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REVIEW

Current perspectives on exosomes in the diagnosis and treatment of hepatocellular carcinoma (review)

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ABSTRACT

The prognosis of hepatocellular carcinoma (HCC), a malignant tumor, is poor. Tumor recurrence and metastasis are the major challenges for the treatment of HCC. Various studies have demonstrated that exosomes, which are loaded with various biomolecules including nucleic acids, lipids, and proteins are involved in the recurrence and metastasis of HCC. Additionally, exosomes mediate various biological processes, such as immune response, cell apoptosis, angiogenesis, thrombosis, autophagy, and intercellular signal transduction. In cancer, exosomes regulate cancer cell differentiation, development, and drug resistance. Circular RNAs, microRNAs, and proteins in the exosomes can serve as early diagnostic and prognostic markers for HCC. As exosomes are characterized by low immunogenicity and high stability in the tissues and circulation, they can be used to deliver the drugs in cancer therapies.

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Introduction

Globally, hepatocellular carcinoma (HCC) is the sixth most common type of cancer and the third leading cause of cancer-related deaths.[1] The morbidity rate of HCC is high (more than 20 cases/100,000 individuals) in the East Asia population. Each year, approximately 782,000 new HCC cases and 600,000 HCC-related deaths are reported worldwide.[2] Approximately 40% of patients are clinically diagnosed with early-stage liver cancer. Most patients exhibit intrahepatic or distant organ metastasis at diagnosis and are not eligible for radical operation.[3] Currently,the primary therapeutic strategies for HCC include surgery, local ablation therapy, and radiation therapy, which have improved the clinical outcomes of patients with the 10-year survival rate reaching approximately 25%.[4] The rapid advances in traditional therapy have not resulted in decreased incidences of recurrence and metastasis of HCC. The prevention of HCC metastasis is a major objective in cancer treatment. Cellular signaling is involved in cancer progression, including drug resistance, metastasis, and recurrence.[5] Therefore, there is a need to identify the correlation between intercellular communication and cancer progression and to identify the underlying mechanisms and potential therapeutic targets for metastasis in HCC. Exosomes, which are produced and secreted by various cells (including tumor cells), are involved in several physiological and pathological processes *in vivo*, including intercellular communication, immune system function, cell differentiation, drug resistance and angiogenesis (Figure 1). Additionally, exosomes are involved in tumor development.[6] This review summarizes the recent recent studies on the role of exosomes in cancer and discusses the correlation between HCC and exosomes.

Overview of the exosomes

Johnstone *et al.*[7] first reported that vesicles with lipid bilayers were released during the culture of sheep reticulocytes *in vitro*. Exosomes are detected in the body fluids, such as the serum, milk, semen, and malignant fluid.[8] Recently, the International Society for Extracellular Vesicles defined extracellular vesicles (EVs) as the generic term for particles naturally released from the cells that are delimited by lipid bilayers and cannot replicate. There has been a marked increase in the number of studies on the physiological and pathological functions of EVs, a collective term encompassing various subtypes of membranous structures released from the cells, such as microparticles, microvesicles, ectosomes, apoptotic bodies, oncosomes, and exosomes.[9] Currently, there is no consensus on the classification of EVs. Some studies have suggested that EV subtypes must be classified based on the physical characteristics(such as size or density), biochemical composition(such as CD63 + EVs), descriptions of conditions, or cell of origin.[9] Traditionally, EVs can be divided into the following three subgroups based on their diameter: exosomes (30–100 nm), apoptotic bodies (50–200 nm), and microbubbles (100–1000 nm).[10] EVs exhibit a particulate structure and contain biomolecules, such as nucleic acids, proteins, lipids.[11] The secreted EVs can be taken up by the recipient cells through endocytosis, phagocytosis, macropinocytosis, or membrane fusion. The contents of EVs are then released into the cells where they exhibit various functions.[12] Exosomes, which are a subtype of EVs, are derived from multivesicular bodys-(MVBs) of the endosomal bodies and special areas of the cell membrane called endosomal domains.[12–14] MVBs can fuse with the plasma membrane and the exosomes are released into the extracellular space.[14] The secretion of exosomes is

