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Review Article

Exosome encapsulated ncRNAs in the development of HCC: potential circulatory biomarkers and clinical therapeutic targets

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Abstract: Hepatocellular carcinoma (HCC) is the sixth most deadly malignant cancer in the world and has the third highest mortality rate among cancer-related deaths worldwide. Its poor prognosis can be attributed to late diagnosis, high risk of recurrence and drug resistance. Therefore, finding a new biomarker to help us in the early diagnosis, and exploring the molecular mechanisms involved in recurrence and drug resistance is a reasonable research direction for clinical treatment of HCC. At present, the exosomes related to HCC have been confirmed to carry ncRNAs, transfer them to target cells, and bind corresponding target molecules. Furthermore, they affect the proliferation and metastasis of hepatocellular carcinoma by promoting angiogenesis, epithelial-mesenchymal transition (EMT), and inhibiting the function of the body's immune system. They play an important role in the recurrence and resistance of HCC. Besides, exosomes are stably expressed in body fluids such as sera, are easy to collect and cause little harm to the human body. They are the best candidates for liquid biopsy. Therefore, exosomal ncRNAs have application prospects as biomarkers and targeted molecules for therapy. This article summarizes the current research involving ncRNAs in HCC-related exosomes.

Keywords: Exosomes, ncRNAs, biomarker, targeted molecules, HCC

Introduction

Exosomes are tiny vesicles of nanometer size (50-100 nm) that secreted fromcell culture supernatant and body fluids, such as serum/plasma, urine, amniotic fluid, and ascites [1, 2]. Evidence indicates that exosomes control both normal physiological processes, such as immune response and lactation [3], and the expansion and development of diseases, especially cancer [4]. Cancer cells produce more exosomes than normal cells, which have a powerful ability to modify the local and remote microenvironment [5]. In HCC, exosomes can contribute to the development of HCC by promoting angiogenesis, inducing resistance and inhibiting the body's immune system.

Non-coding RNAs (ncRNAs) are functional transcripts in exosomes that cannot be translated into proteins, including miRNAs, lncRNAs, circRNAs, etc. [6]. They transferred by exosomes, participate in the communication between tumor cells and between tumor cells and stromal cells to targeted cells, thereby affecting tumor angiogenesis, metastasis, and drug and radiotherapy resistance [7-9]. At the same time, due to the protection of exosomes, these ncRNAs can be stably expressed in serum, are easy to detect, and have the potential as new biomarkers and therapeutic targeting molecules.

Therefore, we reviewed the current research status of ncRNAs in hepatocellular carcinoma exosomes to further emphasize the potential value of these abnormally expressed exosome ncRNAs in HCC as biomarkers for diagnosis, prognosis and treatment of HCC.

miRNAs in exosomes secreted by HCC

MicroRNA (miRNA, usually 22-25 nucleotides) can bind to the miRNA response element (MRE) on the 3'-untranslated region (UTR) of the target messenger RNA (mRNA) to promote mRNA degradation or inhibit the translation of mRNA [6, 10]. It has been confirmed that exosomes can transfer miRNAs to corresponding target cells and participate in the regulation of tumor proliferation, invasion, metastasis, drug resistance and immune escape [9, 11-14]. We summarized the current status of research on the functions and molecular mechanisms of exosomal miRNAs in the development of hepatocellular carcinoma (**Table 1**).

Exosomal miRNAs involved in regulating the angiogenesis and epithelial-mesenchymal transition (EMT) of hepatocellular carcinoma

Tumors need nutrients and oxygen to grow. The new blood vessels formed through the angiogenesis process provide these substrates [15]. Therefore, angiogenesis is considered to be the basic prerequisite for tumor progression, proliferation, and metastasis [16]. The vascular endothelial growth factor (VEGF) family is the most important part of the angiogenesis pathway [15]. The exosomes in HCC can promote the secretion of VEGF by entering the matrix cells, such as hepatic exogenous cells. And VEGFs have a mitogenic and an anti-apoptotic effect on endothelial cells, increasing the vascular permeability and cell migration to promotes angiogenesis [17].

Exosomes secreted by HCC cells carry miRNAs and transfer them to recipient cells. These miRNAs can inhibit the expression of Phosphatase and tensin homolog (PTEN) via targeting the 3'-UTR of PTEN and activating the PI3K-Akt pathway. They promote the expression of VEGF by corresponding recipient cells, leading to angiogenesis [18]. miR-21 is one of the miRNAs that target PTEN directly. They can convert hepatic stellate cells (HSCs) into cancer-associated fibroblastic cells (CAFs) via the above-mentioned pathways. The activated cancer-related fibroblasts secrete angiogenic factors (including VEGF, MMP2, MMP9, bFGF and TGF-β) which promote angiogenesis, and then strengthen the proliferation, invasion and metastasis of HCC [1, 8, 19, 20] (**Figure 1**). Furthermore, miR-32-5p also promotes the secretion of VEGF by inhibiting PTEN and activating the PI3K/Akt pathways [21]. Besides, miR-155 can also down-regulate the expression of PTEN, and its enrichment in HCC-related exosomes mediates the development of HCC [22, 23] (**Figure 1**).

Some studies have also found that exosomal miRNAs can play their role in promoting angiogenesis by targeting other targeted molecules. miR-210 in exosomes secreted by HCC can be transferred to endothelial cells, targeting SMAD4 and signal transducer and activator of transcription 6 (STAT6), inhibiting their negative regulation of angiogenesis, thereby promoting angiogenesis [24]. The low expression of miR-451 can up-regulate the expression of IL-6 receptor (IL-6R). This will activate signal transducer and activator of transcription 3 (STAT3) signaling to increase VEGF and ultimately promote angiogenesis [25].

