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Review

Exosome plays an important role in the development of hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most malignant cancers around the world. However, the early biomarkers for its detection and treatment are limited currently. Exosomes, classified as intercellular messenger shuttling their cargoes between cells, regulate cell differentiation and tissue development. They contain messenger RNA (mRNA), microRNA (miRNA), long non-coding RNA (lncRNA), circular RNA (circRNA), proteins, lipids and transcription factors. Therefore, exosomes play a crucial role in the development of HCC. In this review, we highlight the exosomal cargoes which could serve as biomarkers for the prediction and diagnosis of HCC. Exosomes are involved in metastases of HCC and they show great potential in immunotherapy and drug resistance mechanism. In summary, exosome suggests new clues in clinical application of HCC.

1. Introduction

Hepatocellular carcinoma (HCC), one of the most malignant cancers worldwide, accounts for approximately 75%–85% of primary liver cancers (PLCs) [1]. Over the past decades, heavy alcohol intake, obesity, smoking and type-2 diabetes became several major risk factors of HCC [2,3]. Patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection have a high probability to develop into HCC patients [4]. The overall incidences and mortality rates of HCC are still high. Five year survival rates for patients diagnosed with HCC is 6% and HCC carries an unfavorable prognosis with aggressive growth behavior and a high rate of recurrence [1,5,6]. Moreover, etiological heterogeneity of HCC leads to a challenge for designing clinical trials [7]. Classical chemotherapy and radiotherapy have limited effect on HCC and shown on more than two thirds of HCC patients who have experienced advanced stages [8,9]. In the past decades the serum α-fetoprotein (AFP) is widely used for early detection of HCC, but increased level of AFP has also been shown in large disease, such as acute viral hepatitis A (AHA) [10,11]. Dual phase CT scan and MRI show high diagnostic value only when the nodules are larger than 1–2 cm [12]. Thus, it is necessary to render specific and early biomarkers to detect HCC. Furthermore, in order to find more optimal therapies for HCC, a better understanding of progression of HCC is urgently required.

Extracellular vesicle (EV) is one of major targets for liquid biopsy. EVs include exosomes, microvesicles (MVs), ectosomes and apoptotic bodies [13], among which exosomes exist in a wide range of biofluids, such as serum, pregnancy-associated serum, plasma, tears, saliva, urine, breast milk, semen, malignant pleural effusions, synovial fluid, bronchial lavage fluid, amniotic fluid and nasal lavage fluid [14]. Exosomes are classified as intercellular messengers shuttling cargoes between cells, regulating cell differentiation and tissue development [15,16]. Emerging evidence has shown exosomes are associated with tumor tumorigenesis, progression, pre-metastatic niches and metastasis [17,18]. Additionally, exosomes regulate different pathophysiological conditions and influence the treatment outcome [19]. The rich and biologically active contents of exosomes are being identified as biomarkers and potential targets for exosome-based therapy [20]. Exosomes have been confirmed to be involved in various diseases, for example, lung cancer, gastric cancer and HCC [21–24]. In this review, we summarized the function of exosome in HCC, which might suggest certain new clues in diagnosis and treatment of HCC.

2. Structure, biogenesis and secretion of exosome

Exosomes, 30–100 nm in diameter and 1.13–1.19 g/mL in density [25–27], are firstly discovered in sheep reticulocyte maturation [28]. Exosomes presents cup-shaped morphology after negative staining or delimited round when observed via transmission and cryo-electron microscopy [29]. Exosome contains messenger RNA (mRNA), microRNA (miRNA), long non-coding RNA (lncRNA), circular RNA (circRNA), proteins, lipids and transcription factors [30]. They transmit signals from donor cells to recipient cells and exhibit strong effects on

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recipient cells [31,32].

