disease, resulting in a high mortality rate (4). Despite significant progress and breakthroughs in liver cancer treatment in recent years, encompassing interventional therapies, local ablation, chemotherapy, targeted treatments and immunotherapy, the prognosis for patients with HCC remains unsatisfactory, with a 5-year survival rate of no more than 18% (5). This is largely attributed to the propensity of the tumor to metastasize and its resistance to various therapeutic approaches. Malignant HCC can exhibit drug resistance that is classified into two categories: Primary and acquired resistance. The development of acquired resistance in HCC is influenced by a variety of factors, including alterations in the tumor microenvironment (TME), modifications in cellular signaling pathways, dysregulated apoptosis, the presence of cancer stem cells (CSCs), the involvement of microRNAs (miRNAs), mechanisms related to DNA repair, variations in the immunophenotype, shifts in drug metabolism and drug efflux and uptake as well as conditions of tumor hypoxia (6). Since acquired resistance to HCC can significantly reduce the therapeutic effect of anti-cancer drugs, resulting in poor patient prognosis, reducing HCC drug resistance has become a critical task in the field of liver cancer research and treatment and is also one of the key issues that need to be urgently addressed.

The advancement of high-throughput and second-generation sequencing technologies has significantly enhanced the capacity to identify aberrant non-coding RNAs (ncRNAs), leading to the discovery of an increasing number of these transcripts. Circular RNAs (circRNAs) are distinguished by their unique covalently closed configuration, setting them apart from the plethora of ncRNAs. circRNAs play a pivotal role in modulating gene expression both during and after transcription through various mechanisms, such as serving as sponges for miRNAs, coding for polypeptides, functioning as scaffolds for proteins and establishing stable complexes with RNA and proteins to influence subsequent biological activities (7). Numerous studies indicate that circRNAs are fundamentally associated with HCC progression and treatment resistance (8-13).

Exosomes are small extracellular vesicles originating from endocytosis, released by various cells, measuring 50-150 nm in diameter; they contain a rich and diverse array of biologically active substances such as proteins, nucleic acids, lipids and metabolites (14). These bioactive compounds are pivotal in critical tumor processes, including proliferation, invasion, metastasis, metabolism and resistance to treatment, all of which significantly influence tumor initiation and progression (15). In 2015, a study first revealed that circRNAs are present within exosomes. This groundbreaking finding suggested that serum exosomal circRNAs may serve as promising circulating biomarkers for cancer diagnosis (16). Furthermore, studies have shown that exosomal circRNAs can be transferred between HCC and non-HCC cells. In this process, they can promote or inhibit the progression of HCC and mediate the therapeutic resistance of HCC cells (17-19). It can therefore be seen that exosomal circRNAs are a highly promising cancer diagnostic marker and therapeutic target, and an in-depth exploration of the role of exosomal circRNAs in the occurrence and development of HCC and drug resistance is of significant clinical value.

The present review provides a thorough overview of the various roles and intricate mechanisms of exosomal circRNAs in the progression of HCC. In particular, how these molecules influence HCC resistance to a range of treatment strategies, including chemotherapy, radiotherapy, targeted therapies and immunotherapy, is discussed. Through a comprehensive analysis of current evidence, exosomal circRNA-mediated mechanisms of HCC resistance, which involve alterations in cell signaling pathways, modulation of the TME and metabolic reprogramming of cancer cells, are described. These findings provide a solid theoretical foundation for overcoming HCC resistance and highlight innovative strategies to advance HCC treatment. Furthermore, targeting exosomal circRNAs critical to treatment resistance has emerged as a highly promising research direction in HCC therapeutics, garnering notable attention and investment from the scientific community.

## 2. Biogenesis of exosomes and drug resistance transfer

Exosomes, small extracellular vesicles surrounded by a lipid bilayer, were first identified in 1983 in sheep reticulocytes and are released by a wide range of cells under physiological and pathophysiological conditions (20,21). Their generation involves the inward folding of localized membranes within late endosomes, leading to the creation of intraluminal vesicles (ILVs). These ILVs accumulate, resulting in the formation of multivesicular bodies (MVBs). Subsequently, an MVB merges with the cell membrane, which releases the ILVs into the extracellular environment, transforming them into exosomes (22). Exosomes are packed with a diverse array of biologically active components, including DNA, mRNA, miRNAs, long ncRNAs (lncRNAs), circRNAs, proteins and lipids. These biologically active substances can be transmitted between different cells, thus mediating transcellular communication and regulating biological processes such as tumor proliferation, metastasis, drug resistance, stemness and metabolism (Fig. 1) (23). Exosomes are pivotal in mediating the transfer of molecules that imbue drug resistance between tumor cells. Drug-resistant tumor cells transfer biologically active substances such as proteins and ncRNAs encapsulated in exosomes to sensitive tumor cells, which can interfere with tumor cell signaling pathways or promote drug efflux, resulting in a decrease in the concentration of the drug in the tumor cells, which in turn affects the cell cycle, invasion and metastasis, apoptosis, angiogenesis and metabolic reprogramming of the cells (24-26). In addition, exosomes can mediate tumor drug resistance by acting on tumor stem cell phenotypes, epithelial-mesenchymal transition (EMT) and DNA repair damage, among other mechanisms. For examination, exosomes are typically obtained from blood or cell culture fluids, and their detection hinges on the extraction of exosomes of high purity. Of the various methods available, ultracentrifugation stands out as the most prevalent technique and is often considered the 'gold standard' for isolating exosomes (27). In addition to ultracentrifugation, size exclusion chromatography, ultrafiltration, immunoaffinity chromatography, microfluidics and other new exosome isolation techniques have also emerged (28).

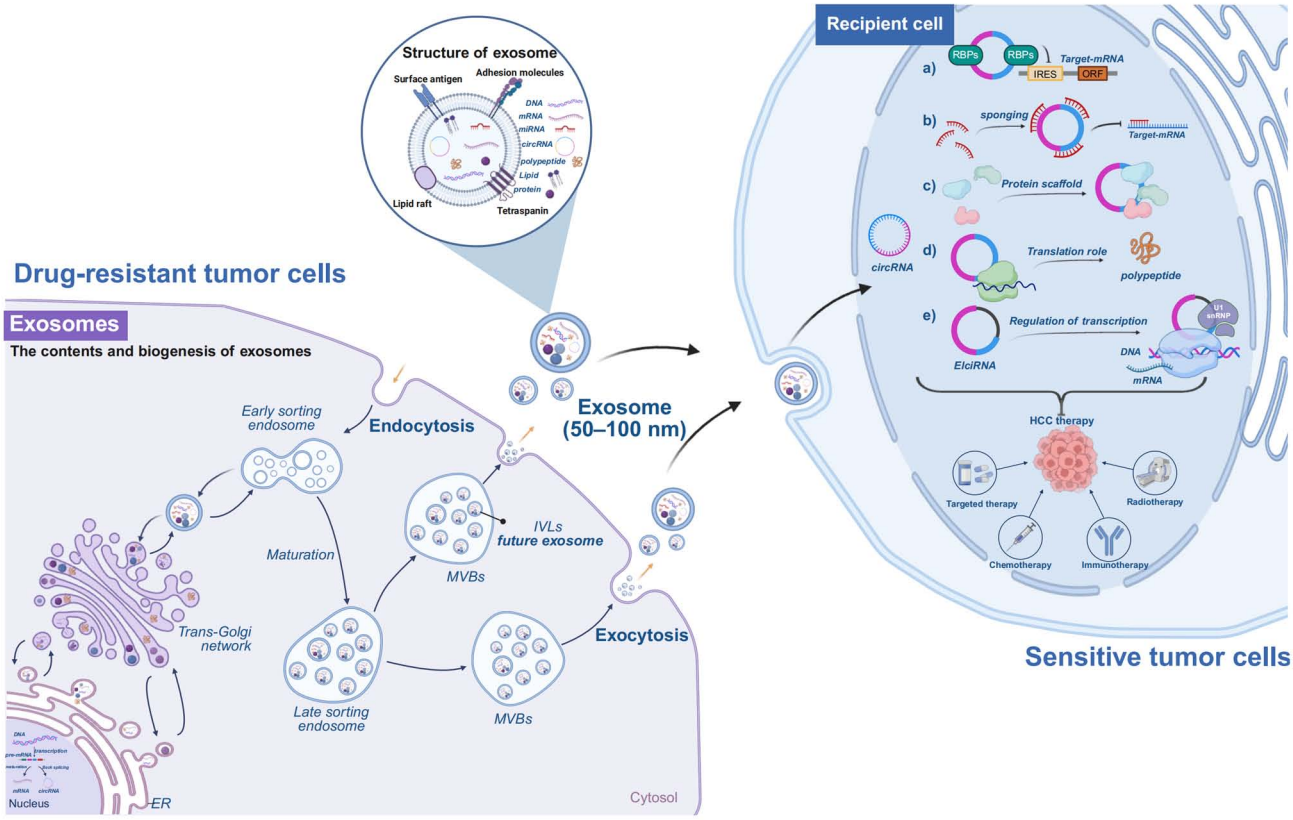


Figure 1. Schematic illustrating the formation and secretion process of exosomes as well as their structure. Secretory cells form early endosomes through inward budding, which gradually evolve into mature MVBs. These MVBs fuse with the plasma membrane to release exosomes. Exosomes contain bioactive substances such as DNA, mRNA, miRNA, circRNA, proteins and lipids. These components are delivered to recipient cells via endocytosis, enabling them to exert biological effects. The primary biological functions of circRNAs include. (A) Interacting with RBPs to regulate gene expression (B) acting as competing sponges for miRNAs to modulate target gene expression (C) serving as protein scaffolds to facilitate interactions between different proteins (D) some circRNAs can be translated by ribosomes into protein polypeptides to perform regulatory functions; and (E) binding to U1 snRNP, which forms complexes with RNA polymerase II to regulate gene transcription or splicing. circRNA, circular RNA; ER, endoplasmic reticulum; RBPs, RNA-binding protein; MVBs, multivesicular bodies; IVLs, intraluminal vesicle; IRES, internal ribosome entry site; ORF, open reading frame; U1 snRNP, U1 small nuclear ribonucleoprotein particles. Figure was created with biorender.com.

## 3. circRNAs in exosomes

Among the numerous biologically active substances in exosomes, circRNAs and ncRNAs are of paramount importance and have been extensively studied. circRNAs and ncRNAs are present in all eukaryotic cells. Primarily, they are generated through the 'aberrant splicing' (also termed reverse splicing) of precursor mRNAs (pre-mRNAs) (7). circRNAs can be classified into various subtypes based on their distinct splicing patterns. These include exon circRNAs (ecircRNAs), exon-intron circRNAs (EIciRNAs), circular intron RNAs and tRNA intron circRNAs (tricRNAs) (29). In contrast to traditional linear RNAs that feature distinct 5' and 3' ends, circRNA molecules possess a unique closed-loop structure. This design not only shields them from RNA exonuclease activity but also enhances their stability during expression. As a result, circRNAs are less susceptible to degradation and exhibit specificity to particular tissues and cells (30). circRNAs serve several key biological roles that can be grouped into five main categories (Fig. 2): i) Influencing gene transcription and splicing. circRNAs can engage in RNA-RNA interactions, forming R loops at gene loci, which may modify the splicing of parent transcripts or linear mRNAs. Additionally, they can collaborate with transcription factors to enhance transcriptional activity. CircSEP3, which originates from exon 6 of the SEPALLATA3 gene, facilitates the accumulation of its homologous exon 6-skipped splice variant. This is achieved by binding to the parental genomic locus, leading to the formation of an RNA-DNA hybrid (R-loop), which subsequently induces transcriptional pausing and recruits splicing factors (31). Similarly, circSMARCA5 promotes the formation of an R-loop at exon 15 of its host gene, SNF2 related chromatin remodeling ATPase 5 (SMARCA5), which results in premature transcriptional termination and consequently elevates the level of a truncated, non-functional isoform of SMARCA5 mRNA (32). ii) Functioning as sponges for RNA-binding proteins (RBPs). RBPs play vital roles in RNA cleavage, stability and the translation of mRNAs. circRNAs, through their unique sequences with specific RBP binding sites, can bind these proteins, forming RNA-protein complexes that inhibit the activity of RBPs and affect the expression of their associated genes (33). For example, the circRNA CIARS (hsa_circ_0008367) interacts with ALKBH5 to modulate ferroptosis in HCC cells, thereby underscoring the significant role of circRNAs in the regulation of cell death pathways (34). iii) Serving as miRNA sponges. circRNAs possess numerous binding sites for miRNAs, effectively soaking up these molecules and preventing them from interacting with mRNAs,