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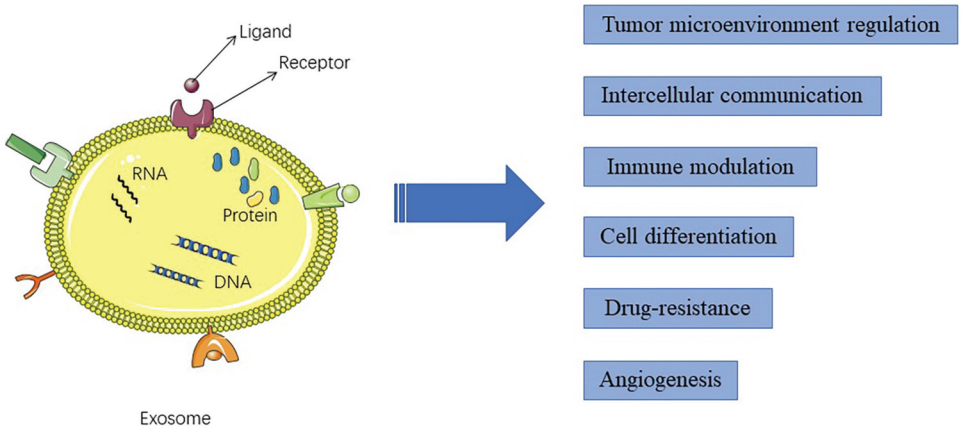

Figure 1. Functions of exosomes in hepatocellular carcinoma development. Exosomes, which harbor proteins, mRNAs, microRNAs, long non-coding RNAs, circular RNAs, and DNAs, are involved in tumor microenvironment regulation, intercellular communication, immune modulation, cell differentiation, drug-resistance, and angiogenesis.

reported to be dependent on the the calcium concentration and pH value.[10] In tumor cells (such as HCC cells), the secretion of exosomes is dependent on the GTPase (Rab) family proteins, such as Rab35.[15] Zou *et al.*[16] demonstrated that the secretion of exosome was regulated by mechanistic target of rapamycin complex 1(mTORC1) and was dependent on the amino acid changes and growth factor conditions. These findings indicate that exosomes are secreted through multiple pathways. Proteomic analysis has revealed that CD63, TSG101, and flotillin are exosome markers.[10] Exosomes function as an intercellular messenger during cell differentiation and cancer development. Additionally, exosomes contain various biomolecules, such as nucleic acids and proteins,[17] and are involved in complex biological functions (Table 1). Some studies have reported that exosomes are involved in various biological processes (such as inflammatory immune response, apoptosis, angiogenesis, thrombosis, and autophagy), as well as in the occurrence, development, and metastasis of tumors.[18–20] These findings suggest that exosomes may serve a pivotal role in intercellular signaling. Recent studies have highlighted the role of exosomes in the tumor microenvironment (TME), which is critical for the occurrence, development, invasion, and metastasis of HCC.[21] Previous studies have confirmed that tumor cells release a large number of exosomes during tumorigenesis and that exosome-mediated intercellular signaling can potentially regulate the TME, which affects the progression of tumor.[22] Additionally, exosomes are associated with various pathological conditions, such as neurological disorders, drug addiction, and collagen diseases.[20,23] Thus, exosomes may exert therapeutic effects. However, the underlying mechanisms involved in the therapeutic effects of exosomes have not been elucidated.

Exosomal RNAs as a diagnostic marker and a therapeutic target for HCC

As the early diagnosis of HCC is challenging, there are ongoing efforts to develop noninvasive diagnostic methods for HCC. The advances in sequencing technology have enabled the elucidation of the role of exosomes in cancers.[24] Previous studies have indicated that exosomes mediate the transportation of proteins, DNAs and various RNAs (such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and messenger RNAs (mRNAs)) in the cells, which promotes the development of HCC.[25,26] Thus, the contents of the exosomes can be utilized for the early diagnosis and follow-up of patients with cancer. The exosomal proteins, RNAs and DNAs may be potential diagnostic markers for HCC. Additionally, exosomes can be potential therapeutic targets for HCC.[23] This section summarizes the functions of RNAs from HCC-derived exosomes (Figure 2).

Non-coding RNAs, which are abundant in exosomes, are involved in all stages of tumor development.[27] miRNAs can regulate various target genes through their short sequences that are not completely complementary. Therefore, miRNAs may regulate tumor progression, including proliferation, metabolism, and apoptosis.[28] For example, miR-194 inhibits the growth and migration of primary liver cancer cells by suppressing the Wnt/β-catenin signaling pathway via the downregulation of polyclonal inhibitory complex 1 (PRC1).[29] Sun *et al.*[30] demonstrated that miR-155 was enriched in the exosomes released by HCC cells. These miR-155-containing exosomes were taken up by other HCC cells, which resulted in enhanced proliferation. In addition, exosomal miR-155 can directly bind to the 3′-untranslated region of PTEN (tumor suppressor), which results in the downregulation of target genes in the recipient liver cells. Animal experiments have demonstrated that the exosomes enriched with miR-155 promoted the development of HCC xenotransplants. The expression of miRNAs markedly varied between the benign tumors or non-tumorous cells and the cancer cells. Compared with those in patients with chronic hepatitis B (CHB), the serum levels of miR-18a, miR-221, miR-222, and miR-224 were significantly higher, while those of miR-101, miR-106b, miR-122, and miR-195 were markedly lower in patients with HCC. This suggested that these miRNAs may act as biomarkers for HCC.[31] Compared with the biomarkers detected in the conventional specimens, exosomes are highly stable. The plasma levels of exosomal tumor-specific molecules (such as miR-718) in patients with HCC are significantly higher than those in healthy control.[32]

Table 1. Overview of the roles of exosomal contents in HCC.