Exosomes are formed as intraluminal vesicles (ILVs) by inward budding in the multivesicular bodies (MVBs) [33,34]. MVBs are formed during early to late endosome maturation. MVBs can fuse with lysosomes which leads to degradation of the contents, and they also fuse with plasma membrane, releasing the contents into the extracellular space as exosomes [35,36]. Several proteins play crucial roles in the biogenesis and secretion of exosomes. RAB GTPase proteins regulate intracellular vesicular trafficking, for instance, vesicle budding and mobility through cytoskeleton interaction. RAB GTPase proteins also mediate the docking of intracellular compartments, which leads to membrane fusion [37,38](such as RAB27A/B, RAB35 and RAB11) [39]. Following membrane docking, the soluble NSF-attachment protein receptor (SNARE) complex promotes the fusion of lipid bilayers [40,41]. The endosomal sorting complex required for the transport (ESCRT)-dependent pathway is also involved in exosome secretion. ESCRT complex is composed of ESCRT-0, -I, -II and -III. ESCRT-0 initiates the pathway of MVBs and recognizes ubiquitinated proteins. ESCRT-I and ESCRT-II contribute to the constriction of the budding neck of vesicle. ESCRT-III is hypothesized to be linked to membrane budding and vesicle scission [42–44]. These multiprotein complexes cooperatively work with ALIX, VPS4 and VTA1 contributing to the ubiquitination of proteins and the sorting of proteins into ILVs [45]. Additionally, Ca^{2+} is instrumental in regulating the fusion of secretory lysosomes with plasma membrane and elevated level of intracellular Ca^{2+} can stimulate exosome secretion [46,47] (Fig. 1).

3. Exosomal cargo serves as biomarkers in HCC

A growing number of studies has demonstrated that exosomal cargoes, such as mRNAs, miRNAs, lncRNAs and proteins could serve as diagnostic, prognostic and predictive biomarkers for liver cancer through their differential expression level.

4. Exosomal MicroRNA (miRNA)

miRNA, a subset of the short non-coding RNAs, regulate tumor progression by suppressing the expression of target mRNAs including oncogene and anti-oncogene. In recent studies, the expression levels of serum exosomal miRNAs have been measured. The level of serum exosomal miRNAs varied in different stage of HCC. A literature listed that the level of exosomal *miRNA-18a*, *miRNA-221*, *miRNA-222* and *miRNA-224* was remarkably higher while the level of *miRNA-101* was lower in serum of HCC patients compared to chronic hepatitis B (CHB) or liver cirrhosis (LC) patients. Besides, the level of exosomal *miRNA-106b*, *miRNA-122* and *miRNA-195* in serum was lower in HCC than that in CHB but exhibited no difference in LC [48]. Data suggested *miRNA-10b* and *miRNA-21* increased during the progression of HCC, whereas *miRNA-122* and *miRNA-200a* decreased in exosomes. More importantly, the outcome of receiver operating characteristics (ROC) analysis revealed that the combination of AFP, *miRNA-10b*, *miRNA-21*, *miRNA-122* and *miRNA-200a* yielded the highest AUC of 0.993, which could be considered as a superior strategy to diagnose HCC in early stage [49]. In addition, exosomal *miRNA-125b*, *miRNA-665*, *miRNA-21* and *miRNA-1247-3P* increased in serum, whereas *miRNA-638* and *miRNA-9-3p* decreased in serum and *miRNA-320* decreased in cancer-associated fibroblasts (CAFs) [50–55]. *miRNA-125b* levels were lower in HCC patients than that in CHB and LC patients. Additionally, the level of *miRNA-125b* in exosomes was significantly higher than that in the serum of HCC patients. The level of exosomal *miRNA-125b* level in serum was significantly associated with tumor proliferation, differentiation and TNM stages. HCC patients with lower level of exosomal *miRNA-125b* had shorter overall survival (OS) and recurrence rates. Therefore, exosomal *miRNA-125b* could serve as a promising prognostic marker for HCC patients [50]. The level of serum exosomal *miRNA-665* significantly increased in HCC patients suggesting a positive correlation with tumor size, clinical stage, local invasion and metastasis. Moreover, overexpression of exosomal *miRNA-665* exhibited a shorter survival time for HCC patients, which suggested exosomal *miRNA-665*'s role as a potential diagnosis and prognosis biomarker for HCC patients [51]. Exosomal *miRNA-21* was positively correlated with cirrhosis and advanced tumor stage. Besides, compared to serum *miRNA-21*, serum exosomal *miRNA-21* showed a higher sensitivity to HCC detection [52]. Furthermore, serum exosomal *miRNA-1247-3p* elevated in HCC patients. Higher level of serum exosomal *miRNA-1247-3p* suggested lung metastasis and a poor treatment outcome of HCC. *miRNA-1247-3p* was expected to be a diagnostic biomarker for HCC, especially for prediction of lung metastasis [53]. Serum exosomal *miRNA-638* was down-regulated in HCC patients, and lower levels of serum exosomal *miRNA-638* predicted a poor OS in HCC patient than those with higher levels.