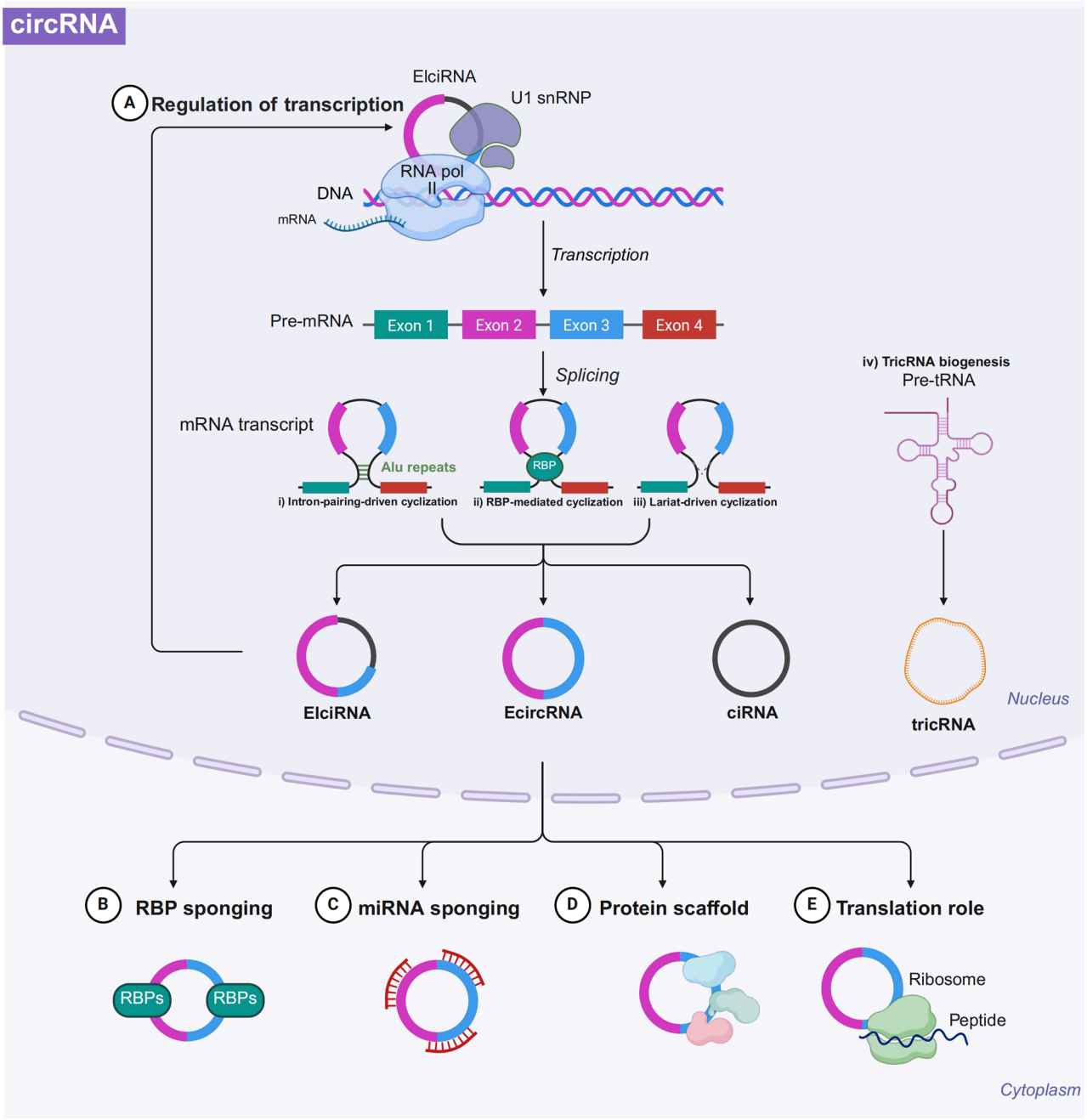


Figure 2. Biogenesis and function of circRNAs. circRNAs are primarily generated from pre-mRNA through back-splicing, which encompasses three unique mechanisms: i) Intron pairing-driven cyclization, which depends on base-pairing interactions between reverse complementary sequences, such as ALU repeats, found in the introns adjacent to exons; ii) RBP-mediated cyclization utilizes the involvement of RBPs to bring splicing sites closer together, thereby facilitating the creation of circRNAs; iii) lariat-driven cyclization aids in forming an exon-containing lariat structure during exon skipping events, leading to the production of EIciRNA or ecircRNA; and iv) the generation of tricRNAs occurs through the enzymatic cleavage of pre-tRNA, yielding tricRNAs and the remaining fragment which is further processed into mature tRNAs. The functions of circRNAs can be categorized into the following five classes. (A) Regulation of RNA transcription (B) acting as sponges for RBPs (C) acting as sponges for miRNAs (D) functioning as protein scaffolds; and (E) translation of proteins. circRNA, circular RNA; EIciRNA, exon-intron circRNA; EcircRNA, exonic circRNA; ciRNA, intronic circRNA; TricRNA, tRNA intronic circular RNA; U1 snRNP, U1 small nuclear ribonucleoprotein particles. Figure was created with biorender.com.

which in turn modulates the expression of target genes and influences cellular processes (35). The circ-0001649 acts as a molecular sponge for miR-127-5p, miR-612 and miR-4688, thereby derepressing their target gene SHPRH and functioning as a tumor suppressor in HCC (36). iv) Acting as protein scaffolds. circRNAs can serve as scaffolding agents, facilitating interactions and assembly among various proteins. circRNAs facilitate protein-protein interactions and promote the spatial colocalization of associated proteins by engaging target proteins at specific subcellular compartments. This is mediated through their intrinsic binding sites, which may include domains for enzyme or substrate association (37). An illustration of this mechanism is the formation of a ternary complex involving circACC1 and the regulatory β and γ subunits of AMP-activated protein kinase (AMPK). This association confers stabilization and potentiates the catalytic activity

of the complete AMPK holoenzyme (38). v) The ability of circRNA to undergo translation was originally discovered by Pamudurti *et al* (39) in 2017. Comprising translatable circRNAs and their resulting products, recent studies have highlighted that a minority of circRNAs, which have open reading frames and internal ribosome entry sites, or those modified by m6A in their 5' untranslated region, possess the capability for translation into polypeptides that are crucial for cellular functions (33,40). circRNA-encoded proteins constitute a newly recognized regulatory layer in HCC. Acting as a key effector from tumor-associated macrophages, circPETH drives HCC metastasis and immune evasion via its encoded peptide (41). These proteins not only modulate oncogenic signaling cascades and serve as critical functional effectors in tumor biology and clinically relevant biomarkers, but also significantly contribute to the regulation of chemotherapy resistance in cancer cells (33). circRNA-encoded proteins are instrumental in dictating HCC drug resistance. Mechanistically, these proteins influence pivotal signaling cascades, modulate key drug efflux mechanisms and engage with the TME, thereby conferring resistance to diverse therapies (42,43).

Based on the aforementioned biological functions, circRNAs play a crucial role in key biological processes such as cancer proliferation, invasion, metastasis and drug resistance, highlighting them as potential targets for the early diagnosis and treatment of various disease states (44).

## 4. Function of exosomal circRNAs in HCC progression

Cancer markers are typically seen as a collection of traits that human cells develop as they transition from a normal state to one of tumor growth, and these traits are crucial for the emergence of malignant tumors. As our understanding of the TME evolves, the discussion surrounding cancer markers is becoming increasingly refined. Recently, several new potential cancer markers have emerged, including aspects such as the unlocking of phenotypic plasticity, mutation-free epigenetic reprogramming, a diverse microbiome and the presence of senescent cells, among others (45). Exosomes play a pivotal role in facilitating the transfer of circRNA, thereby enabling signal transduction among cells. This process not only fosters communication between nearby or distant recipient cells but also influences several vital biological functions within those cells. Such functions include cell proliferation, invasion and metastasis, angiogenesis, apoptosis, metabolic reprogramming in tumor cells and the attainment of stem cell characteristics (Fig. 3). Recently, research on exosomal circRNAs has shown that they play an essential role in the development and progression of cancer (46,47). This section examines the role of exosomal circRNAs in the development and progression of HCC, highlighting relevant markers that are currently under extensive investigation.

*Exosomal circRNA and the proliferative capacity of HCC cells*. Sustained cell proliferation, a well-known cancer hallmark, and the proliferative ability of HCC are crucial for its malignant progression. In recent years, the role played by exosomal circRNAs in regulating HCC cell proliferation has become increasingly prominent. Certain exosomal circRNAs can exert an inhibitory effect on the proliferative capacity of HCC, thereby helping to impede disease progression. For example, plasma exosomes and tissues from patients with HCC exhibit significantly lower levels of exosomal circ-0051443 compared with healthy controls (48). Research focusing on molecular mechanisms has revealed that circ-0051443 is capable of transferring from normal cells to HCC cells through exosomes; it enhances the expression of Bcl-2 homologous antagonist/killer 1 (BAK1) in HCC cells by competing with miR-331-3p for binding sites. Additionally, exosomal circ-0051443 reduces proliferation through pro-apoptotic proteins and halts the cell cycle (48). A related study revealed that exosomal hsa_circ_0004658, originating from macrophages that have upregulated recombination signal binding protein for immunoglobulin κJ region (RBPJ), a key transcription factor which functions as the central effector of the Notch signaling pathway, is transferred to HCC cells. Subsequently, it acts as a competing endogenous RNA (ceRNA) to sponge miR-499b-5p, resulting in the inhibition of junctional adhesion molecule 3 (JAM3) and suppression of HCC cell growth (49).

Conversely, certain exosomal circRNAs promote the malignancy of HCC cells, thereby facilitating disease advancement toward a more malignant state. For example, exosomal circ-100284, released by human L-02 liver epithelial cells that have undergone malignant transformation due to prolonged arsenite exposure, can be transmitted to healthy hepatocytes, enhancing cell cycle progression and increasing proliferation via interactions with miR-217 (50). This illustrates that exosomal circRNAs serve as communicators for transcellular interaction, facilitating malignant advancement in healthy hepatocytes. Circ_0061395, an exosomal circRNA significantly upregulated in the serum of patients with HCC, promotes tumor progression by enhancing cell proliferation; it functions by regulating the miR-877-5p/phosphoinositide-3-kinase regulatory subunit 3 (PIK3R3) axis, where PIK3R3 (a key regulatory subunit of the oncogenic PI3K signaling pathway) is upregulated. Knockdown of circ_0061395 suppresses tumor growth *in vivo* and induces cell cycle arrest, apoptosis, and inhibition of proliferation, invasion and migration *in vitro* (51). Moreover, the expression of circ_002136 is elevated in HCC tissues and cells and it can be transmitted from one cell to another via exosomes secreted by HCC cells (52). Functionally, circ_002136 acts as a molecular sponge for miR-19a-3p, which leads to the upregulation of RAB1A (an isoform of the Rab1 protein) and consequently enhances HCC cell proliferation, migration and invasion (52). Similarly, the exosomal circANTXR1 released by HCC cells can promote the proliferation and metastatic capacity of HCC by sponging miR-532-5p to inhibit the expression of X-ray repair cross-complementary protein 5 (XRCC5) (53); exosomal circTTLL5 can bind to miR-136-5p, relieving its suppression on KIAA1522 expression, thereby enhancing the proliferative ability of HCC cells (54); and circ-ZNF652 enhances HCC cell growth via the miR-29a-3p/guanosine cyclase domain-containing protein 1 (GUCD1) pathway (55).