In addition, EMT can loosen cell-cell structure, weaken cell-cell adhesion, and give cells enhanced migration and invasiveness [26]. AdipoR1 is the direct target of miR-221. Overexpressed miR-221 inhibits AdipoR1 to initiate EMT of HCC cells [27]. Simultaneously, miR-10b can target cell adhesion molecules (CADMs), which have the function of maintaining cell polarity and inhibiting tumors. miR-10b highly expressed in HCC activates focal adhesion kinase (FAK)/AKT signaling pathway to promote EMT, by inhibiting CADMs. This will enhance the metastasis and aggressiveness of HCC cells [28].

Exosomal miRNAs involved in regulating the drug resistance of hepatocellular carcinoma cells

Multidrug resistance has become a major obstacle in the treatment of hepatocellular carcinoma [21]. It is currently believed that exosomes secreted by drug-resistant cells in patients with hepatocellular carcinoma play an important role in the development of multidrug resistance of sensitive cells.

At present, for patients with advanced liver cancer, sorafenib is an effective systemic therapy [29]. However, the efficacy of sorafenib is not satisfactory, for the average life expectancy of patients using it is only one year [30]. Studies

Table 1. miRNAs involved in pathways affecting HCC

miRNA	Target gene	Up or down in exosomes	Up or down in HCC	Cancer promotion or suppression	Function	Mechanism	Refs
miRNA-638	unknown	down	down	cancer suppression	inhibit the proliferation and invasion of HCC	unknown	[64]
miR-335	unknown	down	down	cancer suppression	inhibit the proliferation and invasion of HCC	unknown	[65]
miR-125b	unknown	down	down	cancer suppression	inhibit the proliferation and invasion of HCC	unknown	[66]
miR-320d	unknown	down	down	cancer suppression	inhibit the proliferation and invasion of HCC	unknown	[67]
miR-93	unknown	up	up	cancer promotion	promote the proliferation and invasion of HCC	unknown	[68]
miR-106a	unknown	up	up	cancer promotion	promote the proliferation and invasion of HCC	unknown	[69]
miR-224	unknown	up	up	cancer promotion	promote the proliferation and invasion of HCC	unknown	[70]
miR-518d	unknown	up	down	cancer suppression	inhibit the proliferation and invasion of HCC	unknown	[63]
miR-584	unknown	up	down	cancer suppression	inhibit the proliferation and invasion of HCC	unknown	[63]
miR-215	unknown	up	down	cancer suppression	inhibit the proliferation and invasion of HCC	unknown	[63]
miR-142-5p	unknown	up	down	cancer suppression	inhibit the proliferation and invasion of HCC	unknown	[63]
miR-378	unknown	up	down	cancer suppression	inhibit the proliferation and invasion of HCC	unknown	[63]
miR-21	PTEN	up	up	cancer promotion	promote the proliferation, invasion and metastasis of HCC	angiogenesis	[1, 8, 19, 20]
miR-155	PTEN	up	up	cancer promotion	promote the proliferation, invasion and metastasis of HCC	angiogenesis	[22, 23]
miR-210	SMAD4 and signal transducer and activator of transcription 6 (STAT6)	up	up	cancer promotion	promote the proliferation, invasion and metastasis of HCC	angiogenesis	[24]
miR-451	IL-6 receptor (IL-6R) and	up	down	cancer suppression	promote the proliferation, invasion and metastasis of HCC	angiogenesis and the nuclear factor-kappa B (NF-κB) pathway	[25, 56]
miR-221	AdipoR1	up	up	cancer promotion	promote the proliferation, invasion and metastasis of HCC	EMT	[27]
miR-10b	cell adhesion molecules (CADMs)	up	up	cancer promotion	promote the metastasis of HCC	EMT	[28]
miR-103	VE-Cadherin (VE-Cad), p120-catenin (p120) and zonula occludens-1 (zonula occludens-1)	up	up	cancer promotion	promote the metastasis of HCC	vascular permeability	[13]
miR-32-5p	PTEN	up	up	cancer promotion	promote multidrug resistance	angiogenesis and epithelial-mesenchymal transition (EMT)	[21, 31-33]
miR-744	the PAX (paired box) genes PAX2	down	down	cancer suppression	inhibit proliferation and multidrug resistance	antiapoptosis and cell cycle	[29, 34]

miR-122	SerpinB3	up	down	cancer suppression	inhibit proliferation and multidrug resistance	unknown	[35-37]
miR-199a-3p	ataxia-telangiectasia mutated (ATM), mammalian target of rapamycin (mTOR) and DNA methyltransferase 3A (DNMT3A)	down	down	cancer suppression	inhibit proliferation and multidrug resistance	apoptosis	[38]
miR-23a-3p	PTEN	up	up	cancer promotion	immune escape	T cell apoptosis	[43]
miR-146a-5p	unknown	up	up	cancer promotion	immune escape	unknown	[42, 44, 47, 48]
miR-92b	unknown	up	up	cancer promotion	immune escape	inhibiting NK cells	[49]
miR-4661-5p	tristetraprolin	up	up	cancer promotion	immune escape	increase IL-10	[45, 46]
miR-1228	p53	up	up	cancer promotion	promote the proliferation and metastasis of HCC	acceleration of the cell cycle	[50]
miR-222	PPP2R2A	up	up	cancer promotion	promote the metastasis of HCC	AKT signaling pathway	[51]
miR-367	PTEN	up	up	cancer promotion	promote the proliferation and metastasis of HCC	unknown	[52]
miR-18a	Bcl2L10	up	up	cancer promotion	promote the proliferation and metastasis of HCC	unknown	[53]
miR-520f	TM4SF1	up	down	cancer suppression	inhibit proliferation and invasion of HCC	unknown	[54]
miR-517c	Pyk2	up	down	cancer suppression	inhibit the proliferation of HCC	unknown	[55]
miR-133b	LASP1, Sirt1 and TONSL	up	down	cancer suppression	inhibit the proliferation and invasion of HCC	unknown	[57-59]
miR-376a	p85α	up	down	cancer suppression	inhibit the proliferation of HCC	reduce HCC cell apoptosis	[60]
miR-519d	MKi67 and Rab10	up	down	cancer suppression	inhibit the proliferation of HCC	unknown	[61, 62]