Types of exosomal contents	Functions in tumor	Mechanism	References
Exosomal proteins			
SMAD	Detaching HCC cells and facilitating their adhesion	SMAD3/ROS signaling pathway	93
Caveolin	HCC motility and malignant progression	-	94
MET caveolins S100	Enhancing the migratory and invasive abilities of non-motile cell lines	PI3K-AKT-mTOR, RAS-RAF-MEK-ERK	95
ITGαvβ5	HCC metastasis	Specifically bind to Kupffer cells	96
OXL4	Promoting migration and angiogenesis	Activate FAK/Src pathway	97
SDF-1α	Promoting the migration and invasion	MMPs secretions to facilitate lymph node metastasis	98
IL-6 IL-8	Promoting cells migration and increasing tube formation	NF-κB signaling pathway	99
Golgim1	Accelerating cell proliferation and migration	GSK-3β/MMPs signaling axis	100
VASN	Promoting proliferation and Migration of recipient HUVECs	-	101
HMGB1	Higher infiltration	Activating TLR-MAPK pathway	102
AFP GGT	Inducing EMT	-	103
Exosomal miRNA			
miR-320a	Suppressing HCC cells proliferation, migration and metastasis	MAPK pathway	51
miR-200b-3p	Decreased miR-200b-3p in cancer cells promotes angiogenesis in HCC tissues	Enhancing endothelial ERG expression	104
miR-451a	Inhibiting hepatocellular tumorigenesis	Targeting LPIN1 to regulate tumor cells apoptosis and angiogenesis	105
miR-744	Downregulated miR-744 promotes HepG2 cells proliferation and inhibits the chemosensitivity of HepG2 cells to sorafenib	PAX2 is identified as the functional target of miR-744	106
miR-92a-3p	Promoting metastasis	Targeting PTEN and regulating its downstream Akt/Snail signaling to promote EMT	52
miR-224	Tumor promotor Increasing in cells proliferation	Targeting glycine N-methyltransferase	107
miR-21	Promoting cancer progression	Targeting PTEN, leading to activation of PDK1/AKT signaling	108
miR-10b	Promoting HCC cells proliferation, migration, and invasion	Activating HIF-1α and HIF-2α	53
miR-665	Promoting HCC cells proliferation	Activating MAPK/ERK pathway	109
miR-150-3p	The loss of antitumoral miR-150-3p in CAFs-derived exosomes greatly promotes HCC progression	-	110
miR-9-3p	Overexpression of miR-9-3p reduces HCC cell viability and proliferation	Regulating HBGF-5 expression Reducing ERK1/2 expression	111
miR-103	Increasing vascular permeability and promoting tumor metastasis	Inhibiting the expression of VE-Cadherin (VE-Cad), p120-catenin (p120) and zonula occludens 1	112
miR-490	Inhibiting HCC cell metastasis	Inhibiting the ERK1/2 pathway	113
miR146a	Anti-HCC function	Promoting M2-polarization and suppresseing the function of T-cells	114
miR-155	Stimulating the proliferation of HCC cells	Bounding to 3 -UTR of PTEN leads to the reduction of relevant targets in recipient liver cells	22
miR-93	Increasing proliferation and invasion ability of HCC cells	TP53INP1, TIMP2 and CDKN1A are direct targets of miR-93	115
miR-92b	Enhancing the migration ability of liver cancer cells	Suppressing CD69 on NK cells	116
miR-1247-3p	Activated CAFs further promote cancer progression via secreting pro-inflammatory cytokines	Activating β1-integrin-NF-κB signaling pathway in fibroblasts	41
miR-32-5p	Multidrug resistance via modulating angiogenesis and EMT	Activating the PI3K/Akt pathway	65
miR-145	Suppressing tumorigenesis and metastasis	GSK-3β/MMPs signaling axis	100
miR-1273 f	Directly replicating the effects of hypoxic exosomes within HCC cells	Activating the Wnt/β-catenin signaling	117
miRNA-25-5p	Increasingly recognized as key instigators of cancer progression by facilitating cell-cell communication	-	118
Exosomal lncRNA			
TUC339	Regulating macrophage activation	Regulating macrophage M1/M2 polarization	119
lncRNA H19	Accelerating the proliferation and motility while hampering the apoptosis of HCC cells	H19/miR-520a-3p signaling	120
lnc-FAM72D-3	Functions as an oncogene in HCC	-	121
lnc-EPC1-4	Functions as a tumor suppressor gene	-	121
lncRNA MALAT1	Increasing hepatic cell invasion and migration	Extracellular signal-regulated kinase 1/2 (ERK1/2) signaling	122
ATB	Promoting invasion and metastasis	Upregulation of TGF-β signaling pathway	123
Exosomal circular RNA			
circRNA Cdr1as	Greatly accelerating HCC cells to proliferate and migrate	Sponging miR-1270	124
circPTGR1	Promotes metastasis	-	32
circRNA-100,338	Enhancing the metastatic ability of HCC cells	Affect proangiogenic activity by regulating angiogenesis	35
circUHRF1	Driving resistance to anti-PD1 immunotherapy in HCC patients	Expression of TIM-3 via degradation of miR-449 c-5p	67
circ-1441443	Suppressing the malignant biological behaviors	Via BAK1 upregulation	125
circFBLIM1	Facilitatign HCC progression and glycolysis	MiR-338/LRP6 axis	126127128129130