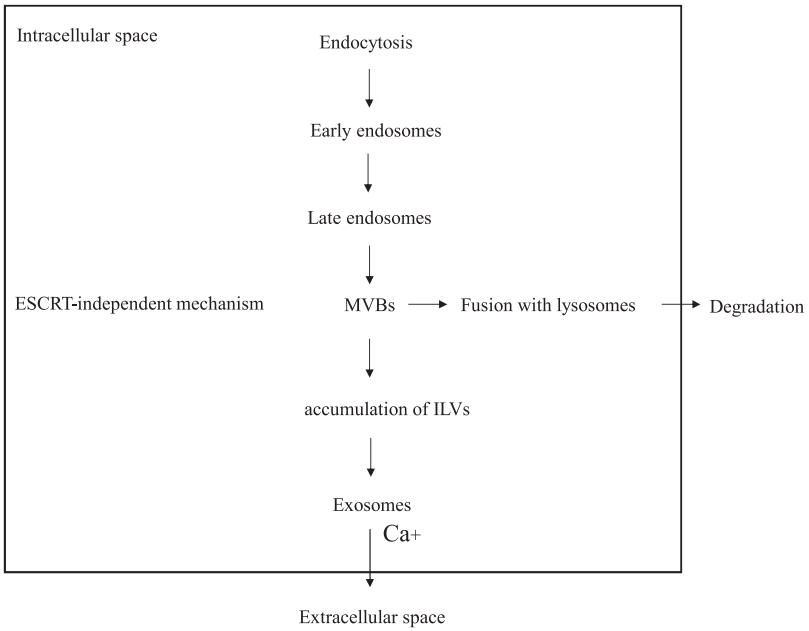

Fig. 1. The secretion progression of exosome.

miRNA-638 was thus a prognosis factor for HCC patients [54]. Exosomal *miRNA-9-3p* decreased in HCC and influenced cell proliferation by targeting fibroblast growth factor 5 (*HBGF-5*) which could be a potential therapeutic target of HCC [55]. After living donor liver transplantation (LDLT), *miRNA-718* remarkably decreased in HCC patients with recurrence compared to those without recurrence. However, only *miRNA-718* had a correlation with clinicopathological factors. The lower expression of *miRNA-718* showed poorer histological differentiation, higher incidence of tumor, and larger tumor size and number [56]. Results above showed that exosomal miRNAs could be novel biomarkers for diagnosis and predicting the recurrence and therapeutic strategy of HCC.

5. Exosomal long noncoding RNA (lncRNA)

The expression of *lncRNA-HEIH* increased both in plasma and exosomes of HCV-related HCC patients, HCV-induced cirrhosis patients compared with controls [57]. Besides, *lncRNA-FAL1* is up-regulated in the HCC tumor tissues, cells and serum exosomes directly targeting *miRNA-1236* [58]. Overall, *lncRNA-HEIH* and *lncRNA-FAL1* might be promising biomarkers to diagnose HCC. Exosomal *ENSG00000258332.1* and *LINC00635* in the HCC patients were significantly higher than those in controls. The high expression of *ENSG00000258332.1* was associated with TNM stage, portal vein tumor emboli, lymph node metastasis and OS. The high expression of *LINC00635* was related to TNM stage, lymph node metastasis and OS. *ENSG00000258332.1* could distinguish HCC from CHB, gaining a good area under the ROC curve (AUC) of 0.719 [59]. Exosomal *CASC9* and *LUCAT1* was up-regulated in a subset of HCC-derived cell lines and both were related to tumor size and recurrence after surgery of HCC patients, suggesting they might serve as putative, non-invasive prognostic biomarkers of recurrence [60].