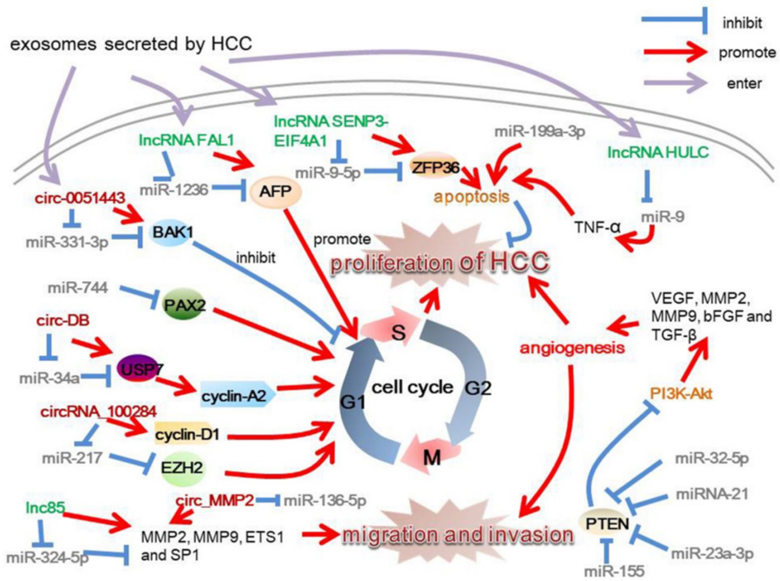

Figure 1. ncRNAs involved in the regulation of proliferation and metastasis of HCC. The exosomes secreted by HCC change the content of ncRNAs in the recipient cells, thereby affecting downstream targeting molecules. By changing the cell cycle, cell apoptosis, and the secretion of VEGF and other factors, they affect the proliferation and metastasis of HCC.

have found that sensitive cells resist the inhibition of sorafenib's angiogenesis by receiving miR-32-5p-containing exosomes secreted from drug-resistant cells, and become resistant cells to sorafenib [21, 31-33]. MiR-32-5p directly targets the 3'-UTR of PTEN, inhibits PTEN, and activates the PI3K/Akt pathway in sensitive cells [21]. In particular, this approach is not generally believed to promote tumorigenesis or treatment resistance by inhibiting apoptosis, but by promoting the secretion of VEGF, which enhances angiogenesis and epithelial-mesenchymal transition (EMT) (**Figure 2**). That is because the anti-tumor activity of sorafenib is largely attributed to the blockade of the signals from growth factors, such as vascular endothelial growth factor receptor and platelet-derived growth factor receptor [33].

Another research found that the level of miR-744 in the HCC patients' serum is lower than that in healthy people. This finding suggests that serum exosomal miR-744 may be a potential biomarker for HCC. It is also significantly lower in exosomes derived from sorafenib-resistant HCC cells than from sensitive HCC cells. Moreover, the sensitivity of HCC cells to sorafenib was augmented when HCC cells were treated with miR-744-enriched exosomes. So exosomal miR-744 may be an effective therapeutic target for sorafenib-resistant HCC patients. They also found that the PAX (paired box) genes PAX2 is the direct target of miR-744, which exerts an anti-apoptotic effect by activating the expression of certain apoptosis-inhibiting genes [34] (**Figure 1**). It can also promote the proliferation of cancer cells by re-entering the mitotic cycle of cancer cells. So studies believe that down-regulating miR-744 in HCC cells is related to an increase of PAX2 expression, thereby promoting HCC proliferation and sorafenib resistance [29]. miR-122 is down-regulated in HCC and increases the expression of SerpinB3. This will enhance cell proliferation and cell invasion [35]. Another study also found that injecting exosomes containing miR-122 into tumors will significantly increase the anti-tumor efficacy of sorafenib against HCC in vivo. Therefore, MiR-122 combined with sorafenib has certain research prospects in the treatment of sorafenib-resistant HCC [36]. Interestingly, the level of miR-122 in serum exosomes is higher than normal [37].

In addition to sorafenib, cisplatin is also the first-line chemotherapeutic drug used clinically to treat HCC [38]. Studies have found that miR-199a-3p can be transferred to HCC cells. And it may down-regulate the expression of ataxia-telangiectasia mutated (ATM), mammalian target of rapamycin (mTOR) and DNA methyltransferase 3A (DNMT3A). This promotes apoptosis and inhibits cell viability and invasion. Through intravenous injected with exo-199a-3p mimics, refractory HCC in mice regained sensitivity to cisplatin. It indicates that the delivery of miR-199a-3p through exosomes may help solve the resistance of HCC to cisplatin [38, 39] (**Figure 1**).

By the way, lenvatinib has also become the first-line therapy for HCC in recent years. But the relationship between HCC exosome miRNAs and lenvatinib resistance has not been studied.