In other studies, circRNAs have been shown to play essential roles in HCC cell cycle regulation. For example, circ_0036412 enhances the expression of GLI family zinc finger protein 2, which is a target gene within the Hedgehog signaling pathway. This process occurs as circ_0036412 competes with miR-579-3p for binding, ultimately influencing the Hedgehog

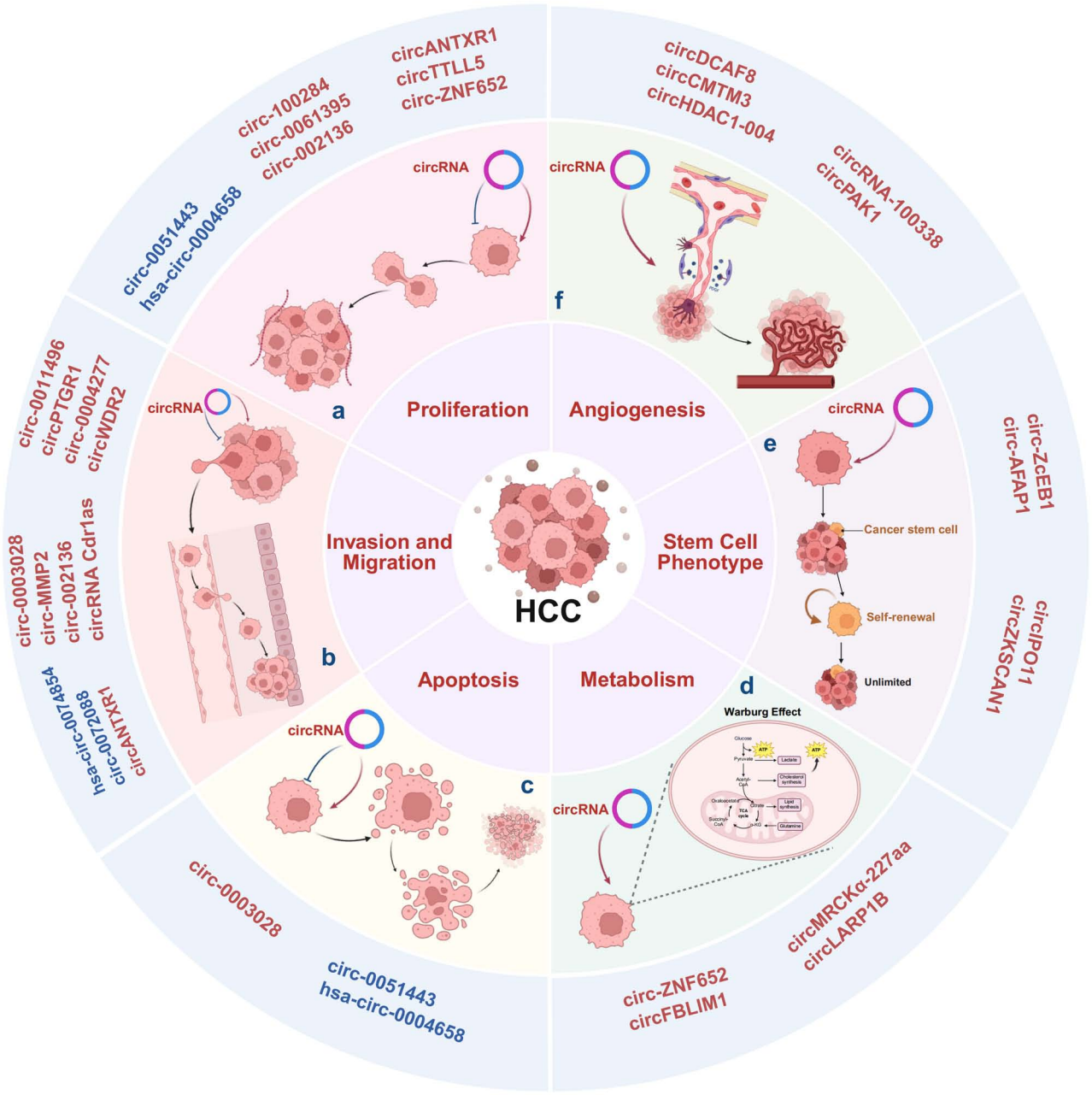


Figure 3. Effects of exosomal circRNAs on the initiation and progression of HCC. (A) Exosomal circRNAs can either promote or inhibit HCC cell proliferation; (B) exosomal circRNAs can may enhance or suppress HCC invasion and metastasis; (C) exosomal circRNAs can either facilitate or attenuate the apoptotic process in HCC cells; (D) exosomal circRNAs can drive metabolic reprogramming in HCC cells; (E) exosomal circRNAs can augment the self-renewal capacity of HCC cells and enhance the expression of their stem cell phenotype; and (F) exosomal circRNAs can promote the angiogenic capacity of HCC. HCC, hepatocellular carcinoma; circRNA, circular RNA. Figure was created with biorender.com.

signaling pathway and driving the proliferation of HCC cells as well as their progression through the cell cycle (56). In another study, circMDK was shown to promote HCC progression by sponging miR-346/874-3p to upregulate autophagy related 16 like 1, a key autophagy-related protein essential for autophagosome formation. Notably, this study was the first to show that the poly(β-amino ester)-small interfering RNA (siRNA) complex, a nanoparticle-based delivery system for siRNA, targeting circMDK offers a direct and effective way to suppress HCC, presenting a promising nanotherapeutic strategy (57).

In summary, exosomal circRNAs play the role of signaling molecules for transcellular communication. Through this mechanism, exosomal circRNAs can promote the proliferation of HCC cells, ultimately contributing to the malignant progression of HCC.

*Exosomal circRNA and the invasive metastatic ability of HCC cells*. The metastatic stage represents the most critical and life-threatening phase of tumor progression, as the majority of cancer-related mortalities are attributed to the proliferation of metastatic lesions at secondary sites, rather than the primary tumor itself (58,59). Given this, significant attention should be given to the mechanisms of tumor cell invasion and metastasis, and targeting these mechanisms is a key means of preventing

the development of malignant tumors. Considerable research has studied the impact of exosomal circRNAs on the invasion and metastasis of HCC. One notable study revealed that benzo[a]pyrene, a carcinogenic byproduct of combustion, significantly elevates the levels of exosomal circ_0011496 secreted from HCC cells. This particular exosomal circRNA is transferred to lung fibroblasts, where it competitively binds to miR-486-5p. This interaction facilitates the transformation of fibroblasts into cancer-associated fibroblasts (CAFs) by influencing the downstream mechanisms of Twinfilin-1 (TWF1) and matrix metalloproteinase-9 (MMP-9). Furthermore, the upregulation of TWF1 enhances the communication between cancer cells and the surrounding matrix by boosting the angiogenic potential of vascular endothelial growth factor. Through both these regulatory mechanisms, exosomal circ_0011496 promotes the metastatic ability of HCC by regulating the TME and thus promoting metastasis (60). circPTGR1 exists in three different isoforms and is specifically expressed in the exosomes of metastatic HCC cells, both in low-metastatic (97L) and high-metastatic (LM3) varieties; its expression is elevated in the serum of patients with HCC and is linked to clinical stage and overall prognosis. Further mechanistic investigations revealed that circPTGR1 enhances the expression of MET proto-oncogene, receptor tyrosine kinase (MET), encoding the hepatocyte growth factor receptor, a tyrosine kinase known to promote cell motility and invasion. This upregulation, mediated via the sponging of miR-449a, consequently increases the invasive and metastatic potential of HCC cells (61).

EMT is a key process in cancer cell metastasis, which enables cancer cells to break through the basement membrane, dismantle intercellular junctions, downregulate E-calmodulin and break free from the primary site restrictions, ultimately allowing the cancer cells to migrate and invade and obtain mesenchymal cell properties, which further facilitates their mobility in tissues (62). This helps these cancerous cells to enter the circulatory system, where they are carried to distant sites through the bloodstream or lymphatic flow. Exosomal circRNAs serve as key regulators in EMT. Numerous reports have revealed that exosomal circRNAs can enhance the invasive and metastatic capabilities of HCC by influencing EMT (63-66). Previous findings indicate that circ-0004277 is markedly elevated in HCC cells, tissues and plasma exosomes. Upregulated expression of circ-0004277 promotes the proliferation, migration and EMT of HCC cells both *in vivo* and *in vitro*. Mechanistically, circ-0004277 contributes to the aggressive traits of HCC cells by competing for binding to Hu antigen R (HuR) proteins, leading to the inhibition of tight junction protein 1 and promoting EMT progression. Notably, exosomal circ-0004277 can be secreted by HCC and serves as a transcellular communication molecule to enhance the EMT process in peripheral cells, further escalating the invasive and metastatic potential of HCC (67). In a separate study, the suppression of hsa_circ_0074854 similarly inhibited the migration and invasion of HCC cells by interacting with HuR. Moreover, the exosomes secreted by HCC cells following the downregulation of hsa_circ_0074854 impeded M2 macrophage polarization, thereby hampering the migration and invasion of HCC cells both *in vitro* and *in vivo* (68). Similarly, exosome-derived circWDR2 from hepatic stellate cells advanced HCC development via regulation of the circWDR25/miR-4474-3p/arachidonate 15-lipoxygenase axis and EMT pathways (69). Additionally, circ_0003028 was shown to exert tumorigenic effects through the miR-498/ornithine decarboxylase 1 (ODC1) signaling axis and induced EMT of HCC cells via an exosomal pathway (70). Together, these studies show that exosomal circRNAs can influence EMT in HCC cells, affecting the invasion and metastasis of these cells. Exosomal circRNAs may serve as a biomarker for HCC invasion, metastasis and malignant advancement.

In other studies, exosomal circRNAs have been shown to affect the invasive and metastatic ability of HCC cells. For instance, highly metastatic HCC cell lines, particularly the 97H and LM3 variants, release exosomal circ_MMP2, which targets L02 and HepG2 cells. This process enhances the metastatic potential of HCC cells by increasing the expression of MMP2 by sponging miR-136-5p (71). It has been reported that high-abundance exosomal circ_002136 targets the miR-19a-3p/RAB1A pathway in cancer cells, disrupts the stable microenvironment inside tumors, exacerbates the malignant progression of HCC tumors and can promote the higher invasive capacity of recipient cells through exosome delivery (52). circRNA Cdr1as has been found to be significantly upregulated in both HCC cell lines and tissues, and its upregulation enhances the proliferation and migration of HCC cells. Mechanistically, Cdr1as facilitates the upregulation of human α-fetoprotein by sponging miR-1270 and it promotes the proliferation and migratory capacity of normal cells nearby via exosomal transport (72). Similarly, circANTXR1 is stably and highly expressed in HCC, where it positively regulates XRCC5 to promote the proliferation and metastasis of HCC cells by sponging miR-532-5p and mediates transcellular communication via exosomes (53). Notably, exosomal circRNAs can also hamper the invasive and migratory capacity of HCC cells. For example, exosomal circ-0072088 secreted by HCC cells can impede HCC metastasis by facilitating the degradation of miR-375 and increasing the expression of MMP16 (73).

As outlined above, exosomal circRNA may serve as diagnostic and/or prognostic indicators of HCC invasion and metastasis and may serve as promising therapeutic targets for the management of HCC.