6. Messenger RNA (mRNA)

Heterogeneous nuclear ribonucleoprotein H1 (*hnRNPH1*) extracted from the serum exosomes increased in HCC patients than that in controls. A higher level of exosomal *hnRNPH1* indicated a worse OS. Besides, its expression level was strongly relevant to the TNM stage, Child-Pugh classification, portal vein tumor emboli and lymph node metastasis. The results of ROC curve analysis implied *hnRNPH1* could discriminate HCC from CHB, especially when it combined with AFP [61].

7. Protein

The DNA methyltransferase inhibitor 5-Aza-CdR could enhance exosomes secretion and the concentration of exosomal total proteins, including immune-associated protein (HLA-I) and tumor-associated antigens (NY-ESO-1) by regulating *p53* expression [62]. Furthermore, experiments have demonstrated that motile HCC cells tend to secret more sugar metabolism regulatory proteins into the tumor microenvironment via exosomes. These proteins mediated glycolysis I, gluconeogenesis I and pentose phosphate pathways, reflecting the metabolism feature of HCC cells and differentiating motile cells from non-motile cells [63].

8. Function of exosome on progression of HCC

Exosomes were gradually recognized as critical regulators of cell-cell communication in cancer progression through delivering RNAs and proteins to neighboring or distant cells. The dysregulation of RNAs and proteins in cancer was associated with cancer proliferation, angiogenesis, metastasis and apoptosis. Exosomes derived from metastatic HCC cell lines contain a large number of pro-tumorigenic RNAs and proteins, such as MET proto-oncogene, caveolins and S100 family. They could be internalized by hepatocytes, and then remarkably promote the migration and invasion of non-motile hepatocytes through the activation of PI3K/AKT and MAPK signaling pathways and the overexpression of matrix metalloproteinase 2 (MMP-2) and MMP-9 [64]. Tumor-derived exosomes, which were enriched in MHC-I molecules and heat shock protein (HSPs), enhanced the antitumor activities of bone marrow stromal cells (BMSCs). BMSCs could promote migration of homologous hepatocellular carcinoma when pulsed with tumor-derived exosomes *in vitro* [65]. Lung metastasis occurred frequently in the long-distance invasion of HCC. In lung pre-metastatic niche, exosomal *miRNA-1247-3p*, which was released by high-metastatic HCC cells, down-regulated the expression of β-1,4-galactosyltransferases III (*B4GALT3*) in fibroblasts, resulting in activation of β1-integrin-NF-κB signaling and further promoting lung metastasis of liver cancer. The positive correlation of the high expression of serum exosomal *miRNA-1247-3p* with lung metastasis showed a promising prevention and therapeutic strategy for HCC patients [53]. *miRNA-335-5p* could be uptaken by HCC cell through exosomes released from fibroblasts. As a tumor suppressor in HCC, *miRNA-335-5p* inhibited growth, proliferation, invasion and enhanced apoptosis of HCC cells [66]. Cell growth and Transwell assays demonstrated that HCC cell-derived exosomes could promote proliferation and metastasis of HCC cell. Vps4A, a key regulator of exosome biogenesis, might serve as a tumor suppressor in HCC cells. It reduced the response of cells to exosomes, inhibited the bioactivity of exosomes and enhanced the excretion of exosomes' oncogenic miRNAs. More importantly, the PI3K/Akt signaling pathway was considered to be the most likely target pathway of Vps4A-related miRNAs [67]. Mast cells (MCs), which were enriched in the tumor microenvironment, promote tumor occurrence and development. MCs suppressed the metastasis of HCC cells through down-regulation of the ERK1/2 pathway via transferring the exosomal *miRNA-490* to HCC cells stimulated by the hepatitis C virus E2 envelope glycoprotein (HCV-E2), which suggested that exosomal *miRNA-490* is expected to a potential target for the biological therapy of HCC induced by HCV [68]. In addition, exosomal *miRNA-638*, *miRNA-9-3p*, *miRNA-320a* and *lncRNA-FAL1* all inhibited proliferation while *miRNA-665* promoted proliferation of HCC cells [54,55,58,69]. Negative correlation of serum exosomal *miRNA-638* with TNM stage, tumor size, and vascular infiltration was observed in HCC patients [70]. *miRNA-9-3p* reduced the expression of fibroblast growth factor 5 (*HBGF-5*) and extracellular signal-regulated protein 1 and 2 (*ERK1/2*), which played an important role in HCC cell proliferation [55]. *miRNA-320a* was transferred to HCC cells and then inhibited HCC cell proliferation, migration and metastasis by suppressing *PBX3* expression and MAPK pathway activation [69]. The proliferation, migration and invasion of HCC cells were remarkably enhanced by exosomes transmitting *lncRNA FAL1* to Huh7 and HepG2 cells [58]. Exosomes derived from HCC cells transferred Lysyl oxidase-like 4 (*LOXL4*) to human umbilical vein endothelial cells (HUVECs) according to a paracrine mechanism to promote angiogenesis [71]. Besides, *circPTGR1* was upregulated in serum exosomes derived from HCC patients and was associated with clinical stage and prognosis. Knockdown of *circPTGR1* suppressed the invasion and migration of HepG2 and 97 l cells as a result of co-culturing with LM3 exosomes [72].