Abbreviation: AFP (alpha-fetoprotein), GGT (gamma-glutamyl transpeptidase), HCC(Hepatocellular Carcinoma), EMT (epithelial-stromal transformation), CAFs (cancer-related fibroblasts).

These studies suggest that the miRNA in the exosomes can be detected using noninvasive methods, which can aid in the early diagnosis of cancer, especially the diagnosis of HCC.136137138139140

LncRNAs are also involved in the pathogenesis of HCC. Yang *et al.*[15] reported that lncRNA HOTAIR regulated the secretion of exosomes from the liver tumor cells. HOTAIR promotes the release of exosomes via inducing the transport of MVBs to the plasma membrane and regulating the expression and localization of RAB35. The expression level of lncRNA HULC in serum exosomes and liver cancer tissues is correlated with the tumor TNM stage. The overexpression of HULC promotes the growth and invasion and inhibits apoptosis of HCC cells. Notably, HULC promotes the secretion of exosomes from the HCC cells.[33] Conigliaro *et al.*[34] demonstrated that lncRNA H19 in CD90+ HCC modulates the TME balance via promoting angiogenesis. These findings illustrate the importance of the lncRNAs in HCC and provide novel insights into the molecular mechanisms involved in the secretion of exosomes from HCC cells. Therefore, lncRNAs may serve as therapeutic target for HCC.141142143144145146

Recent studies have reported that circRNAs can serve as a diagnostic biomarker and a therapeutic target for cancer. CircRNAs are endogenous non-coding RNAs without 5′ to 3′ polarity and contain a covalent closed-loop structure of polyadenylated tail.[35] Previous studies have reported that circRNAs can stably bind to miRNAs and regulate gene expression.[36] The analysis of the correlation between exosomes and circRNAs may aid in understanding the biological functions of exosomal circRNAs. However, the analysis of exosomal circRNAs is a double-edged sword as exosomes containing circRNAs can transfer biological information to the target cells but also contribute to the clearance of circRNAs.[37] At present, the exosomal circRNAs are detected in various cancer cell lines, including the liver, lung, gastric, and breast cancer cell lines.[38,39] The differentially expressed circRNA genes promote the tumor-related signaling pathways, suggesting that circRNAs are associated with the occurrence and development of tumors.[40] For example, cSMARCA5 (a circRNA derived from exons 15 and 16 of the SMARCA5 gene) binds miR-17-3p and inhibits the proliferation and migration of HCC by promoting TIMP3 expression.[41] Huang *et al.*[42] proved that the overexpression of circRNA-100338 activates mTOR signaling pathway in HCC and is correlated with poor prognosis. Zhang *et al.*[43] found that the exosomes secreted by adipocytes contain a circRNA named circ-deubiquitination(circ-DB), which promoted HCC growth and decreased DNA damage via the suppression of miR-34a and the activation of deubiquitination-related USP7. These studies suggest that circRNAs are correlated with the progression and metastasis of HCC. However, the clinical application of exosomal circRNAs is associated with several challenges. circRNAs cannot be easily detected in the exosomes due to their low abundance and complex structures. Thus, the precise evaluation of circRNA expression and function is challenging.[37] Future studies must investigate exosomal RNAs in cancer and other diseases to elucidate their functions. Although exosomal RNA function and mechanisms have not been completely elucidated, they can serve as potential biomarkers and novel therapeutic targets for HCC owing to their applicability, specificity, and accessibility.