*Exosomal circRNAs and HCC angiogenesis*. Tumor angiogenesis plays a crucial role throughout the life cycle of a tumor, from initial occurrence to subsequent gradual development to infiltration of surrounding tissues and metastasis to distant sites (74). Exosomal circRNAs originating from HCC cells can foster the development of vascular endothelial cells and stimulate the creation of new vasculature, which in turn aids in the distant metastasis of tumor cells (75). An earlier study has indicated that circRNA-100338 derived from HCC cells influences the proliferation of cells, angiogenesis, permeability and the ability to form new vasculature in human umbilical vein endothelial cells (HUVECs) through both *in vitro* and *in vivo* analyses. Mechanistic experiments have shown that circRNA-100338, which is delivered via exosomes, can be transferred to HUVECs and bind to its target receptors to promote tumor neoangiogenesis through the mammalian target of rapamycin (mTOR) signaling pathway, thereby promoting HCC progression (76). circPAK1 is a newly discovered circRNA significantly expressed in HCC tissues and cell

lines and is correlated with poor prognosis in patients with HCC. *In vitro* experiments have demonstrated that circPAK1 is capable of promoting angiogenesis in HCC in a controlled environment; it achieves this by competing with Yes-associated protein (YAP) to bind to 14-3-3ζ, facilitating the nuclear localization of YAP. This process ultimately contributes to the advancement of HCC by inhibiting the Hippo signaling pathway (77). Moreover, circDCAF8 is transferred from HCC cells to HUVECs through exosomes, which stimulates angiogenesis in HCC (19). Exosomal circCMTM3 directly binds to miR-3619-5p, targeting the downstream sex-determining region Y (SRY)-box transcription factor 9 (SOX9). This interaction acts as a catalyst for the proliferation, migration, invasion and angiogenesis of HUVECs; it also promotes their viability and induces tumor growth (78). A recent study showed that circHDAC1_004 expression is upregulated in HUVECs, where it promotes HCC angiogenesis through exosomes (79).

These studies show that exosomal circRNAs produced by HCC can be transferred to HUVECs using exosomes as a vector and then bind to the corresponding target receptors to induce HUVEC proliferation and promote the formation of new blood vessels. In turn, the new blood vessels enhance the proliferation, invasion and metastasis of HCC cells, ultimately leading to the malignant progression of HCC. Consequently, focusing on exosomal circRNAs could be an effective approach for reducing tumor metastasis and improving sensitivity to therapy.

*Exosomal circRNAs and HCC cell apoptosis*. Apoptosis results in the removal of damaged cells and can prevent the proliferation of abnormal cells. Apoptosis is an important mechanism for preventing tumorigenesis; however, a hallmark of cancer is overcoming apoptosis. The levels of circ-0051443 were found to be downregulated in HCC tissues and the plasma exosomes of patients with HCC. Conversely, increasing its expression resulted in cell cycle arrest during the G0/G1 phase and facilitated apoptosis in HCC cells (48). BAK1 plays a pivotal role in regulating cell death by triggering mitochondria-dependent apoptosis through various protein interactions (80). In a study, exosomes that carried circ-0051443 secreted by normal cells, were taken up by HCC cells. Within these cells, circ-0051443 acted as a sponge for miR-331-3p, thereby modulating BAK1 and promoting apoptosis in HCC cells, which in turn inhibited the advancement of HCC (48). In another study, exosomal circRNA derived from macrophages with upregulated RBPJ expression, specifically hsa_circ_0004658, hampered the proliferation of HCC cells and promoted apoptosis. hsa_circ_0004658 sponged miR-499b-5p, thereby enhancing the expression of JAM3 (49). In addition, circ_0003028, which is upregulated in HCC tissues and cells, has been shown to promote the expression of ODC1 by targeting miR-498, thus playing a role in tumorigenesis. Research has indicated that silencing circ_0003028 can rein in cell proliferation and metastasis, trigger apoptosis and offer promising biomarkers and therapeutic targets for HCC (70).

In summary, numerous studies have reported the regulation of HCC cell apoptosis by circRNAs. However, the mechanism by which exosomal circRNAs mediate HCC cell apoptosis is incompletely understood and likely involves the interplay of several circRNAs and the regulation of several signaling pathways.

*Exosomal circRNAs and HCC metabolism*. Considerable research has focused on the association of alterations in the metabolism of malignant cells. During the development and progression of a tumor, the metabolic state of its cells undergoes a series of adaptive changes known as tumor cell metabolic reprogramming. These adaptations are of vital significance in the emergence and advancement of tumors, allowing cells to respond and adapt to changing conditions. Exosomal circRNAs primarily influence the glycolysis of HCC cells, a phenomenon also known as the Warburg effect. This effect is characterized by a metabolic shift in cancer cells towards aerobic glycolysis, leading to lactate production (81). For example, exosomal circ-ZNF652 is upregulated in the serum of patients with HCC and can be delivered to HCC cells via exosomes. Mechanistic investigations have revealed that exosomal circ-ZNF652 enhances the glycolytic levels of HCC cells by acting as a sponge for miR-29a-3p to target GUCD1 (55). Exosomal circFBLIM1 has the same effect. circFBLIM1 is upregulated in serum-derived exosomes and HCC cells. CircFBLIM1 promotes glycolysis in HCC cells by sponging miR-338, resulting in the upregulation of low-density lipoprotein receptor-related protein 6 and a consequent enhancement of glucose utilization. This previous study further established a xenograft mouse model to verify that the depletion of circFBLIM1 inhibited the advancement of HCC cells and tumor development *in vivo* (82).

A recent study showed that peptides encoded by circRNAs can also affect metabolic processes in HCC cells. The study revealed that tumor-associated macrophages promote glycolysis and the advancement of tumors by increasing the expression of circMRCKα in HCC cells. This particular circRNA can encode a novel functional peptide consisting of 227 amino acids, referred to as circMRCKα-227aa. On a mechanistic level, circMRCKα-227aa interacts with ubiquitin-specific peptidase 22, elevating its protein expression levels. This interaction prevents the degradation of hypoxia-inducible factor 1 α, a key transcription factor that mediates cellular responses to low oxygen, via the ubiquitin-proteasome pathway, ultimately boosting glycolysis and tumor progression in HCC (83). Previous circRNA research has focused on their functioning as miRNA sponges. However, research on the role of the peptides encoded by circRNAs is now gaining traction.

In addition to affecting glucose metabolism, certain circRNAs can affect lipid metabolism in HCC cells. For example, circLARP1B promotes cell metastasis and lipid accumulation by promoting fatty acid synthesis in HCC. Mechanistically, circLARP1B interacts with heterogeneous nuclear ribonucleoprotein D (HNRNPD) in the cytoplasm. This interaction results in the binding of HNRNPD to liver kinase B1 (LKB1) mRNA, ultimately destabilizing it and lowering LKB1 protein levels. Consequently, this process influences the AMPK pathway, facilitating the metastasis of HCC and impacting lipid metabolism (84). Of note, in another study, an effective traditional Chinese medicine, FZXZP, significantly inhibited HCC growth by improving lipid and glucose metabolism in HCC cells and regulating

a circRNA-miRNA-mRNA network to restore metabolic homeostasis (85). This highlights a potential treatment for targeting metabolic reprogramming in HCC cells.

The idea of targeting the circRNAs associated with the metabolic reprogramming of HCC cells for therapeutic benefits remains in the exploratory phase and requires in-depth investigation. Moreover, the role of exosomal circRNAs in the metabolic processes of HCC cells, apart from the recognized metabolic pathways, remains unclear. Additionally, in-depth analysis and interpretations are required.

*Exosomal circRNAs and HCC stem cells*. CSCs represent a distinctive subset within the broader category of cancer cells. These cells possess the remarkable ability to self-renew and play a crucial role in the onset and progression of cancer. CSCs are instrumental in driving the metastatic spread of tumors and contribute to the challenges of treatment resistance and recurrence. Recent research indicates that circRNAs from exosomes released by liver cancer CSCs are crucial in HCC progression. For instance, exosomal circ-ZEB1 and circ-AFAP1, which are primarily secreted by liver cancer CSCs, are markedly upregulated in HCC tissues compared with adjacent non-cancerous tissues. Moreover, there is a positive correlation between their expression levels and that of the stemness marker CD133 in HCC cells, indicating their potential role in processes related to stemness within these cancerous cells. Subsequent experiments have demonstrated that upregulation of circ-AFAP1 not only promotes tumor growth but also increases the stemness of HCC cells and EMT. This shows that circ-ZEB1 and circ-AFAP1, present in the exosomes of liver CSCs, may facilitate the malignant transfer between CSCs and non-CSCs. Thus, they may mediate the increase in malignancy of non-CSCs and the poor prognosis of patients with HCC by enhancing the stemness and EMT process of HCC (86).

circIPO11, which is highly expressed in HCC tumor tissues and liver CSCs, is necessary for the self-renewal of liver cancer CSCs; it functions by recruiting DNA topoisomerase I to the promoter region of the glioma-associated oncogene homolog 1 (GLI1) gene. This recruitment consequently triggers GLI1 transcription, leading to the activation of the Hedgehog signaling pathway, which in turn drives both the self-renewal of liver CSCs and HCC progression (87). Certain highly expressed circRNAs can enhance the stemness of HCC cells, while the downregulation of other circRNAs has the same effect. circZKSCAN1, which is downregulated by the quaking protein in HCC cells, serves as a promising regulator of stemness in HCC and can inhibit multiple malignant behaviors by suppressing stemness. circZKSCAN1 functions as a sponge for RBPs, competing with fragile X mental retardation protein to inhibit the Wnt/β-catenin signaling pathway, ultimately leading to its inactivation (88). The Hedgehog and Wnt signaling pathways are critically involved in tumorigenesis, progression and therapeutic response (89). These pathways participate in crucial processes, including tumor cell proliferation, differentiation, invasion, metastasis and the maintenance of CSC properties (90). Following aberrant activation of these pathways, CSCs promote cancer progression via their stem cell characteristics, such as continuous self-renewal and drug resistance, hampering the effectiveness of cancer treatments. These pathways also make CSCs the main targets of anti-CSC therapy (91).

Taken together, circRNA can affect the stem cell phenotype of HCC cells by influencing key effector molecules in signaling pathways, indicating that targeting circRNAs may be an essential means of addressing naturally drug-resistant CSCs, reducing cancer recurrence rates and increasing the effectiveness of tumor therapies. Further studies are necessary to understand the means by which exosomal circRNAs facilitate communication between HCC CSCs and their non-stem cell counterparts, ultimately fostering the increased stemness of HCC cells.

## 5. Effects of exosomal circRNAs on drug resistance

The current treatment options for HCC primarily consist of chemotherapy, radiotherapy, targeted therapy, immunotherapy and novel cell and gene therapies. In clinical treatment, the commonly used chemotherapeutic drugs are cisplatin, oxaliplatin and doxorubicin. In terms of targeted therapy, sorafenib, lenvatinib and regorafenib are widely employed molecular targeted drugs. Immunotherapy, as a relatively novel treatment method, primarily involves the selection of immune checkpoint inhibitors/monoclonal antibodies such as programmed cell death protein 1 (PD-1), PD-1 ligand (PD-L1) and receptor cytotoxic T lymphocyte antigen-4 (92). Furthermore, while studies on cell and gene therapy of the tumor immune microenvironment exist, the research is relatively limited. However, HCC can develop drug resistance, resulting in the failure of treatments. In this section, the effects of exosomal circRNAs on the drug resistance of HCC (Fig. 4 and Table SI) are discussed.

*Exosomal circRNAs in HCC chemotherapy treatment resistance*. Chemotherapy is a cornerstone treatment in the management of malignant tumors; however, the challenge of acquired drug resistance undermines its effectiveness, resulting in the setback of treatment for several patients. Research has highlighted that exosomal circRNAs play a crucial role in the development of chemotherapy resistance in a range of cancer types (93).

Cisplatin remains the primary chemotherapeutic agent in the clinical management of HCC, yet resistance poses a significant challenge to its effectiveness. Research has established that exosomal circ-G004213 is positively associated with the prognosis of patients with HCC following transarterial chemoembolization. Specifically, it enhances cisplatin sensitivity by sponging miR-513b-5p to upregulate pre-mRNA processing factor 39 (PRPF39), a critical splicing factor, thereby modulating the miR-513b-5p/PRPF39 axis (94). circZFR is upregulated in CAFs and CAF exosomes. Mechanistically, it can be delivered by exosomes and it suppresses the STAT3/NF-κB pathway in HCC cells, in turn facilitating HCC progression and cisplatin resistance (95). The STAT3/NF-κB pathway is a key pathway in HCC, and the crosstalk between the two in the development of HCC is an essential factor in HCC progression (96). circARNT2, which is upregulated in HCC, can regulate cisplatin resistance in HCC cells through the miR-155-5p/pyruvate dehydrogenase kinase 1 (PDK1) axis, where PDK1 is a central metabolic kinase that shifts energy production toward glycolysis and confers survival advantages to cancer cells (97). circRNAs can also promote cisplatin sensitivity in HCC cells.