Proteins also play significant roles in the development of HCC. Vasorin (VASN), a type I transmembrane protein had been confirmed to promote cell proliferation and migration. Experiments proved that VASN transported by HepG2-secreted exosomes effectively promoted HUVECs' migration, but not proliferation [73]. CD90 was involved in cell-to-cell and cell-matrix interaction, apoptosis, adhesion, migration, fibrosis and cancer development. Exosomes secreted by CD90+ liver cancer cells transferred *lncH19* to HUVEC leading to angiogenesis and promotion of cell-cell adhesion [74].

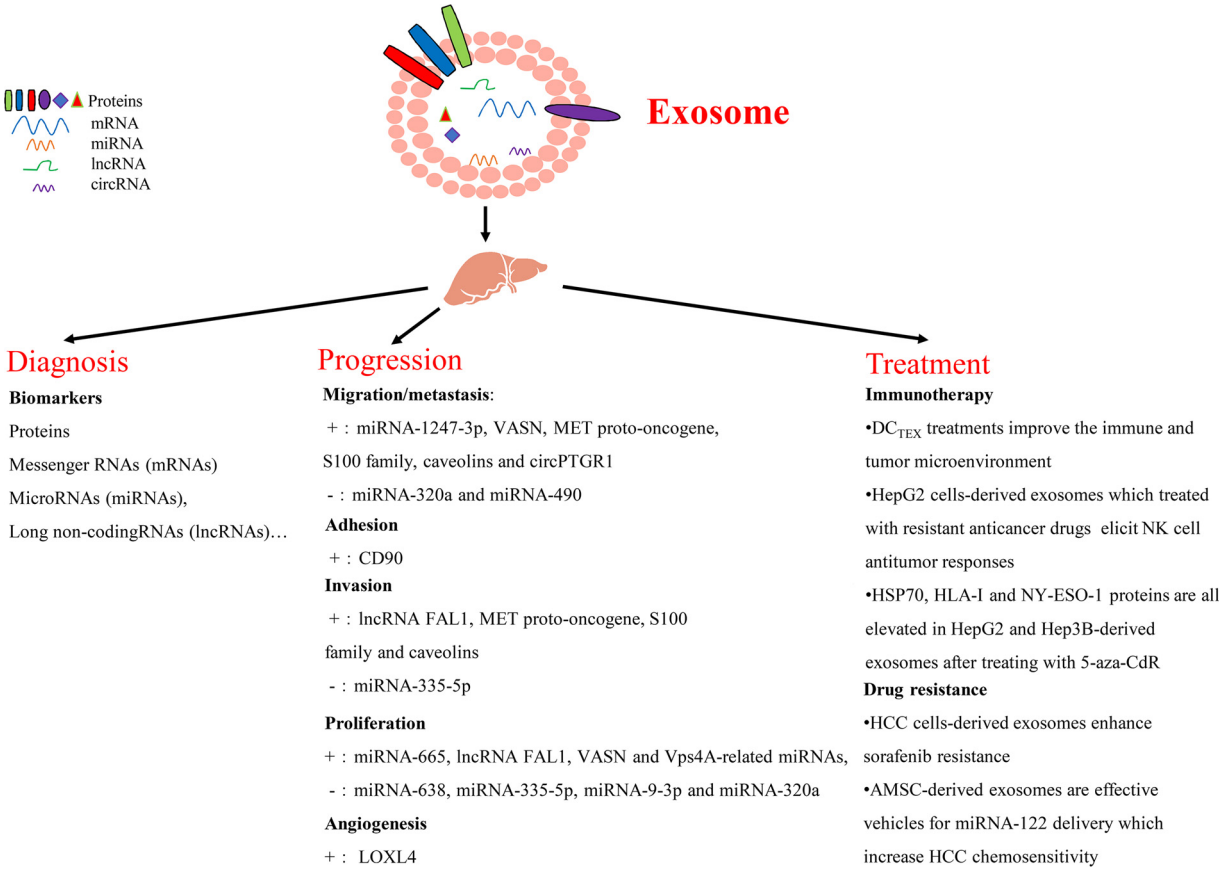

Fig. 2. Exosome plays critical roles in diagnosis, progression and treatment of HCC. +: Positive effect. -: Negative effect.

9. Treating application of exosome in HCC

9.1. Immunotherapy

The liver had a unique immune tolerogenic microenvironment which invoked great challenges for immunotherapy in HCC [75]. An increasing number of studies have demonstrated that exosome-derived interactions could regulate the tolerogenic and immunosuppressive microenvironment [76]. For example, exosomes were able to induce specific cytotoxic T lymphocytes *in vivo* and suppressed the growth of established murine tumors in a T cell-dependent manner [77]. Studies have demonstrated tumor cell-derived exosomes (TEXs) could potently carry HCC antigens to dendritic