Compared with those on non-coding RNAs, studies on exosomal mRNAs in tumors are limited. miRNAs are stable in biological fluids. In contrast, mRNAs that are not enclosed within exosomes undergo degradation in the biological fluids.[44] However, exosomal mRNAs have a critical role in tumors. A chimeric mRNA called GOLM1-NAA35 is detected

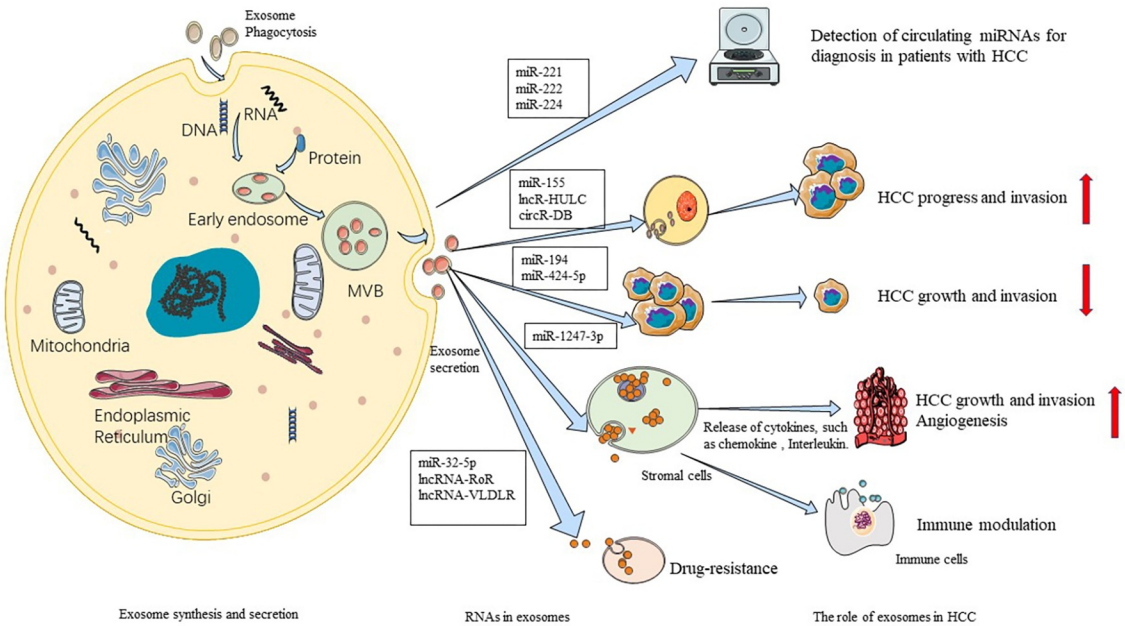

Figure 2. Roles of RNAs from hepatocellular carcinoma (HCC)-derived exosomes. Exosomes mediate the transport of various RNAs. Exosomes-associated miRNAs, such as miR-221, miR-222, and miR-224 can be potential diagnostic biomarkers for HCC. miR-155, lncR-HULC, and circR-DB promote HCC progression and invasion, whereas miR-194 and miR-424-5p suppress HCC growth and invasion. Exosome-associated RNAs, such as miR-1247-3p, which are transferred from the donor cells, can regulate stromal cells, such as cancer-related fibroblasts. The secretion of cytokines, such as chemokine and interleukins from the exosomes promotes HCC growth and invasion, including angiogenesis. miR-32-5p, lncRNA-RoR, and lncRNA-VLDLR are involved in the development of drug-resistance.131132133134135

in the salivary exosomes of patients with esophageal squamous cell carcinoma (ESCC). The levels of chimeric GOLM1-NAA35 mRNA in salivary exosomes served as a noninvasive biomarker for ESCC detection, postoperative surveillance, therapeutic response, and tumor recurrence.[44] The expression of PCA3 mRNA, a typical biomarkers of prostate cancer, is significantly upregulated in PSMA-positive (PSMA: prostate-specific membrane antigen) exosomes.[45] Xu *et al.*[46] examined the serum levels of exosomal heterogeneous nuclear ribonucleoprotein H1 (hnRNPH1), a type of RNA-binding protein and splicing factor essential for the development of HCC mRNA in the HCC group were significantly higher than those in the liver cirrhosis, chronic hepatitis B, and healthy control groups. Patients with upregulated exosomal hnRNPH1 mRNA levels exhibited poorer overall survival than those with downregulated hnRNPH1 mRNA levels. Additionally, the expression level of exosomal hnRNPH1 mRNA is correlated with the Child-Pugh classification, portal vein tumor emboli, lymph node metastasis, and TNM stage in patients with HCC.[46] These findings suggest that the serum level of exosomal hnRNPH1 mRNA is a prognostic biomarker for HCC. Sasaki *et al.*[47] reported that the copy number of hepcidin mRNA variant was significantly upregulated in the serum exosomes of patients with HCC. This suggested that exosomal hepcidin mRNA may serve as a novel diagnostic biomarker for HCC. These studies offered novel insights into the potential applications of exosomal mRNAs for cancer surveillance and early diagnosis. However, further prospective studies are needed to elucidate the role of exosomal mRNAs.