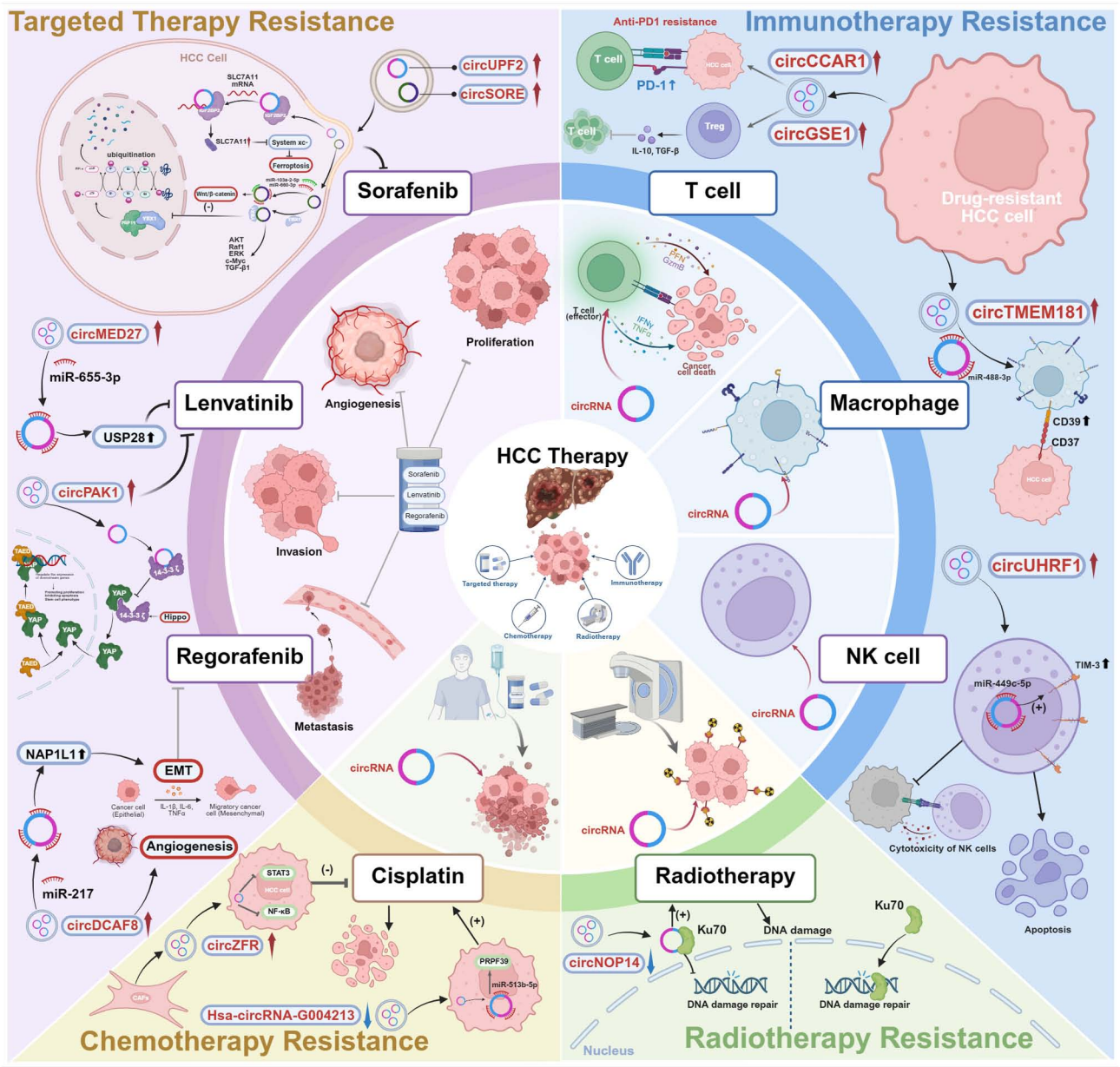


Figure 4. Exosomal circRNAs related to therapeutic resistance in HCC. The mechanism of representative exosomal circRNAs that show regulatory effects in chemotherapy, radiotherapy, targeted therapy and immunotherapy resistance of HCC. circRNA, circular RNA; SLC7A11, solute carrier family 7 member 11; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; USP28, ubiquitin specific peptidase 28; YAP, Yes-associated protein; NAP1L1, nucleosome assembly protein 1 like 1; EMT, epithelial-mesenchymal transition; Ku70, Ku autoantigen, 70kD. Figure was created with biorender.com.

For example, when circRNA_101505 is upregulated in HCC cells, it sponges miR-103, resulting in the upregulated expression of oxidored-nitro domain-containing protein 1, increasing the sensitivity of HCC cells to cisplatin (66). circ_0003418, an antitumor circRNA, is downregulated in HCC tissues and cell lines; it can enhance the cisplatin sensitivity of HCC cells by activating the Wnt/β-catenin pathway within these cells (98).

In studies of other cancer types, exosomal circRNAs can also affect the cisplatin resistance of tumor cells. For example, exosomal circVMP1 promotes the progression and cisplatin resistance of non-small cell lung cancer (NSCLC) by targeting the miR-524-5p/methyltransferase-like 3/SOX2 axis (99); exosomal circ_PIP5K1A modulates the miR-101/ATP binding cassette subfamily C member 1 (ABCC1) pathway to enhance the advancement and cisplatin resistance of NSCLC (99,100). ABCC1 is a multidrug resistance protein which exports chemotherapeutic agents such as cisplatin out of cancer cells, thereby conferring treatment resistance (101). In esophageal cancer, exosome-mediated circ_0000337 transfer regulates Janus kinase 2 (JAK2; a non-receptor tyrosine kinase and pivotal component of the JAK-STAT signaling pathway) via miR-377-3p, promoting resistance to cisplatin in esophageal cancer cells (102).

It has been shown that circ_0000098 can increase doxorubicin (DOX) resistance by sponging miR-383 to increase the expression of P-glycoprotein and intracellular ATP levels in HCC cells. More notably, it was demonstrated that DOX/sh-1@PLT, produced by encapsulating DOX and short hairpin RNA (sh-1) targeting circ_0000098 using platelets (PLTs) as drug carriers, showed favorable therapeutic effects

in mouse models (103), and thus provides guiding significance for the use of targeted circRNAs in the management of HCC. As for oxaliplatin (OXA) resistance, a study has shown that hsa_circ_0088036 promotes HCC tumorigenesis and OXA resistance by activating the PI3K/Akt and Notch pathways through regulation of the miR-140-3p/KIF2A signaling cascade (104); circFBXO11 promotes OXA resistance in HCC via the circFBXO11/miR-605/FOXO3/ABCB1 axis (105).

Based on the current research progress, exosomal circRNAs have been confirmed to play a crucial regulatory role by mediating resistance to chemotherapy in HCC and are hypothesized to serve as potential interventional targets for reversing resistance to chemotherapy. However, the specific molecular mechanism by which drug-resistant phenotypes mediated by exosomal circRNA are transmitted between HCC cells remains relatively understudied. This direction urgently requires more in-depth studies. Understanding the mechanisms will not only help to clarify the drug-resistant transmission networks at play in the TME but may also highlight a theoretical basis for the clinical development of novel diagnostic markers or treatment strategies, which have scientific significance and clinical applications.

*Exosomal circRNAs in HCC radiotherapy treatment resistance*. Radiotherapy is a widely used treatment for solid tumors, which suppresses tumor progression primarily by inducing DNA damage in tumor cells. Research has indicated that $^{125}$I seed brachytherapy, as a burgeoning adjuvant therapy, holds great promise for treating HCC (106). Recent research has revealed that elevated serum levels of exosomal circTMEM56 are positively correlated with improved radiotherapy response and favorable clinical outcomes in patients with HCC. Mechanistically, elevated exosomal circTMEM56 specifically targets dendritic cells, thereby enhancing radiotherapy-induced antitumor immune responses in HCC. This occurs through the promotion of cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway activation via the miR-136-5p/STING axis, effectively remodeling TME (107). cGAS is characterized as a key DNA sensor that initiates innate immune responses by producing the secondary messenger cyclic GMP-AMP, which subsequently binds to and activates the adaptor protein STING. The cGAS-STING pathway represents an attractive therapeutic target, as it functions as an intrinsic barrier to tumorigenesis by linking DNA damage to multiple antitumor mechanisms, including immune surveillance, cellular senescence and cell death (108). By focusing on the interplay between exosomal circTMEM56 and the cGAS-STING pathway, the aforementioned study introduces a novel approach to augment the efficacy of radiotherapy in HCC treatment (107). Another significant novel discovery is circSNX25 (has_circ_0004874), a circRNA identified with coding potential that is strongly associated with HCC radioresistance. The novel protein SNX25-215, encoded by circSNX25, promotes HCC cell resistance to radiotherapy both *in vitro* and *in vivo*. The underlying mechanism of circSNX25 involves the interaction of the amino acid residues H207 and E214 of SNX25-215 with the Golgi-associated endoplasmic reticulum transporter 4 homolog (GET4). This interaction inhibits the binding of BCL2-associated anaplastic gene 6 (BAG6) to GET4. Crucially, this disruption exposes the nuclear localization sequence of BAG6, which subsequently facilitates its nuclear translocation. Nuclear BAG6 then enhances DNA damage repair, ultimately resulting in an increased resistance of HCC cells to ionizing radiation and thereby augmenting overall HCC radioresistance (43). A study revealed that exosomal circNOP14 is strongly associated with the radiosensitivity of HCC cells; it can enhance the radiosensitivity of HCC cells both *in vitro* and *in vivo* (109). Ku70 is abundantly expressed and plays a role in the DNA damage response (DDR). Specifically, it is involved in the C-NHEJ pathway, which is the most prevalent DNA double-strand break repair pathway, to fix the DNA damage caused by radiotherapy (110). circNOP14, conversely, increases the sensitivity to radiotherapy by interacting with Ku70 and preventing its nuclear translocation, thereby increasing irradiation-induced DNA damage (109). Other research has indicated that cZNF292 activates the Wnt/β-catenin pathway by interacting with SOX9 protein to inhibit it's nuclear translocation, enhancing DDR capacity and radiotherapy resistance in HCC cells (111); circ-LARP1B silencing suppresses HCC tumorigenesis and increases radiosensitivity by modulating the miR-578/insulin-like growth factor 1 receptor axis (112); circSMARCA5 is markedly upregulated in HCC cells and has been shown to promote resistance to radiotherapy (113); circ_0071662 downregulation in HCC cells may be associated with the development of radiotherapy resistance (114); and high expression of circROBO1 in HCC can promote HCC radiotherapy resistance by targeting miR-136-5p to regulate a novel adhesion protein core subunit RAD21 (115).

Exosomal circRNAs also play a crucial role in inducing radiotherapy resistance in other types of cancer. For example, in endometrial cancer (EC), M2-polarized tumor-associated macrophages can markedly reduce the radiosensitivity of EC cells by releasing exosomes rich in hsa_circ_0001610. Among these exosomes, hsa_circ_0001610 attenuates the radiosensitivity of EC cells by binding miR-139-5p to allow cyclin B1 expression (116). In glioblastoma (GBM), low-dose radiation-induced exosomal circ-METRN can promote GBM progression and radiation resistance via the miR-4709-3p/growth factor receptor bound protein 14 (GRB14)/platelet derived growth factor receptor α (PDGFRα) pathway (117), where GRB14 is a signaling adapter protein and PDGFRα is a key tyrosine kinase receptor for cell proliferation.

Radiotherapy can inhibit tumor progression by inducing DNA damage, and exosomal circRNA can significantly affect tumor radiosensitivity by regulating the DDR. The aforementioned findings suggest that exosomal circRNAs are key regulators of the response of a tumor to radiotherapy, and analysis of their mechanisms may highlight novel targets for developing resistance reversal strategies or increasing radiosensitization.