cells (DCs), leading to a stronger immune response than cancer cell lysates. TEX-pulsed DCs (DC$_{TEX}$) significantly suppressed tumor growth both in ectopic and orthotopic HCC mice compared with cell lysates-pulsed DCs. Additionally, in orthotopic HCC mice, DC$_{TEX}$ treatments improved the immune and tumor microenvironment by increasing interferon-γ and T lymphocytes and decreasing tumor growth factor-β and interleukin-10 in tumor sites [78].

Lv LH et al. found that resistant anticancer drugs (irinotecan hydrochloride or carboplatin) could elevate the secretion of exosomes derived from HepG2 cells compared with heat shock for 1.5 h and sensitive anticancer drugs (paclitaxel and etoposide) for 36 h. Resistant anticancer drugs stimulated the production of exosome-carried heat shock proteins (HSPs), which promoted cytotoxic response. Therefore, exosomes derived from HepG2 cells treated with resistant anticancer drugs elicited HSP-specific NK cell responses [79]. Meanwhile, epigenetic drug MS-275, a subset of histone deacetylase inhibitor (HDACi) drug, could enhance the non-specific immune response (cytotoxic effect of NK cells) of HepG2 cell-derived exosomes through up-regulating the expression of major histocompatibility complex (MHC) class I polypeptide-related sequence A (MICA), MICB and HSP70 [80]. These results provided new clues for HCC immunotherapy.