Role of exosomes in the formation of HCC microenvironment

Approximately 70% of HCC cases exhibit recurrence and metastasis within 5 years after surgery or radiofrequency ablation.[48] The mechanisms underlying HCC progression or metastasis must be elucidated to prevent recurrence and metastasis of HCC. The complex TME is critical for various cellular processes, such as maintenance of cell surface structure and adhesion, angiogenesis, cell migration, epithelial-to-stromal transition (EMT), matrix remodeling, and immune regulation.[49,50]

Matrix cells (such as fibroblasts, macrophages, and T cells), extracellular matrix (ECM; comprising inflammatory cytokines, chemokines, and matrix metalloproteinases), and exosomes constitute the TME, which has a critical role in cancer initiation and progression.[51] For example, cancer-related fibroblasts (CAFs) regulate the inflammatory microenvironment, promote lung metastasis of HCC, and induce tumor occurrence, EMT, and chemotherapy resistance.[52] The dysfunction of immune cells provides a microenvironment for immunosuppression in tumor cells, which leads to immune tolerance and escape.[53] The loss of physiological balance in the microenvironment results in disrupted cell behavior and tumor development. Exosomes are an important component of the TME that transduce signals between cells.[54] The exosome-mediated activation of toll-like receptor 3 (TLR3) in hepatic stellate cells (HSCs) exacerbates liver fibrosis via enhancing IL-17A production.[55] Wang *et al.*[56] demonstrated that 14-3-3ζ inhibited the anti-tumor functions of tumor-infiltrating T cells in the HCC microenvironment and that 14-3-3ζ can be partially transferred from HCC cells to T cells through the exosomes. These findings suggest exosomes indirectly affect the progression of HCC by influencing the composition of the TME.

Recently, exosomes were reported to mediate anti-tumor immune response and immune escape of tumor cell.[57] Macrophages, which are abundant in the liver, are involved in the innate immune response. In response to tumor-derived stimuli, macrophages can be polarized into the classical (M1) or alternative (M2) phenotypes. M1 macrophages exhibit anti-tumor activity, whereas M2 macrophages exhibit pro-tumorigenic activity.[58] The exosomes derived from HCC cells promote macrophage activation and M2 polarization, which enables tumors to evade immune surveillance.[59] LncRNA TUC339, which is upregulated in HCC-derived exosomes, is transferred among HCC cells and promotes HCC growth and metastasis. Furthermore, exosomal lncRNA TUC339 can be transferred to neighboring macrophages where it regulate the M1/M2 polarization and inhibits the anti-tumor immune response *in vitro*.[60] HCC-derived exosomal miR-23a-3p upregulates PD-L1 expression in the macrophages via the STAT3 signaling pathway, which attenuates the anti-HCC immune response *in vitro and in vivo*.[61] The exosomes derived from melatonin-treated HCC cells mitigate the immunosuppressive status by downregulating PD-L1 expression on macrophages *in vitro and in vivo*.[59] Dendritic Cells (DCs) are also involved in initiating innate and adaptive immune responses. Yu *et al.*[62] demonstrated that tumor-derived exosomes promoted immunosuppression by inhibiting DC differentiation and maturation through the IL6-STAT3 signaling pathway. In contrast, Rao *et al.*[63] found that HCC tumor cell-derived exosomes exhibiting various HCC antigens, elicit a strong immune response by activating DCs. The activated DCs increased T lymphocytes and interferon-γ levels and decreased tumor growth factor-β levels in the HCC TME. Another study[64] investigating exosomes from HCC antigen-expressing DCs in different HCC mouse models reported that alpha fetoprotein-enriched DCs-derived exosomes could trigger potent antigen-specific anti-tumor immune responses and remodel the TME in HCC mice. Thus, these exosomes can be a potential immunotherapeutic target for HCC. Natural killer (NK) cells, a critical component of the TME, can be inhibited by exosomal circUHRF1, which results in immunosuppression. Exosomal circUHRF1 can confer resistance to anti-PD1 immunotherapy in patients with HCC. Thus, exosomal circUHRF1 can be a potential therapeutic target for HCC.[65] HCC-derived exosomes harbor various non-coding RNAs and proteins that mediate immunoregulation. Therefore, exosomes may serve as prospective diagnostic biomarkers and therapeutic targets for HCC.