*Exosomal circRNAs in targeted treatment resistance in HCC*

*Sorafenib*. Sorafenib was the first molecular-targeted drug approved by the FDA for clinical use as first-line therapy for advanced HCC. However, after a period of sorafenib therapy, drug resistance may emerge (118). Resistance limits the therapeutic effectiveness of sorafenib and severely impacts the prognosis of patients with HCC. Recently, numerous studies have indicated that exosomal circRNAs affect the emergence

of sorafenib resistance in HCC (Table SI). For example, circUPF2 is significantly enriched in exosomes produced by sorafenib-resistant HCC cell lines and can transmit resistance to non-resistant HCC cells via exosomes. circUPF2-enriched exosomes increase resistance to sorafenib by upregulating solute carrier family 7 member 11 (SLC7A11, also known as xCT) expression and preventing ferroptosis in HCC cells. Subsequent research on the resistance mechanism showed that circUPF2 serves as a scaffolding structure to promote the formation of the circUPF2-insulin-like growth factor 2 mRNA-binding protein 2-SLC7A11 ternary complex. This complex, in turn, increases SLC7A11 expression (a cystine/glutamate reverse transporter protein) and enhances the functionality of System Xc- in HCC cells. As a result, the cells become less prone to ferroptosis and more resistant to sorafenib (17). The increased activity of System Xc-, which is closely associated with the advancement of HCC, comprises a transport component (SLC7A11) alongside a heavy chain element referred to as 4F2hc (SLC3A2). This mechanism plays a crucial role in exchanging extracellular L-cystine for intracellular L-glutamate, with SLC7A11 primarily driving the functional role of the transporter (119-122). A recent study identified circTTC13, which is upregulated in HCC tissue and is associated with tumor malignancy and the ferroptosis of tumor cells. Further investigation of the mechanism revealed that circTTC13 directly targets and reduces the expression of miR-513a-5p, leading to the upregulation of SLC7A11 to inhibit the ferroptosis process in HCC cells. In addition, silencing circTTC13 induces tumor ferroptosis and reverses sorafenib resistance in HCC (123). Another study showed that circRNA-SORE, upregulated in sorafenib-resistant HCC, is loaded into exosomes, facilitating the transfer of sorafenib resistance to HCC cells. On a mechanistic level, circRNA-SORE interacts with the key oncogenic protein Y-box binding protein-1 (YBX1) within the cytoplasm (18). YBX1, commonly referred to as YB-1, is strongly associated with tumor proliferation, resistance to drugs, cancer advancement and overall prognosis across multiple cancer types (124). Notably, it is circRNA-SORE that stabilizes YBX1 by impeding its PRP19-mediated ubiquitination and degradation. The stabilized YBX1 then promotes the expression of its downstream oncogenic targets, such as AKT, Raf1, ERK, c-Myc and TGF-β1 (125,126), thereby driving sorafenib resistance. It was previously shown that sorafenib resistance could be effectively tackled and the therapeutic effectiveness could be increased in various HCC mouse models by locally injecting siRNA to silence circRNA-SORE (18). In another study, it was demonstrated that circRNA-SORE can competitively trigger the Wnt/β-catenin pathway and induce sorafenib resistance by functioning as an miRNA sponge that specifically binds to miR-103a-2-5p and miR-660-3p (8). New research indicates that CSF3R-AS, an antisense circRNA, is significantly upregulated in HCC and is strongly correlated with a poor patient prognosis. Mechanistically, CSF3R-AS functions by directly binding to its parental mRNA, CSF3R, through base-complementary pairing sites. Crucially, CSF3R-AS acts as an intermediate scaffolding molecule to recruit the RBP RBMS3, a key post-transcriptional regulator, which subsequently leads to the stabilization of CSF3R mRNA. This stabilization further promotes the activation of the downstream JAK2/STAT3 signaling pathway, thereby enhancing acquired resistance to sorafenib in HCC cells (127).

Additionally, certain circRNAs can boost the sensitivity of HCC cells to sorafenib. circMEMO1 is significantly downregulated and its expression levels are an independent prognostic factor for patients with HCC. From a mechanistic perspective, circMEMO1 inhibits HCC metastasis and stemness by regulating the miR-106b-5p/ten-eleven translocation methylcytosine dioxygenase 1 (TET1)/5-hydroxymethylcytosine (5hmC) axis and suppressing the EMT process. Specifically, it upregulates TET1, an enzyme that catalyzes the oxidation of 5-methylcytosine to form 5hmC, thereby initiating active DNA demethylation and altering the transcriptional program (128). Moreover, it also modulates the sensitivity of HCC cells to sorafenib treatment (129). circRNA-encoded secreted peptides can similarly influence the progression of sorafenib resistance. A recent study found that circZKSaa, a peptide secreted by circZKSCAN1, plays a crucial role in reducing HCC progression while also increasing the sensitivity of HCC cells to sorafenib. Through mechanistic investigations, it was found that the overexpression of circZKSaa increased the interaction between F-box and WD repeat domain-containing 7, a critical tumor-suppressing E3 ubiquitin ligase, and mTOR. This interaction facilitated the ubiquitination of mTOR, leading to the inhibition of the PI3K/AKT/mTOR signaling pathway, which ultimately influenced how HCC cells responded to sorafenib treatment (42).

*Lenvatinib*. Lenvatinib is the second first-line agent approved for advanced HCC after sorafenib. Lenvatinib demonstrates non-inferior overall survival compared with sorafenib in patients with previously untreated advanced HCC (130). Furthermore, it represents a valuable therapeutic option for patients with HCC recurrence following liver transplantation (131). Although the initial effectiveness of lenvatinib in sorafenib-resistant HCC cells seems promising, based on incomplete data, >60% of patients with HCC become tolerant to lenvatinib within a year and only a small proportion of patients show long-term advantages (132). Exosomal circRNAs are an essential factor in the development of resistance to levatinib. According to a recent study, circPAK1 expression is upregulated in HCC tumor tissues and cell lines, correlating with a poor prognosis in patients with HCC. The overexpression of circPAK1 accelerates HCC progression, while reducing its levels results in a decrease in cell proliferation, migration, invasion and angiogenesis. Mechanistically, circPAK1 facilitates YAP nuclear localization by competitively binding 14-3-3ζ of YAP, ultimately disrupting the Hippo signaling pathway. Furthermore, circPAK1 is transferred by exosomes from levatinib-resistant cells to those sensitive to the drug, thereby promoting drug resistance in the recipient cells. More notably, this study found that applying chitosan (a biocompatible polysaccharide nanomaterial)/si-circPAK1 nano complexes showed favorable therapeutic effects on tumor growth and metastasis. This provides a good guideline for developing novel therapeutic targets for HCC (77). Expression of exosomal circMED27 is markedly increased in the serum of patients with HCC, and higher circMED27 levels are correlated with unfavorable clinical features and prognosis in these patients. Upregulated circMED27 functions as a ceRNA for miR-655-3p to upregulate the expression of ubiquitin-specific

peptidase 28 and promotes lenvatinib resistance in HCC via this mechanism (133). An investigation highlighted the clinical and functional significance of circRNA-mTOR, a circular RNA highly expressed in HCC and strongly correlated with adverse patient prognosis. Mechanistically, circRNA-mTOR exerts its function by specifically binding to pro-RBPs PC4 and SRSF1 interacting protein 1 (PSIP1), thereby modulating the nuclear translocation of PSIP1. This molecular event enhances HCC cell stemness through the subsequent activation of the PSIP1/c-Myc signaling axis. Consequently, this pathway ultimately drives HCC progression and confers resistance to lenvatinib, establishing circRNA-mTOR as a critical regulatory factor in the malignancy of HCC (134). A recent study revealed the molecular mechanism by which circCCNY enhances the therapeutic effect of HCC through a dual mechanism. First, circCCNY promotes the ubiquitin-mediated degradation of HSP60 by recruiting SMURF1, a pivotal E3 ubiquitin ligase that targets specific substrates for proteasomal degradation, leading to the release of Raf kinase-inhibitory protein, which in turn inhibits the MAPK signaling pathway and significantly enhances the antitumor effect of lenvatinib. Second, circCCNY promotes the infiltration of $CD8^+$ T cells in the TME by blocking the MAPK/c-Myc/PD-L1 signaling axis, effectively inhibiting immune escape. These findings suggest that circCCNY not only enhances the sensitivity of HCC to targeted therapy but also regulates the tumor immune microenvironment and could potentially serve as a novel target for the combination therapy of HCC (135). Significant upregulation of hsa_circ_0007132 was observed in serum exosomes from patients with HCC with post-lenvatinib progression. Mechanistically, hsa_circ_0007132 binding to the non-POU domain containing octamer binding (NONO) protein inhibits its ubiquitination, resulting in increased NONO stability and expression. NONO is involved in various steps of RNA metabolism and its stabilization here facilitates the nuclear export of zinc finger e-box binding homeobox 1 (ZEB1) mRNA (136). The transcription factor ZEB1 then acts as a master regulator of EMT, a process strongly linked to drug resistance (137), thereby elevating ZEB1 levels and ultimately mediating lenvatinib resistance (138). circPIK3C3 exhibits significantly reduced expression in HCC and is correlated with patient prognosis, functioning to attenuate lenvatinib resistance. Both *in vitro* and *in vivo* investigations established that circPIK3C3 acts as a ceRNA to sequester miR-452-5p, resulting in the enhanced expression of SOX15. Concomitantly, this regulatory mechanism effectively inhibits Wnt/β-catenin-related signaling pathways. The combined effect of these actions mitigates HCC progression and reverses acquired resistance to lenvatinib, highlighting circPIK3C3 as a crucial suppressor of malignancy in HCC (139). As a potential frontline target in HCC therapeutics, the impact of exosomal circRNA on the development of levatinib resistance in HCC still requires further investigation.

*Regorafenib*. Regorafenib serves as a second-line treatment option for individuals with advanced HCC who have already undergone therapy with sorafenib. Regorafenib stands out as the sole systemic treatment that has demonstrated a survival advantage for patients whose condition has worsened despite sorafenib treatment (140,141). However, despite the richer target profile of regorafenib, resistance remains an issue in clinical use. Research indicates that exosomal circRNAs can affect the development of regorafenib resistance. For instance, circDCAF8 plays a notable role in facilitating the proliferation, migration, invasion and EMT of HCC cells. Of note, exosomal circDCAF8 enhances angiogenesis in HCC and enables the transfer of drug resistance from regorafenib-resistant HCC cells to those that are sensitive, thereby imparting a resistant phenotype. This process operates through the sponging of miR-217, which in turn increases the expression of nucleolus assembly protein 1-like protein 1, influencing both HCC progression and resistance to regorafenib (19). Moreover, another study indicated that berberine could increase the therapeutic effect of regorafenib on HCC via the upregulation of hsa_circ_0032029 and hsa_circ_0008928 in HCC cells (142).

Given the increasingly prominent problem of drug resistance in targeted drug therapy for HCC, a number of recent research efforts have validated that exosomal circRNAs are pivotal in mediating the mechanism behind multidrug resistance. This implies that the targeted regulation of exosomal circRNAs may serve as potential approaches for overcoming therapeutic resistance in HCC.

*Exosomal circRNAs in immunotherapy resistance in HCC*. More recently, as in-depth studies of the immune microenvironment during tumorigenesis and development have increased, immunotherapy has become an essential strategy for treating HCC (143).