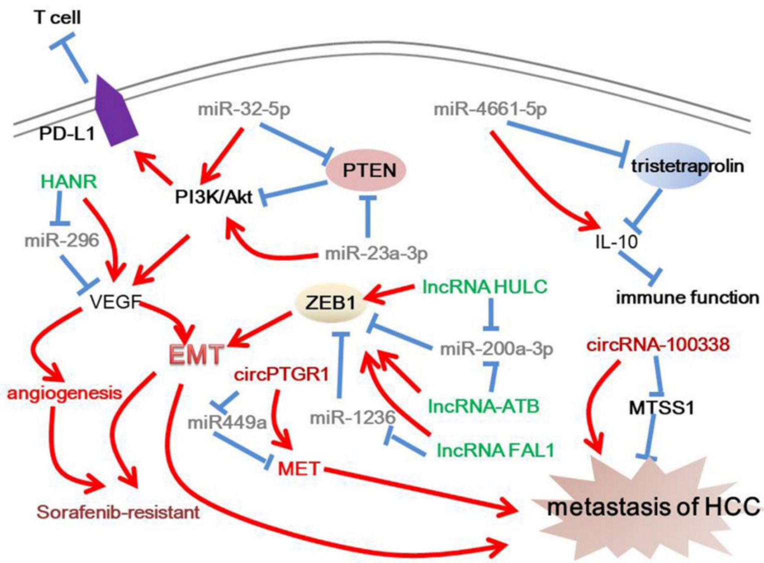

Figure 2. The role of ncRNAs in immune function, sorafenib resistance, and metastasis of HCC. Abnormally expressed ncRNAs can promote angiogenesis and EMT to enhance the metastasis of HCC and resist sorafenib. At the same time, they can also promote the expression of PD-L1 and IL-10 through PI3K/Akt and other pathways, inhibit the function of immune cells such as T cells, and lead to immune escape.

Exosomal miRNAs involved in inhibiting the body's immune function against hepatocellular carcinoma

It has been found that exosomes secreted by tumor cells can be transferred to targeted cells, such as macrophages and so on. They induce immune cell death by activating the programmed death ligand 1 (PD-L1)/PD-1 pathway and producing immunosuppressive factors (VEGF, IL-10, PGE(2)) and other mechanisms [40, 41]. Therefore, immunotherapy against exosomes may be a promising strategy to combat HCC.

Macrophages are key participants in the innate immune response. They can swallow pathogens and apoptotic cells. They also act as antigen presenting cells (APC) to present antigens to adaptive immune cells. Macrophages can be polarized into classic (M1) or alternative (M2) phenotypes. M1 macrophages show antineoplastic activity, while M2 macrophages have tumorigenic effects [42]. Therefore, the exosomes secreted by HCC cells often affect macrophages to reshape the tumor microenvironment and help it escape immune surveillance. Liu et al. showed that exosomes secreted by HCC cells under endoplasmic reticulum stressed are rich in miR-23a-3p. These exosomes can transfer miR-23a-3p to macrophages. MiR-23a-3p inhibits PTEN's expression, activates protein kinase B (AKT), up-regulates the expression of PD-L1, and then reduces the proportion of CD8 + T cells and induces T cell apoptosis through the PD-L1/PD-1 pathway (**Figure 2**). This help HCC escape from immune surveillance [43]. Also, miR-146a-5p is an important mediator involved in the polarization of macrophages to M2. miR-146a-5p transferred to macrophages downregulate the known miR-146a targets, STAT1 and TRAF6, and their downstream signaling pathways [44]. This will weaken the ability of antigen presentation in macrophages, promote the polarization of macrophages to M2, and inhibit the anti-HCC function of T cells [42]. IL-10 is one of the important regulators of the immune system. It mediates the negative regulation of the maturation and activation of macrophages and dendritic cells, as well as the inhibition of T cell activation. The elevated levels of miR-4661-5p in serum exosomes can compete with tristetraprolin, an RNA-binding protein (RBP) that mediates the rapid degradation of IL-10 mRNA to combine with the IL-10 3'untranslated region AU-rich elements in TLR-triggered macrophages. This can prevent the degradation of IL-10 mRNA mediated by tristetraprolin, thereby increasing the level of IL-10 in HCC and inhibiting the body's anti-tumor immune function [45, 46] (**Figure 2**).

T cells also play an important role in the body's immune system against hepatocellular carcinoma. In particular, the transcription factor Sal-like protein-4 (SALL4) can bind to the miR-146a-5p promoter and directly lead to its overexpression in HCC-derived exosomes. Then miR-146a-rich exosomes enter T cells, repress NF-κB activators TNF receptor associated factor 6 (TRAF6) and Interleukin-1 receptor-associated kinase 1 (IRAK1) to down-regulate Nuclear factor κB (NF-κB) activation [47]. This inhibits the activation of T cells. Moreover, blocking the interaction between SALL4 and miR-146a-5p can reduce the expression of inhibitory receptors PD-1 and CTLA4 on T cells in HCC mice, reversing the exhaustion of T cells and delay the progression of HCC. Therefore, targeting SALL4 to influence exosomal miR-146a-5p may be an effective method for the treatment and diagnosis of HCC [48].

In addition to macrophages and T cells, the function of natural killer cells can also be affected by exosomes. HCC-derived exosomes transfer miR-92b to NK cells. By inhibiting the expression of the activation marker CD69 on NK cells, NK cell-mediated cytotoxicity is down-regulated, leading to immune escape. But in fact, miR-92b has many potential target mRNAs needed further research [49].

Exosomal miRNAs involved in regulating the proliferation and metastasis of hepatocellular carcinoma

The expression levels of multiple miRNAs detected in exosomes isolated from HCC cells are significantly different from those of the source cells. And these miRNAs can regulate a variety of targeted molecules, play the role of oncogenes or tumor suppressor genes, and affect the proliferation and metastasis of hepatocellular carcinoma.

p53 was found to be a tumor suppressor and it is regulated by a variety of miRNAs. Highly expressed exosomal miR-1228 in HCC patients can directly target p53 3'UTR and inhibit the expression of p53. The decrease of p53 leads to the acceleration of the cell cycle process and promotes the proliferation and migration of HCC [50]. miR-222 targets protein phosphatase 2A subunit B (PPP2R2A). The overexpression of miR-222 in HCC may enhance the metastasis of HCC by activating the AKT signaling pathway [51]. Overexpressed miR-367 inhibits PTEN and enhances the proliferation and invasiveness of HCC cells [52]. In addition, overexpression of miR-18a inhibits the downstream molecule Bcl2L10. This will promote the proliferation and invasion of HCC [53].