Aza-2′-deoxycytidine (5-Aza-CdR), a DNA demethylation promoter, significantly elevated the expression of immune molecules such as HLA-I and HLA-II [81]. The secretion of exosomes derived from HepG2 and Hep3B cells significantly increased after treated with 5-aza-CdR. HSP70, HLA-I and NY-ESO-1 proteins, which were required for anti-tumor cellular immunity [82–84], all elevated in these exosomes possibly by stimulating anti-tumor-specific immune response. These proteins might provide novel therapeutic vaccines options for HCC immunotherapy [62].

Additionally, evidences revealed that comparing to MV, exosomes induced a higher number of antigen-specific IgG and more efficient antigen-specific responses, and only exosomes triggered the antigen-specific CD8$^+$ T-cells and increased the proportions of germinal center B cells. These results suggested that different types of EV showed diverse immunostimulatory effects and we should focus on the specific immune therapeutic of each type [85].

9.2. Drug resistance

Exosomes derived from HCC cells enhanced sorafenib resistance of hepatoma cells *in vitro* through activating the HGF/c-Met/Akt pathway and reversed sorafenib-induced apoptosis in HCC cells. Moreover, highly invasive HCC cell-derived exosomes had a greater effect on reversing sorafenib-induced apoptosis compared with those less invasive HCC cell-derived exosomes [86].

Exosomes derived from mesenchymal stem cells (MSCs) exhibited an excellent capability of stem cell-based therapy [27,87]. Adipose tissue-derived MSCs (AMSCs) packaged *miRNA-122* into secreted exosomes then exosomes delivered *miRNA-122* into HCC cells *in vitro* mediating the communication between AMSCs and HCC cells. Moreover, *miRNA-122*-modified AMSCs-derived exosomes enhanced the

Table 1
The change and function of exosomal cargoes in HCC.

Cargoes	Change	Source of exosome	Function	Number of samples	Ref.
miRNA-18a, miRNA-221, miRNA-222, miRNA-224 miRNA-101, miRNA-106b, miRNA-122, miRNA-195	Up Down	Serum	Discriminate HCC from CHB or LC	CHB (n = 20), LC (n = 20), HCC (n = 20)	[48]
miRNA-10b, miRNA-21 miRNA-122, miRNA-200a	Up Down	Serum	Diagnose HCC in early stage combining with circulating miRNAs and AFP	Male fisher 344 rats (n = 108)	[49]
miRNA-125b	Up	Serum	Discriminate HCC patients with high risk of recurrence and poor prognosis	Cohort 1: CHB (n = 30), LC (n = 30) and HCC (n = 30) Cohort 2: HCC (n = 128)	[50]
miRNA-665	Up	Serum/Cell culture supernatants (MHCC-97H, MHCC-97 l and LO2 cell lines)	A novel invasive biomarker for HCC diagnosis and prognosis	HCC (n = 30)	[51]
miRNA-21	Up	Serum	Higher sensitivity to diagnose HCC than that in whole serum	HCC (n = 30), CHB (n = 30) and Healthy volunteers (n = 30)	[52]
miRNA-1247-3p	Up	Serum/Cell culture supernatants (HepG2, CSQT-2, MHCC-97 L, HCC-LM3 and SMMC-7721 cell lines)	Provide potential targets for prevention and treatment of HCC metastasis	HCC (n = 85)	[53]
miRNA-638	Down	Serum	Predict a poor prognosis for HCC patient	HCC (n = 126), Healthy controls (n = 21)	[54]
miRNA-9-3p	Down	Serum/ Cell culture supernatants (SMCC7721, HepG2 and QGY-7703 cell lines)	A potential therapeutic target for HCC	HCC (n = 30) and Normal donors (n = 10)	[55]
miRNA-718	Down	Serum	A novel biomarker for HCC recurrence	HCC patients who underwent liver transplantation (n = 59)	[56]
lncRNA-HEIH	Up	Serum	Discriminate and diagnose HCC from CHB or LC	HCV-induced cirrhosis and HCV-related HCC (the number is unknown)	[57]
lncRNA-FAL1	Up	Serum/Cell culture supernatants (LO2, SMMC-7721, Huh7, HepG2 and HepG2.2.15 cell lines)	A new diagnostic biomarker or a novel treatment target for HCC	HCC (n = 30)	[58]
lncRNAENSG00000258332.1, lncRNA LINC00635	Up	Serum	Distinguish HCC from CHB	HCC (n = 60) and CHB (n = 96)	[59]
lncRNACTD-2116N20.1, lncRNA RP11-538D16.2	Up	Serum	Prognostic biomarkers of recurrence	HCC (n = 32) and CHB (n = 28)	[60]
hnRNPH1	Up	Serum	Diagnose HCC patients and predict HCC prognosis in high HBV prevalence areas	HCC(n = 88), LC(n = 67) and CHB(n = 68)	[61]
5-aza-CdR relative miRNAs and proteins	Up	Cell culture supernatants (HepG2, Hep3B cell lines)	Provide new cancer therapeutic strategies for HCC	Not mentioned	[62]
Sugar metabolism regulatory proteins	Up	Cell culture supernatants (Hep3B, 97H and LM3 cell lines)	A new indicator for more motile liver cancer cells	Not mentioned	[63]