*Immunotherapy: Immune checkpoint inhibitors*. Immune checkpoints are regulatory molecules found on immune cells that are crucial for sustaining self-immune function and are involved in various diseases, including NSCLC, melanoma, colon cancer and HCC (144-147). PD-1/PD-L1 has emerged as the predominant target in immunotherapy for HCC. Although immunotherapy targeting immune checkpoints has shown promising efficacy in certain patients with HCC, the problem of relapse and drug resistance remains to be solved. Recent studies suggest that circRNAs may play either immunostimulatory or immunosuppressive roles within the tumor immune microenvironment. circRNAs appear to influence the activity of immune cells and the expression of molecules associated with immunity, highlighting the potential of exosomal circRNAs as crucial contributors to resistance against immunotherapy (147). A recent investigation has elucidated the pivotal role of novel proteins translated from circRNAs in mediating immune therapy resistance and sustaining malignant biological behaviors in HCC cells. The study identified circPETH as a critical component, specifically an exosomal circRNA that is packaged within and secreted by tumor-associated macrophages and subsequently internalized by recipient HCC cells. The findings demonstrated that tumor-associated macrophage-derived exosomal circPETH actively promotes HCC cell invasion, migration and aerobic glycolysis. Mechanistically, a key function of circPETH within the HCC cytosol is its capacity to recruit ribosomes and initiate cap-independent translation, resulting in the expression of the novel protein circPETH-147aa. Further mechanistic dissection revealed that circPETH-147aa maintains HuR phosphorylation at the S100 site by specifically occupying surface MEG pockets. This interaction enhances HuR-dependent SLC43A2 mRNA stability, which consequently promotes the heightened

uptake of methionine and leucine by HCC cells. This metabolic shift compromises $CD8^+$ T cell antitumor cytotoxicity and impairs anti-HCC immunity. Notably, the study also identified norathyriol, a small-molecule compound that reverses the oncogenic effects of circPETH-147aa by competitively occupying the MEG pocket. This targeted intervention potentiates anti-PD-1 efficacy and restores cytotoxic $CD8^+$ T cell function. These results position norathyriol as a highly promising therapeutic agent to improve treatment outcomes for patients with HCC and mitigate resistance to immune checkpoint blockade therapy (41). Emerging evidence indicates that Circ-CDYL plays a critical role in mediating immunotherapy resistance. Mechanistically, Circ-CDYL binds to and interacts with hornerin (HRNR), thereby preventing its degradation via the ubiquitin-proteasome pathway. This stabilization of HRNR promotes activation of the downstream mTORC1 signaling pathway, leading to the increased expression of PD-L1. Consequently, this heightened PD-L1 expression drives the secretion of PD-L1-containing exosomes, which subsequently suppress the proliferation and cytotoxicity of CD8+ T cells within the TME. This Circ-CDYL-mediated cascade ultimately diminishes the efficacy of anti-PD-L1 immunotherapy in HCC and confers resistance to immune checkpoint blockade (148). circCCAR1 is upregulated in the exosomes derived from tumor cells, tumor tissues and the plasma of patients with HCC. Exosomes secreted by HCC cells can be taken up by $CD8^+$ T cells, which leads to the dysfunction of these T cells by stabilizing the PD-1 protein, ultimately increasing resistance to anti-PD-1 immunotherapy. From a mechanistic analysis, a positive feedback loop involving circCCAR1, miR-127-5p and wilms' tumor 1-associating protein, a key regulator of m6A RNA methylation that guides the methyltransferase complex to specific RNA targets, can enhance the expression of circCCAR1. This RNA can be secreted from HCC cells to $CD8^+$ T cells in a manner dependent on heterogeneous nuclear ribonucleoprotein A2/B1, which stabilizes the PD-1 protein and results in T cell dysfunction, thereby increasing resistance to anti-PD-1 treatment. Furthermore, the elevated levels CCAR1 in HCC cells may also contribute to resistance against anti-PD-1 immunotherapy through its interaction with β-catenin, which facilitates the transcription of PD-L1 (149). Focusing on the associated circRNA offers a novel approach to enhance immunotherapy effectiveness in patients with HCC. Another discovery indicated that exosomal circTMEM181 enhances the immunosuppressive environment in HCC and increases resistance to anti-PD-1 therapy in HCC cells. In terms of the underlying mechanism, exosomal circTMEM181 can act as a sponge for miR-488-3p within macrophages, thereby upregulating the expression of CD39 in macrophages. The expression of cell-specific CD39 in macrophages and CD73 in HCC cells synergistically activates the eATP-adenosine pathway increasing adenosine production. As a consequence, the function of $CD8^+$ T cells is hampered and the immune microenvironment of HCC is remodeled, resulting in resistance to anti-PD-1 therapy in HCC cells (150). It has been reported that high circUHRF1 levels are associated with unfavorable clinical outcomes and impairs natural killer (NK) cell function in patients with HCC and that it can be secreted by HCC cells into the plasma in the form of exosomes, resulting in a reduced NK cell ratio and decreased NK cell tumor infiltration. Mechanistic analysis revealed that circUHRF1 inhibits NK cell function by degrading miR-449c-5p to upregulate the expression of T-cell immunoglobulin mucin-3 (TIM-3) and impede the ability of NK cells to generate IFN-γ and TNF-α, thereby inhibiting NK cell function and inducing HCC progression in an NK cell-dependent manner. Additionally, the investigation confirmed that HCC cells with knocked down circUHRF1 expression demonstrated increased sensitivity to anti-PD-1 therapy and exhibited improved overall survival (OS) rates (151). This suggests that targeting exosomal circUHRF1 may be a promising and effective method to restore HCC sensitivity to anti-PD-1 therapy. Moreover, in another study, elevated levels of circMET were shown to trigger EMT in HCC cells; its overexpression induced an immunosuppressive microenvironment in HCC via the miR-30-5p/Snail/dipeptidyl peptidase 4 (DPP4)/C-X-C motif chemokine ligand 10 (CXCL10) axis (152). In this axis, DPP4 functions as a serine protease that cleaves and inactivates the T-cell chemoattractant CXCL10. DPP4 inhibitors are a class of drugs used to treat type 2 diabetes, but in this study, it was shown to increase CXCL10 expression in tumor cells by inhibiting the cleavage of the chemokine CXCL10 by DPP4, thereby triggering effective tumor immunity and enhancing the clinical efficacy of immunotherapy. It is worth noting that in animal experiments, the combination of the DPP4 inhibitor sitagliptin and anti-PD-1 therapy was significantly effective and synergistic, suggesting that sitagliptin can improve the efficacy of PD-1 blockade immunotherapy, highlighting the potential value of repurposing established therapeutics for other diseases in the management of HCC (152). circRHBDD1 exhibits increased expression in patients with HCC responsive to anti-PD-1 therapy and facilitates glycolysis within HCC cells. Targeting the circRHBDD1/YTH N6-methyladenosine RNA binding protein 1/PIK3R1 axis can improve anti-PD-1 therapy in a mouse model with normal immune function (153). circSOD2 can promote immune escape and anti-PD-1 resistance in HCC by targeting the miR-497-5p/Annexin A11 axis (154).

According to the aforementioned studies, exosomal circRNAs can relay information between tumors and immune cells via the secretion of exosomes. These circRNAs can influence immune cells and immune-related molecules within the tumor immune microenvironment, leading to the immunosuppression of tumor cells, which in turn may result in resistance to immunotherapy. Immunotherapy is an effective treatment strategy and its relationship with exosomal circRNAs is still unclear. Exosomal circRNAs may become an effective way to improve sensitivity to anti-PD-1 therapy.

*Immunotherapy: Adoptive cell therapy*. Evidence suggests that monotherapy with immune checkpoint inhibitors alone may not effectively tackle the underlying issues related to immune system failure and the suppression of immune cells responsible for targeting cancer cells (155). The TME is another key factor contributing to resistance to immunotherapy. In the TME, the dysfunction of immune effector cells induces immunosuppression, mediating tumor cell immune escape.

*T cells*. Immunotherapy is a practical approach for improving the efficacy of immune checkpoint inhibitors, especially for patients with cancer who have developed resistance to checkpoint inhibitors, by inducing cancer-specific

T cells (156). Specifically, T cells can be genetically edited to express T cell receptors or chimeric antigen receptors (CARs) on their cell surface that recognize tumor antigens, thereby enhancing the specificity and reactivity of immune cells (157). Nonetheless, certain patients may experience a gradual relapse following a successful response to immunotherapy, leading to acquired drug resistance (158). A key factor that may contribute to this phenomenon is that, throughout treatment, cancer cells can evolve strategies to escape immune detection or diminish the effectiveness of T cells, ultimately resulting in suboptimal treatment outcomes (159).

Studies have shown that exosomal circRNAs are involved in immune cell therapy resistance. For instance, recent research has indicated that exosomal circGSE1 induces the proliferation of regulatory T cells (Tregs) by modulating the miR-324-5p/TGFBR1/Smad3 axis. These proliferated Tregs are capable of regulating the immune escape of HCC by inhibiting $CD4^+$ T cells and stimulating $CD8^+$ T cells, which in turn leads to resistance to HCC immunotherapy (160). In another study, the levels of circCCAR1 were shown to be markedly higher in patients with HCC, and this increase promoted HCC growth and metastasis both *in vivo* and *in vitro*. More notably, exosomes secreted by HCC cells containing circCCAR1 were absorbed by $CD8^+$ T cells, causing $CD8^+$ T cell dysfunction and thus promoting HCC immunosuppression. From a mechanistic perspective, circCCAR1 impairs activated $CD8^+$ T cells by suppressing their proliferation, accelerating their apoptosis, diminishing their cytotoxicity and cytokine secretion as well as increasing the expression of lymphocyte-activation gene 3, PD1, TIM-3 and T cell immunoreceptor with immunoglobulin and ITIM domains on the surface of $CD8^+$ T cells (149).

Exosomal circRNAs often play similar roles in the immunotherapy of other types of cancer. For example, in NSCLC, exosomal circUSP7 from cancer cells triggered $CD8^+$ T cell dysfunction by regulating a miR-934/Src homology 2 domain containing protein tyrosine phosphatase 2 (SHP2) axis. SHP2, a key signaling node that transduces signals from various immune checkpoints, contributes to immunosuppression in NSCLC (161). In bladder cancer (BCa), exosome-derived circTRPS1 from BCa cells can induce immunosuppression by regulating the intracellular reactive oxygen species balance and $CD8^+$ T cell depletion via a circTRPS1/miR141-3p/glutaminase 1 axis, where GLS1 is a key metabolic enzyme that catalyzes the conversion of glutamine to glutamate (162).

*NK cells*. Liver NK cells are a crucial component of the immune system, serving an indispensable function in supporting liver immunity and protection against HCC. NK cells contribute significantly to the liver's immune defense by employing a range of strategies, including the direct elimination of tumor cells and the release of cytokines (163). CAR-NK therapy has become a promising method for treating patients with HCC (164,165). It has been reported that HCC-derived exosomal circRNAs target NK cells to promote the formation of an immunosuppressive microenvironment. For instance, circUHRF1, primarily released by HCC cells in exosomes, plays a role in fostering immunosuppression by breaking down miR-449c-5p to enhance TIM-3 expression. This process leads to the dysfunction and eventual death of NK cells, ultimately impairing their activity. In addition, exosomal circUHRF1 also hinders the production of IFN-γ and TNF-α by NK cells, further suppressing their functionality (151). In addition to targeting NK cells to promote immunosuppression, certain circRNAs promote NK cell-mediated cytotoxicity against HCC. For instance, in HCC cell lines, the expression of hsa_circ_0007456 is significantly decreased. This change significantly affects their susceptibility to NK cells, which may impact the immunotherapeutic effect of HCC. Research into the underlying mechanisms has shown that hsa_circ_0007456 primarily influences the sensitivity of HCC cells to NK cells by sponging miR-6852-3p and regulating the expression of intercellular adhesion molecule-1 (ICAM-1) in HCC cells (166). The expression of ICAM-1 by human cancer cells can affect NK cell function by binding to lymphocyte function-associated antigen 1 on NK cells, thereby regulating the adhesion between NK cells and target cells (167).

*Macrophages*. Studies have found that macrophages are among the key target cells for exosomal circRNAs (168). Within the TME, HCC cells deliver biologically active materials such as circRNAs to macrophages in the form of vesicles. These circRNAs may interfere with the normal immune function of macrophages, for example, by inhibiting their antigen presentation ability (150) and regulating their polarization state (68). This allows cancer cells to evade immune surveillance, creating favorable conditions for tumor growth and metastasis (150). Exosomes derived from HCC containing circTMEM181, are capable of enhancing the expression of CD39 in macrophages. This is achieved through the sequestration of miR-488-3p. As a result, CD39 collaboratively activates the eATP-adenosine pathway along with the expression of CD73 in HCC cells. This joint action leads to the generation of larger quantities of adenosine, ultimately undermining the function of $CD8^+$ T cells (150). Another study revealed that exosomal hsa_circ_0074854 is elevated in HCC tissues and cell lines, and silencing hsa_circ_0074854 reduced HCC proliferation both *in vitro* and *in vivo*. Mechanistically, hsa_circ_0074854 is transferred from HCC cells to macrophages via exosomes. M2 macrophages play a crucial role in creating an immunosuppressive TME and facilitating immune evasion, whereas the exosomes from cells with hsa_circ_0074854 knockdown impeded the polarization of macrophages toward an M2 phenotype (68). This shows that targeting hsa_circ_0074854 may be a novel strategy for preventing immunosuppression in HCC.