miR-520f decreases in HCC, leading to the up-regulation of the target Transmembrane-4 L-Six family member-1 (TM4SF1). This promotes the proliferation and invasion of HCC [54]. Down-regulation of miR-517c increases the expression of Pyk2 and promotes the proliferation of HCC [55]. The expression of miR-451 mentioned above is also reduced, which makes another target IKBKB rise, ensuring that the nuclear factor-kappa B (NF-κB) pathway which promots the proliferation of HCC cells is not inhibited [56]. Moreover, miR-133b is significantly down-regulated in HCC, and its low-level expression is significantly related to the proliferation and invasion of HCC. It has been found that miR-133b may inhibit the growth and metastasis of HCC by targeting LASP1, Sirt1 and TONSL [57-59]. The down-regulation of miR-376a may reduce HCC cell apoptosis and promote HCC proliferation by targeting p85α [60]. In addition, miR-519d is down-regulated in HCC, leading to the up-regulation of the target gene MKi67 and Rab10, which promotes the proliferation of HCC cells [61, 62]. Although the miRNAs described in this paragraph which play the role of inhibitors of HCC are down-regulated in HCC, their expression levels in exosomes are completely opposite to those in HCC. What role they are highly expressed in exosomes needs to be further studied [63].

Exosomal miRNAs as diagnostic and prognostic biomarkers

Many studies have confirmed that the level of miRNAs in serum exosomes of HCC patients is different from healthy people, and the imbalance is related to the clinical features of liver cancer, including tumor stage, size and survival rate. It is reported that the expression of miRNA-638, miR-335, miR-125b and miR-320d is down-regulated in HCC patients, which promote the proliferation and invasion of HCC, predicting a poor prognosis [64-67]. On the other hand, the levels of miR-103, miR-93, miR-106a, miR-518d, miR-584, miR-215, miR-142-5p, miR-378 and miR-224 are significantly higher in HCC patients than those of healthy people. Their upregulation can promote the proliferation and invasion of hepatocellular carcinoma [13, 63, 68-71]. Detecting the level of miRNAs in serum is less harmful to the human body and is easy for early diagnosis. So they are ideal biomarkers for diagnosis and prognosis of HCC. However, the targeted genes and molecular mechanisms of miRNAs in the exosomes mentioned above that affect the occurrence and development of HCC have not yet been discovered, which also provides a direction for us to continue research.

lncRNAs in exosomes secreted by HCC

Long non-coding RNAs, exceeding 200 nucleotides (nt) in length, are a subtype of non-protein coding transcripts [72]. The main mechanism of action is to interact with DNA, RNA or protein, and regulate gene expression at multiple levels, including chromatin, transcription, post-transcription and translation [6]. Studies have found that exosomal lncRNAs are a key determinant of the development of liver cancer. In the exosomes secreted by HCC, lncRNAs mainly act as a sponge of miRNAs by competitively binding to miRNAs in the targeted cells to down-regulate their expression and function, resulting in enhanced expression of target genes. This promotes the proliferation and metastasis of HCC. The differentially expressed-lncRNA RP11-85G21.1 (lnc85) in exosomes can act as a sponge of miR-324-5p, which in turn may lead to increased migration and invasion by regulating the expression of MMP2, MMP9, ETS1 and SP1 in HCC [73, 74] (**Figure 1**). Exosomal lncRNAs can be used as sensitive and non-invasive biomarkers for diagnosis and prognosis since they can remain stable in serum and exhibit unique expression characteristics that reflect the characteristics of cancer cells [75]. We summarized the current status of research on the functions and molecular mechanisms of exosomal lncRNAs in the development of hepatocellular carcinoma (**Table 2**).

Exosomal lncRNAs involved in regulating the proliferation of hepatocellular carcinoma

It has been reported that serum exosomal lncRNA FAL1 which is transferred by exosomal to targeted cells and down-regulate miR-1236 whose targeting molecule is AFP was significantly up-regulated in HCC. And overexpressed AFP can promote the G1/S transition of the cell cycle and promote the proliferation of HCC cells [72, 76] (**Figure 1**). In addition to affecting AFP, exosomes can also transfer lncRNA highly upregulated in liver cancer (HULC). LncRNA HULC binds to DNA methyltransferase and inhibits the expression of miR-9 in endothelial cells, inhibiting the expression of TNF-α, which inhibits apoptosis and promotes the proliferation of HCC cells [77] (**Figure 1**). Interestingly, exosomal long non-coding RNA SENP3-EIF4A1 in the plasma of patients with HCC is reported to significantly reduce. And it can protect zinc finger protein 36 (ZFP36) through competitive binding with miR-9-5p in HCC cells, stimulating-cell apoptosis, and hindering the proliferation of HCC cells (**Figure 1**). So, the transfer of exosomal SENP3-EIF4A1 secreted by normal cells to HCC cells can inhibit apoptosis and the metastatic abilities of HCC cells [78]. Long noncoding RNA (lncRNA) H19 overexpressed in exosomes up-regulates LIMK1 via sponging miR-520a-3p. This will inhibit the apoptosis of HCC cells and promote the proliferation of HCC [79]. Besides, lncRNA TUC339 is highly expressed in HCC-derived exosomes. By transfecting HCC cells with TUC339 expression vector or empty vector control, it was found that HCC cells transfected with TUC339 expression vector grew more than HCC cells transfected with empty vector control. It indicates that lncRNA TUC339 promotes the growth of HCC cells [80]. These findings provide new insights into the role of exosomal lncRNAs in the pathogenesis of HCC, and are expected to serve as a potential diagnosis or treatment strategy for HCC.