HCC: Hepatocellular carcinoma. CHB: chronic hepatitis B. LC: liver cirrhosis. L02: human normal liver cell line 7702.

chemosensitivity of HCC cells by increasing cell cycle arrest and apoptosis and promoted the sensitivity of sorafenib to HCC cells [88].

10. Discussion

Accumulating evidence has revealed that exosomes play vital roles in various cancers, such as lung cancer, breast cancer, gastric cancer, pancreatic cancer and so on. In this review, we focused on clinical applications of exosome in liver cancer (Fig. 2). Exosome cargoes (mRNA, miRNA, lncRNA and protein) could be used as diagnostic, prognostic and predictive markers for HCC (Table 1). In particular, exosomes are crucial for cell-cell communication by delivering information from tumor cells to near or distant cells. Through the interaction of cells, exosomes are closely associated with HCC cells' proliferation, invasion and metastasis. There has been no research studying methylation of DNA and RNA in exosomes. Could methylation of DNA and RNA influence these processes? The underlying mechanisms are still unclear. In addition, exosomes are capable of inducing immune responses and modulating the immune system. It is a challenge to overcome the resistance of HCC to chemotherapy. Interestingly, HCC cells-derived exosomes can enhance sorafenib resistance of hepatoma cells *in vitro*. However, AMSC-derived exosomes are effective vehicles of *miRNA-122* which increases HCC chemosensitivity. These results may provide a strategy to increase therapeutic efficacy.

Apart from blood, exosomes were identified as biomarkers in other body fluids. For example, saliva, milk, urine, cerebrospinal fluid, etc. Exosomal *PD-L1* mRNA from saliva could distinguish periodontitis from healthy group, and its level was related to the severity/stage of periodontitis [89]. Exosomal *GOLM1-NAA35* chimeric RNA constituted an effective noninvasive biomarker in esophageal squamous cell carcinoma [90]. Breast milk exosomes containing high level of *TGFβ2* resulted in changes in benign and malignant breast epithelial cells, which contributed to the development and progression of the breast cancer [91]. High level of *PSA* and *PCA3* mRNA in prostate specific membrane antigen positive exosomes provided excellent diagnostic efficiency for prostate cancer [92]. *miR-204-5p* in urinary exosomes could be a novel biomarker for early diagnosis of Xp11.2 translocation renal cell carcinoma [93]. *miR-590-5p*, *miR-570-3p* and *miR-570-5p* were upregulated in the cerebrospinal fluid and serum of neurosyphilis patients, when compared with patients with syphilis without neurosyphilis [94]. Exosomes in these body fluids are more organ-specific and more sensitive than those in the blood. However, in HCC, most of studies still focus on exosomes in blood. There is a promising field in detecting the function of exosomes in the abdominal cavity effusion or the bile of HCC patients in further studies.

In conclusion, exosome plays a critical role in HCC. It is urgent to improve valid techniques for isolation, purification and storage of exosome for better clinic application.

Conflicts of interest

The authors declare that they have no competing interests.

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