EMT is a reversible process of dedifferentiation in which epithelial cells lose the epithelial characteristics (such as polarity and cell–cell junctions) and acquire the typical mesenchymal characteristics (such as increased migratory and invasive abilities).[66] However, most tumor cells do not undergo a complete EMT. In these cases, tumor cells acquire partial characteristics of mesenchymal cells with some epithelial

characteristics. Moreover, partial EMT (*p*-EMT) can drive distinct migratory properties and enhance the epithelial-mesenchymal plasticity of cancer cells and cell fate plasticity.[67] Yu *et al.*[68] suggested that key *p*-EMT-related genes (P4HA2, ITGA5, MMP9, MT1X, and SPP1) could serve as prognostic biomarkers and therapeutic targets for HCC. Recent studies have demonstrated the role of exosomes in EMT progression in different types of cancer, including HCC.[69] Chen *et al.*[70] revealed that HCC-derived exosomes promoted HCC progression and recurrence by activating EMT through the MAPK/ERK signaling pathway. Rab27a, a small GTPase, regulates exosome secretion by mediating multivesicular endosome docking at the plasma membrane. Zhang *et al.*[71] showed that exosomes derived from CAFs transfered miR-320a to the HCC cells and inhibited EMT. The loss of miR-320a in the CAF-derived exosomes promoted EMT and HCC metastasis. In addition, HCC-derived exosomes transport miR-92-3p to the recipient cells and consequently promote EMT and the conversion of low-metastatic HCC cells into high-metastatic HCC cells via the regulation of the PTEN/Akt pathway. Thus, these exosomes are a biomarker of poor prognosis in patients with HCC.[72] HCC cell-derived exosomal miR-21 and miR-10b, which are overexpressed in the acidic microenvironment, promote HCC cell proliferation and metastasis by facilitating the EMT process.[73] These findings indicate that EMT and exosomes disrupt the homeostatic balance of the TME. Thus the analysis of EMT and exosomes may contribute to the identification of novel therapeutic targets and prognostic markers, and the development of novel treatment strategies for HCC.

HCC, which is highly vascularized, can secrete exosomes with various ncRNAs and cytokines that promote angiogenesis.[42,74] For example, Li *et al.*[75] demonstrated that HCC-derived exosomes promote angiogenesis in the human umbilical vein endothelial cells (HUVECs) by transferring lysyl oxidase-like 4 (LOXL4) through a paracrine mechanism. HCC-derived exosomes harboring angiopoietin-2 (ANGPT2) are endocytosed by HUVECs, which promotes angiogenesis via the Tie2-independent pathway (Tie2: angiopoietin receptor). Additionally, the knockdown of ANGPT2 significantly inhibited angiogenesis.[76] However, not all genes and their products exhibiting upregulated expression in the exosomes promote angiogenesis. One study suggested that exosomal miR-200b-3p from HCC suppressed the expression of endothelial transcription factor ERG (erythroblast transformation-specific (ETS)-related gene). The downregulation of miR-200b-3p in HCC cells promoted angiogenesis through the upregulation of endothelial ERG expression.[77] These studies provide insights into the novel pathways that may be targeted to increase the efficacy of anti-angiogenic therapies.

Chemoresistance and exosome-related drug-resistance of HCC

Traditional chemotherapeutic strategies are associated with poor prognosis, low efficacy, and increased side effects, which can be attributed due to the nonspecific therapeutic targeting and rapid development of multidrug resistance (MDR).[78] MDR is induced in the tumor cells via various mechanisms, including gene mutations, DNA methylation, histone modifications, disrupted membrane transporters, changes in anticancer drug targets, and intracellular metabolism of drugs, to escape the cytotoxic effects of chemotherapy drugs.[79,80] Genetic heterogeneity among cancer cells is the basis of adaptation to the therapeutic interventions with the most resistant cells surviving against the selective pressure.[81] Peitzsch *et al.*[82] indicated that cancer stem cells (CSCs) may serve an important role in tumor drug resistance. Liver CSCs (LCSCs), which are primary stem cells derived from liver cancer, undergo self-renewal and differentiation. Thus, LCSCs contribute to the recurrence and metastasis of HCC. Additionally, LCSCs are resistant to conventional radiotherapy and chemotherapy.[83] Yu *et al.*[84] analyzed clinical liver tumor samples and highlighted the importance of the SDC1-PI3K/AKT signaling in cisplatin resistance. Ding *et al.*[85] confirms that CCND1, a protooncogene, is involved in fluorouracil (5-FU) resistance in the hepatoma cell lines. The silencing of CCND1 increases the sensitivity of HCC to 5-FU and inhibits the expression of the DNA repair protein RAD51. This suggested that MDR is regulated at various levels, including genomics, proteomics and TME levels and that the modulation of a single factor cannot completely mitigate drug resistance. Therefore, combined therapy must be used to overcome drug resistance.