Exosomal lncRNAs involved in regulating the metastasis of hepatocellular carcinoma

There is increasing evidence that epithelial-mesenchymal transition (EMT) contributes to tumor metastasis and recurrence, including those involving HCC. And ZEB1 (zinc finger E-box binding homeobox 1) is one of the transcription factors that can enhance EMT. LncRNA HULC can play the role of competing endogenous RNA (ceRNA) between HCC cells through exosomal transfer, which isolates miR-200a-3p, up-regulates ZEB1, enhances EMT, and promote the metastasis of HCC cells [81] (**Figure 2**). Studies have also found that the lncRNA-ATB can upregulate ZEB1 by competitively binding to the miR-200 family in HCC cells, and then induces EMT. Moreover, lncRNA-ATB can bind IL-11 mRNA, autocrine induction of IL-11, and trigger STAT3 signaling to promote organ colonization of disseminated HCC cells. Also it's reported that the high level of lncRNA-ATB in serum exosomesis positively associated with the poor prognosis of HCC patients. In short, circulating exosomal lncRNA-ATB can be a novel prognostic biomarker for HCC [82, 83]. The aforementioned exosomal lncRNA FAL1

Table 2. lncRNAs involved in pathways affecting HCC

lncRNA	Target gene	Up or down	Cancer promotion or suppression	Function	Mechanism	Refs
lnc85	miR-324-5p	up	cancer promotion	promote the proliferation and invasion of HCC	sponge miRNAs	[73, 74]
LINC00161	unknown	up	cancer promotion	promote the proliferation and invasion of HCC	unknown	[85]
ENSG00000248932.1	unknown	up	cancer promotion	promote the proliferation and invasion of HCC	unknown	[86]
ENST00000440688.1	unknown	up	cancer promotion	promote the proliferation and invasion of HCC	unknown	[86]
ENST00000457302.2	unknown	up	cancer promotion	promote the proliferation and invasion of HCC	unknown	[86]
lncRNA-ROR	unknown	up	cancer promotion	promote the proliferation and invasion of HCC	reduce chemotherapy-induced cell death	[87]
lncRNA-VLDLR	unknown	up	cancer promotion	promote the proliferation and invasion of HCC	reduce chemotherapy-induced cell death	[88]
ENSG00000258332.1	unknown	up	cancer promotion	promote the proliferation and invasion of HCC	unknown	[89]
LINC00635	unknown	up	cancer promotion	promote the proliferation and invasion of HCC	unknown	[89]
lncRNA TUC339	unknown	up	cancer promotion	promote the proliferation and metastasis of HCC	unknown	[80]
lncRNA FAL1	miR-1236	up	cancer promotion	promote the proliferation and metastasis of HCC	sponge miRNAs	[72, 76]
lncRNA HULC	miR-9	up	cancer promotion	promote the proliferation of HCC	sponge miRNAs	[77]
	miR-200a-3p	up	cancer promotion	promote the metastasis of HCC	sponge miRNAs	[81]
lncRNA SENP3-EIF4A1	miR-9-5p	down	cancer suppression	inhibit the proliferation of HCC	sponge miRNAs	[78]
long noncoding RNA (lncRNA) H19	miR-520a-3p	up	cancer promotion	promote the proliferation of HCC	sponge miRNAs	[79]
lncRNA-ATB	miR-200	up	cancer promotion	promote the invasion of HCC	sponge miRNAs	[82, 83]
HCC-associated long noncoding RNA (HANR)	miR-296	up	cancer promotion	promote the invasion and metastasis of HCC	sponge miRNAs	[84]

sponges miR-1236 in HCC cells, enhancing the expression of ZEB1, and EMT (**Figure 2**). And lncRNA FAL1 can be transferred between HCC cells through exosomes to promote the metastasis of HCC [72]. Besides, exosomal HCC-associated long noncoding RNA (HANR) and directly sponges miR-296, which down-regulates the expression of miR-296 and increases the expression level of VEGF in human dermal lymphatic endothelial cells (HDLEC) (**Figure 2**). This promotes the lymphangiogenesis of hepatocellular carcinoma and also promotes the metastasis of hepatocellular carcinoma [84]. The long noncoding RNA (lncRNA) H19 overexpressed in the exosomes mentioned above can also promote the transfer of HCC [79]. Therefore, these findings indicate that exosomal lncRNAs are capable of promoting the matastasis of HCC the and may become a potential target for anti-metastatic therapy.

Exosomal lncRNAs as diagnostic and prognostic biomarkers

Like miRNAs, most of the current studies on the exosomal lncRNAs secreted by HCC only involve the imbalance of serum exosomal lncRNAs levels and the mortality of patients with HCC and tumor size and severity. This proves that they have the potential to be used as diagnostic and prognostic biomarkers, but the targeting molecules and mechanisms have not been fully studied. In addition to lncRNAs we mentioned before, LINC00161, ENSG00000248932.1, ENST00000440688.1, ENST00000457302.2, lncRNA-ROR, ENSG00000258332.1, LINC00635 and lncRNA-VLDLR in exosomes of patients with HCC are up-regulated, which can be used as potential biomarkers to predict tumor occurrence [85-89]. Although the above-mentioned exosomal lncRNAs have the potential to be tools for early diagnosis and screening of HCC, their targets and mechanisms in the development of HCC have not been fully studied. Therefore, a more in-depth study of their targets and mechanisms is needed to develop biomarkers for early diagnosis and prognosis of HCC.

circRNAs in exosomes secreted by HCC

Circular RNA is a new type of non-coding RNA, a type of naturally occurring RNA, synthesized by “head-to-tail” splicing coding or non-coding RNA (ncRNA), which is more stable in vivo than related linear mRNA [90, 91]. There is increasingevidence that exosomal circRNAs can regulate tumor progression through various mechanisms such as sponging miRNAs, regulating protein binding, or acting as transcription regulators [6, 90, 92-94]. Exosomal circRNAs are also a key factor in tumor development which can be used as predictors and potential therapeutic targets for HCC. Yanwei Luo et al. reported the up-regulation of circulating exosomes circAKT3 in HCC, and have confirmed that the high expression of circAKT3 is positively correlated with the risk of recurrence and mortality of HCC. But the related mechanism is not yet clear [95]. It has been confirmed that HCC exosomal circRNAs are capable of inhibiting the expression and function of specific miRNAs through competitive binding, which leads to increased expression of target genes [90, 96], or directly binding to the corresponding RNA-binding protein, causing abnormal expression of gene products. Other possible mechanisms such as exosomal circRNAs as transcriptional regulators need to be further studied. In short, exosomal circRNAs can participate in cell proliferation, migration, invasion and metastasis, and apoptosis through the above-mentioned mechanisms which indicate that they are likely to play an important role in the development of HCC [90]. We summarized the current status of research on the functions and molecular mechanisms of exosomal circRNAs in the development of hepatocellular carcinoma (**Table 3**).