In summary, current research has found that one of the critical factors in immune cell therapy resistance is the activity of immune cells. Therapeutically, circRNAs often suppress immune cell function, which further leads to immunosuppression of HCC cells, making it difficult for immunotherapeutics to achieve the desired effect. However, by targeting circRNAs, which is like a precise 'key', the 'shackles' on the function of immune cells can be removed, thereby lifting the immunosuppression of HCC cells and allowing immune cells to resume their tasks. This could have revolutionary implications for tackling immunotherapy resistance in HCC, offering a novel approach for overcoming this complex issue.

## 6. Potential of exosomal circRNAs in clinical applications

*Exosomal circRNAs function as clinical biomarkers*. Exosomal circRNAs derived from HCC cells are notably abundant and stable. Secreted into the TME and subsequently

disseminated via systemic circulation, these circRNAs are transferred to diverse target cells. This delivery mechanism enables them to critically modulate malignant phenotypes, including tumor proliferation, invasion, metastasis, angiogenesis, immune evasion and drug resistance (169). Emerging evidence consistently demonstrates that exosomes critically contribute to HCC progression by actively remodeling the TME and inducing an immunosuppressive state within it (170). Consequently, exosomal circRNAs are pivotal in mediating intercellular crosstalk within the TME, thereby either promoting or inhibiting the invasion and metastasis of HCC. This regulatory capacity confers upon them significant potential as robust biomarkers for the diagnosis, therapeutic target and prognostic stratification of HCC (171,172). Liquid biopsy represents a non-invasive methodology that harnesses various bodily fluids, including blood, plasma, serum, urine and gastric fluid, to accurately monitor and reflect the overall disease status (173). Given their characteristic dysregulation in disease and notable abundance in stable exosomal carriers, circRNAs are readily detectable in bodily fluids (such as blood, serum, urine, saliva and cerebrospinal fluid). These attributes collectively position circRNAs as ideal biomarkers for liquid biopsy (16,174).

For instance, hsa_circ_0004001, hsa_circ_0004123 and hsa_circ_0075792 have been identified as upregulated in serum exosomes of patients with HCC, exhibiting enhanced diagnostic sensitivity and specificity. Notably, the combined application of these three biomarkers notably improves diagnostic accuracy, achieving a sensitivity of 90.5% and an area under the curve (AUC) of 0.89. This evidence strongly supports the utility of this circRNA panel as a valuable diagnostic signature for HCC (175). circ-0072088 is primarily secreted by HCC cells via exosomes, exhibiting significantly higher expression in HCC tissues and cells compared with adjacent non-cancerous tissues and healthy hepatocytes. Receiver operating characteristic (ROC) curve analysis has revealed the diagnostic efficacy of circ-0072088 for HCC, yielding an AUC of 0.899. Moreover, Kaplan-Meier survival curves and Cox regression analyses consistently established that elevated circ-0072088 expression is associated with significantly reduced 5-year survival rates, thereby positioning it as an independent prognostic factor for patients with HCC. Collectively, these results highlight that extracellular vesicle-derived circ-0072088 functions as both a diagnostic and prognostic marker for HCC (73). The expression level of circ_0051443 in patient plasma exosomes is significantly downregulated compared with healthy controls, positioning it as a potential diagnostic and prognostic biomarker. Mechanistically, circ_0051443 can suppress malignant biological behaviors by regulating key processes such as apoptosis, proliferation and cell cycle arrest (48). In an independent cohort, reverse transcription-quantitative PCR was employed to determine the expression levels of circAKT3 in circulating exosomes from 124 patients with HCC and 100 healthy controls. The results demonstrated that exosomal circAKT3 expression was significantly elevated in patients with HCC compared with the healthy subjects. More critically, high circAKT3 expression was correlated with increased tumor recurrence rates and elevated mortality among patients with HCC, thereby establishing circAKT3 as a crucial biomarker for predicting HCC recurrence and unfavorable prognosis (176). A recent study demonstrated that circYTHDC2 is significantly upregulated across HCC tissues, serum and cell lines, and exhibits notable stability against RNase degradation. ROC analysis confirmed the high diagnostic accuracy of circYTHDC2 in both tissue (AUC=0.846) and serum (AUC=0.788) samples. Furthermore, elevated levels of circYTHDC2 significantly were correlated with adverse clinicopathological features, including advanced Barcelona Clinic Liver Cancer staging, larger tumor volume, intrahepatic metastasis and portal vein invasion. Collectively, these findings establish circYTHDC2 as a stable and clinically viable HCC biomarker with notable diagnostic accuracy and prognostic value (177). Furthermore, another preliminary investigation assessed the diagnostic and prognostic utility of circulating circ_0009910 and circ_0027478 in conjunction with miR-1236-3p in patients with HCC. The study reported a significant upregulation of circ_0009910 and circ_0027478 in the plasma of these patients, contrasted by the downregulation of miR-1236-3p. Notably, circ_0009910 exhibited excellent diagnostic performance (AUC=0.90), and its elevated expression was positively correlated with adverse clinicopathological features, including tumor size, metastasis and α-fetoprotein levels. These findings underscore the potential of circ_0009910 as an independent diagnostic and prognostic biomarker for HCC (178). Although this study primarily utilized total plasma samples for detection, its findings offer compelling evidence that circulating circRNAs accurately reflect the pathological characteristics and malignancy of HCC. Furthermore, in a separate analysis, circSMARCA5 expression levels in the plasma from patients with HCC were found to be significantly lower than those in healthy controls. This downregulation conferred high discriminatory accuracy (AUC=0.938), demonstrating the potential of circSMARCA5 as a robust biomarker for distinguishing patients with HCC from healthy subjects (179). A recent study has demonstrated significant progress, clinically validating a nanobiosensor that successfully detects circSMARCA5 expression levels in both liver tissue and whole blood samples, thus enabling the accurate discrimination of patients with HCC from healthy individuals. This breakthrough establishes a highly promising circulating RNA-based liquid biopsy tool with clinical application potential (180).

Exosomal circRNAs are also capable of reflecting the presence of tumor-infiltrating lymphocytes (TILs) within HCC tissues, thereby serving as a robust prognostic biomarker. Research indicates that patients with HCC presenting with high TIL levels typically exhibit significantly improved OS outcomes (181). Specifically, the expression of hsa_circ_0064428 was found to be significantly reduced in high-TIL patients but conversely increased in those with low-TIL infiltration. Furthermore, hsa_circ_0064428 expression demonstrated a significant negative correlation with patient survival rates, tumor size and metastasis. These findings collectively establish hsa_circ_0064428 as a potent prognostic biomarker for HCC, potentially reflecting the antitumor immune microenvironment (181). Most notably, exosomal circRNA also serves as a prognostic biomarker for treatment resistance in HCC. A study has indicated that hsa_circ_0000615 is significantly upregulated in patients with sorafenib-resistant HCC compared with those with

chemotherapy-sensitive HCC, with its expression level positively correlated with advanced disease stage. Furthermore, hsa_circ_0000615 exhibits moderately good AUC values, and elevated expression strongly correlates with shorter OS in patients with chemotherapy-resistant HCC. These findings suggest that hsa_circ_0000615 holds promising value as a novel prognostic biomarker for sorafenib resistance, thus offering diagnostic utility for detecting chemoresistance in HCC (182). Additionally, specific exosomal circRNAs exhibit potential as markers for the early identification and differential diagnosis of HCC from high-risk populations, such as individuals with chronic hepatitis B virus infection and cirrhosis. Examples include serum exosomal hsa_circ_0028861, exosomal circ_0070396 and hsa_circ_0003998, which demonstrate utility in discriminating HCC from these background liver diseases (183-185).

Given the established potential of exosomal circRNAs as emerging clinical biomarkers for HCC diagnosis and prognosis, targeted clinical validation trials remain essential. Supported by the accumulation of robust future research data, exosomal circRNA is highly anticipated to evolve into a more reliable and clinically actionable tumor biomarker, ultimately facilitating its successful translation into routine clinical applications.

*Therapeutic strategies based on exosomal circRNA*. Exosomal circRNAs have emerged not only as biomarkers but also as a promising therapeutic strategy. Specifically, the utilization of exosomal RNA delivery systems for the treatment of malignant tumors, including HCC, has demonstrated considerable potential as a novel and robust approach in modern cancer therapy.

Strategies targeting oncogenic circRNAs can be employed to inhibit HCC progression or drug resistance. Specifically, technologies such as RNA interference, antisense oligonucleotides and CRISPR-Cas13a have been engineered for the effective targeting of these oncogenic circRNAs (186). For example, a prior study reported that the oncogenic circRNA, circ_0000098, drives HCC progression via the miR-383/mitochondrial calcium uniporter regulator 1 axis. Notably, this research engineered PLTs to encapsulate both DOX and a short hairpin RNA targeting circ_0000098, termed DOX/sh-1@PLT. In both *in vitro* and *in vivo* models, DOX/sh-1@PLT demonstrated effective delivery to HCC cells, promoting intracellular DOX accumulation and successfully reversing drug resistance in HCC (103). The superior stability, minute size and low toxicity of exosomes establish them as compelling candidates for drug delivery systems. Therefore, strategies employing exosome-mediated transfer of anticancer circRNAs hold great promise for the inhibition of HCC progression and the reversal of acquired drug resistance (42,94,107,129,135).

Beyond the aforementioned studies, research exploring the potential utility of circRNAs in cancer vaccines, gene editing therapies and adoptive cell therapies continues to rapidly expand (187,188). However, further research is essential to fully delineate the potential of circRNAs as a therapeutic intervention for HCC. Collectively, exosomal circRNA is emerging as a novel category of RNA therapeutics. While challenges persist, its distinctive benefits poise it to become a significant asset in the future of HCC therapy.

## 7. Conclusions and future perspectives

In conclusion, the regulatory roles of exosomal circRNAs in HCC pathogenesis, including their impact on proliferation, invasion-metastasis capabilities, angiogenesis, metabolic reprogramming and stem cell-like phenotypes, have been discussed. The present comprehensive review highlights recent advances in understanding how exosomal circRNAs mediate therapeutic resistance in HCC. Moreover, the promising role of exosomal circRNAs as prospective therapeutic targets is highlighted, shedding light on their clinical significance and presenting innovative approaches to address treatment resistance and enhance patient prognosis. However, compared with lncRNAs, studies on the precise functional mechanisms and clinical applications of exosomal circRNAs remain limited.

Significant knowledge gaps exist. Current research primarily emphasizes the effect of miRNA sponging by circRNAs, leaving other regulatory mechanisms insufficiently investigated. Notably, certain circRNAs encode functional peptides with specific biological activities, suggesting that protein-coding circRNAs may represent a novel frontier in HCC therapeutics. Additionally, key inquiries concerning the biogenesis of exosomal circRNAs continue to be unanswered, especially the intricate molecular regulatory networks that dictate their selective packaging, directional sorting and eventual degradation. Elucidating these mechanisms holds significant scientific value for developing innovative technologies to regulate exosomal circRNA secretion and uptake within TMEs.

Breakthroughs in this field will improve our understanding of tumor evolution and advance translational research, ultimately enabling targeted modulation of exosomal circRNAs for precision oncology. With continuous advancements in detection technologies and bioinformatics algorithms, the diagnostic and therapeutic significance of exosomal circRNAs in malignancies is becoming increasingly apparent. Further investigations into the functional mechanisms of exosomal circRNAs in HCC may critically inform the optimization of clinical management strategies and accelerate their practical implementation in personalized cancer therapy.

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## Authors' contributions

ZL and YuW collected the literature and wrote the manuscript. YaW and YZ wrote, conceived and reviewed the manuscript

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**Ethics approval and consent to participate**

Not applicable.

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**Competing interests**

The authors declare that they have no competing interests.

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