Exosomal circRNAs involved in regulating the proliferation of HCC

The cell cycle is a complex sequence of events. The cell repeats its content and divides through this event, and involves many regulatory proteins, including cyclins and cyclin-dependent kinases, oncogenes and tumor suppressor genes, and mitotic checkpoint proteins [97]. More and more evidences have shown that exosomal circRNAs can indirectly affect these regulatory proteins by targeting miRNAs, which in turn makes the cell cycle process dysregulated and ultimately leads to the abnormal proliferation of hepatocellular carcinoma cells.

CircRNA_100284 was significantly up-regulated in arsenite-transformed cancerous liver cells and transferred to normal liver cells through exosomes. It up-regulates the level of EZH2, a possible proliferation biomarker, and

Table 3. circRNAs involved in pathways affecting HCC

lncRNA	Target gene	Up or down	Cancer promotion or suppression	Function	Mechanism	Refs
circAKT3	unknown	up	cancer promotion	recurrence of HCC	unknown	[95]
circRNA_100284	miR-217	up	cancer promotion	promote the proliferation of HCC	sponge miRNAs	[98]
circRNA deubiquitination (circ-DB)	miR-34a	up	cancer promotion	promote the proliferation of HCC	sponge miRNAs	[96]
circRNA Cdr1as	miR-1270	up	cancer promotion	promote the proliferation of HCC	sponge miRNAs	[99]
circ-ZNF652	miR-29a-3p	up	cancer promotion	promote the proliferation of HCC	sponge miRNAs	[100]
circTMEM45A	miR-665	up	cancer promotion	promote the proliferation of HCC	sponge miRNAs	[101]
circ_0061395	miR-877-5p	up	cancer promotion	promote the proliferation and metastasis of HCC	sponge miRNAs	[102]
circ-0051443	miR-331-3p	down	cancer suppression	inhibit the proliferation of HCC	sponge miRNAs	[103]
circRNA-100338	miR-141-3p	up	cancer promotion	promote the metastasis of HCC	sponge miRNAs	[105]
	NOVA2	up	cancer promotion	promote the metastasis of HCC	bind protein	[106]
circPTGR1	miR449a	up	cancer promotion	promote the metastasis of HCC	sponge miRNAs	[10]
circFBLIM1	miR-338	up	cancer promotion	promote the metastasis of HCC	sponge miRNAs	[107, 108]
circ_MMP2	miR-136-5p	up	cancer promotion	promote the metastasis of HCC	sponge miRNAs	[109]
circular ubiquitin-like with PHD and ring finger domain 1 RNA (circUHRF1)	miR-449c-5p	up	cancer promotion	immune escape	sponge miRNAs	[110, 111]

cyclin-D1 in hepatocytes by sponging miR-217, and regulates the transition from G1 to S phase, accelerating cell cycle and cell proliferation [98] (**Figure 1**). CircRNA deubiquitination (circ-DB), which can indirectly up-regulate ubiquitin-specific protease 7 (USP7) through sponging miR-34a, was up-regulated in exosomes secreted from adipose tissue in HCC patients with high body fat ratio. The up-regulated USP7 drives the cell cycle process and promotes the proliferation of HCC by reducing the ubiquitination of many proteins including cyclin A2 [96] (**Figure 1**). CircRNA Cdr1as transfers directly from HCC cells to surrounding normal cells through exosomes, and acts as ceRNA, sponging miR-1270 to up-regulate AFP. As mentioned above, the over-expressed AFP can promote the G1/S transition of the cell cycle and promote the proliferation of HCC cells [99]. The exosomal circ-ZNF652 was up-regulated in HCC patient serum and HCC cells. Circ-ZNF652 silences miR-29a-3p to overexpress the target gene GUCD1 of miR-29a-3p. This will promote the proliferation of HCC [100]. CircTMEM45A is up-regulated in serum exosomes and HCC cells of HCC patients. CircTMEM45A up-regulates IGF2 by acting as a miR-665 sponge, thereby promoting the progress of HCC [101]. Circ_0061395 is up-regulated in HCC tissues and serum exosomes. Circ_0061395 up-regulates the expression of PIK3R3 by inhibiting miR-877-5p, thereby promoting the proliferation of HCC [102]. In contrast, circ_0051443 in plasma exosomes of patients with HCC is significantly lower than that of healthy people. Circ_0051443 mediates the up-regulation of BRI1-associated kinase1 (BAK1) by competing with miR-331-3p to promote cell apoptosis and prevent cell cycle to inhibit the proliferation of HCC [103] (**Figure 1**).

Exosomal circRNAs involved in regulating the metastasis of HCC

Studies have confirmed that exosomes communicate with nearby or distant cells by transferring circRNAs horizontally to recipient cells, thereby affecting cancer metastasis [104]. CircRNA-100338 is highly expressed in advanced metastatic HCC and exosomes secreted by HCC cells than in HCC with low metastasis. It directly targets miR-141-3p in HCC cells, and currently believed that metastasis suppressor 1 (MTSS1), one of the downstream genes of miR-141-3p, in HCC cells may be a potential target. circRNA-100338 may affect MTSS1 of HCC cells by down-regulating miR-141-3p which ultimately leads to an increase in the metastasis capacity of HCC (**Figure 2**). Besides, exosomal circRNA-100338 can be ingested by human umbilical vein endothelial cells (HUVECs) where it can be directly combined with NOVA2, an RNA binding protein that can regulate vascular development and luminal formation, to regulate angiogenesis, thereby promoting the transfer of HCC [105, 106]. In addition to circRNA-100338, circPTGR1 is also up-regulated in serum exosomes of HCC patients with high metastasis. While co-cultivating with higher metastatic HCC cells, it has been reported that HCC cells with lower or no metastatic potential gain metastatic abilities via exosomes with circPTGR1 which competes for binding to miR449a in HCC cells, which increases MET, thereby enhancing the metastatic ability of HCC [10] (**Figure 2**). CircRNA filamin binding LIM protein 1 (circFBLIM1) is a sponge of miR-338, leading to overexpression of low-density lipoprotein receptor-related protein 6 (LRP6). Overexpression of LRP6 contributes to the excessive activation of Wnt/β-catenin signaling pathway in human HCC cells. This will enhance the metastasis and invasion of HCC [107, 108]. Circ_MMP2 in exosomes secreted by highly metastatic HCC cells up-regulates matrix metallopeptidase 2 (MMP2), a metastasis-related protein that can promote the metastasis of HCC, by sponging miR-136-5p in HCC cells with lower or no metastatic potential [109] (**Figure 1**). In addition, the aforementioned circ_0061395 is up-regulated in HCC tissues and serum exosomes, inhibiting miR-877-5p to up-regulate the expression of PIK3R3, thereby promoting the metastasis of HCC [102]. In short, studying the role of exosomal circRNAs in HCC metastasis is necessary to discover new therapeutic strategies.

Exosomal circRNAs involved in immune suppression

High levels of circular ubiquitin-like with PHD and ring finger domain 1 RNA (circUHRF1) in plasma exosomes of patients with HCC have been reported to be associated with the decrease in the proportion of NK cells. HCC-derived exosomes deliver circUHRF1 to NK cells and up-regulate the expression of TIM-3, one of the main inhibitory receptors for natural killer (NK) cells [110], by sponging miR-449c-

Table 4. ncRNAs in serum or tumer as diagnostic and prognostic biomarkers in clinical practice

ncRNAs	up or down in serum exosomes	up or down in HCC tissue	Ref
miR-21	up	up	[19, 20]
miR-210	up	up	[24]
miR-744	down	down	[29]
miR-4661-5p	up	up	[45]
miR-146a-5p	up	up	[48]
miR-92b	up	up	[49]
miRNA-638	down	down	[64]
miR-125b	down	down	[66]
miR-320d	down	down	[67]
miR-103	up	up	[13]
miR-93	up	up	[68]
miR-224	up	up	[70]
lnc85	up	up	[74]
lncRNA FAL1	up	up	[72]
long non-coding RNA SENP3-EIF4A1	down	down	[78]
lncRNA-ATB	up	up	[82]
LINC00161	up	up	[85]
ENSG00000248932.1	up	up	[86]
ENST00000440688.1	up	up	[86]
ENST00000457302.2	up	up	[86]
ENSG00000258332.1	up	up	[89]
LINC00635	up	up	[89]
circ_0061395	up	up	[102]
circ-0051443	down	down	[103]
circRNA-100338	up	up	[105]
circPTGR1	up	up	[10]
circFBLIM1	up	up	[107]
circUHRF1	up	up	[111]

5p, inhibiting the production and release of IFN-γ and TNF-α of NK cells which eventually promotes immune escape [111]. At present, there are few reports on the relationship between HCC-related exosomes circRNAs and immune cell functions. Therefore, the relationship between other immune cells and circRNAs needs further study.

Conclusion

Exosomal ncRNAs secreted by HCC have been reported relevant with the proliferation, metastasis, drug resistance, and immune escape of HCC. In this review, we summarized the current status of research on the functions and molecular mechanisms of exosomal ncRNAs in the development of hepatocellular carcinoma (**Tables 1-3**). Several studies have found that the levels of exosomal ncRNAs in HCC patients' plasma and/or liver cells will be significantly dysregulated. Differentially expressed exosomal ncRNAs are related to clinical characteristics such as mortality and tumor stage. ncRNAs, protected by exosomes, are not easily degraded. They are stably expressed in body fluids such as serum, and are easy to collect, which is helpful for early diagnosis of hepatocellular carcinoma [67, 68, 82, 85]. Therefore, exosomal ncRNAs are one of the most promising biomarkers for early diagnosis of HCC in the future. We summarize the ncRNAs in serum or tumer as diagnostic and prognostic biomarkers in clinical practice in one table (**Table 4**). Besides, exosomes can help biologically active substances escape the clearance by the macrophages to improve their biological activity, and exosomes from normal cells had lower immunogenicity and better tolerance than other artificial drug carriers [112, 113]. So, the ability of exosomes to carry biologically active substances into targeted cells has also attracted the attention of many researchers. We believe that by changing the types and contents of biologically active substances carried by exosomes, biological effects can be targeted to inhibit tumor proliferation, metastasis, and improve drug resistance. However, the study of exosomal ncRNAs still faces many challenges. So far, the most widely used and reliable method to extract exosomes is hypercentrifugation [114], which may contain small extracellular vesicles or other components while extracting exosome. At the same time, normal cells in the body can also secrete exosomes. Therefore, how to extract exosomes from disease-specific sources remains to be solved. The lack of effective extraction limits the clinical application of ncRNAs in exosomes, though the change of the expression of ncRNAs commences earlier than the traditional biomarker AFP [112]. We have known that exosomes uptaken by recipient cells is cell-specific, the mechanism by which recipient cells and exosomes recognize each other is unclear. As a result, how to deliver exosomes containing specific biologically active substances to the targeted cells accurately is one of the major challenges while using exosomes as drug carriers [112, 115]. Other problems like off-target effects also exist. Due to the short study of exosomes, there is no specific report on it. Therefore, there are still many gaps in the research field of HCC-related exosomal ncRNA, especially its molecular mechanism.

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Disclosure of conflict of interest

None.

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