Exosomes are involved in conferring resistance to antitumor drugs. However, the role of exosomes in inducing drug resistance has not been completely elucidated.[86] Current studies suggest that exosomes induce drug resistance through the delivery of cargos from drug-resistant cancer cells to the recipient drug-sensitive cells, which enhances the proliferation, survival, migration, and drug resistance of drug-sensitive cells. Alternatively, exosomes may phagocytose drug molecules and expel them out of cells, which reduces the drug concentration in the cells.[87,88] The tumor-derived exosomes are rich in miRNAs, which are associated with the drug resistance phenotype. Some molecules (such as ncRNA) loaded in the exosome interact with molecular receptors in cells and modulate their drug resistance phenotypes.[79] Fu *et al.*[89] revealed that exosomes deliver miR-325p from resistant cells to sensitive cells, which results in the activation of the PI3K/Akt pathway. Additionally, these exosomes induce MDR by modulating angiogenesis and EMT. Exosomal miR-199a-3p(Exo-miR-199a-3p), which represses the invasion of cancer cells and stimulate cancer cell apoptosis, was isolated from the HCC cells. Animal experiments revealed that the upregulation of miR-199a-3p mitigated the resistance of HCC to cisplatin and delayed tumor growth *in vivo*.[90] Zhang *et al.*[65] showed that exosomal circUHRF1, which is predominantly secreted by the HCC cells, promotes immunosuppression via inducing NK cell dysfunction. Additionally, circUHRF1 may promote resistance to anti-PD1(Programmed death 1) immunotherapy. These studies indicate that the regulation of exosomal ncRNAs can be a potential therapeutic strategy for HCC.

Exosomes may clear drugs and metabolites from the tumor cells and consequently mitigate the therapeutic effect of drugs through various transporters.[91] Meena *et al.*[92] indicated that paclitaxel promoted exosome releasing from HCC cells, which conferred drug resistance to ajacent cells as the exosomes transported the drug out of the cells. This process was partly

mediated by the ATP-binding cassette (ABC) transporter family. The ABC transporter family, which contributes to MDR in cancer cells, is subdivided into seven subfamilies (A to G).[93] The relatively active proteins include ABC subfamily B member 1 (ABCB1, also known as MDR1 and *P*-glycoprotein or *P*-gp), ABC subfamily C member 1 (ABCC1, also known as multidrug resistance-associated protein 1), and ABC subfamily G member 2 (ABCG2, also known as breast cancer resistance protein [BRCP]).[94] The exosomal delivery of ABCB1, which is the most studied transporter, confers chemoresistance in HCC. In particular, ABCB1 expression is upregulated in HCC cells that are resistant to paclitaxel, epirubicin, and doxorubicin.[91] The other efflux pumps ABCB2 and ABCA3 also contribute to chemoresistance by transferring exosomal drugs.[94] This is a potential novel mechanism of chemoresistance in cancer cells. Thus, exosome-mediated drug transportation must be considered to overcome MDR.

Exosomes and HCC targeting therapy

The identification of drug targets can aid in the development of targeted therapy to improve the efficacy of therapeutics and reduce the toxic and side effects. However, the development of targeted therapy for tumors is challenging.[95] Recently, several potential molecular targets (such as PD-1/PD-L1, cytotoxic T lymphocyte antigen 4 (CTLA-4), vascular endothelial growth factor (VEGF) pathway, tumor suppressor p53, skin cell adhesion molecule (EpCAM), and Wnt/β-Catenin) and therapeutics (such as nivolumab, pembrolizumab, and lenvatinib) have been widely used for the clinical treatment of HCC.[95–97] However, most target molecules for HCC exhibit poor clinical performance. Approximately 25% of HCC cases exhibit resistance to the currently used drugs.[98] Thus, there is a need to develop methods to accurately deliver anti-cancer drugs to the tumor and specially kill the cancer cells.

EVs can be a potential drug delivery system to mitigate the side effects of chemotherapy and enhance treatment effect.[99] Zhang *et al.*[100] presented the challenges of EV-based drug delivery, including the selection and production of vesicles and cargos and the methods to load the cargo into the vesicles, modify the vesicle surface, and prolong the half-life of vesicles in the circulation. The membrane permeability, biocompatibility, and non-toxic immunogenicity of exosomes can be an advantage for transferring drugs, proteins, and nucleic acids.[101] Exosomes are characterized by low immunogenicity and high stability in the tissues and circulation. Thus, exosomes may be a better drug delivery vehicle in cancer therapies than previously reported compounds, such as liposomes.[102] For example, Hood *et al.*[103] loaded superparamagnetic iron oxide nanoparticles (SPIONs) in exosomes through electroporation to obtain exosomes loaded with 5 nm iron nanoparticles, which can be used for diagnosis or treatment. To achieve the targeted delivery to the tumor cells and improve the applicability of treatment, the exosomal surface was modified. One study[104] transfected EV-producing cells with vectors encoding anti-epidermal growth factor receptor nanobodies, which served as targeting ligands for tumor cells, fused to glycosylphosphatidylinositol (GPI) anchor signal peptides. EVs were isolated using ultrafiltration/size-exclusion liquid chromatography. The analysis of EV-tumor cell interaction revealed that nanobodies can be anchored on the surface of EVs via GPI, which alters their cell-targeting behavior. Tian *et al.*[105] engineered immature DCs (imDCs) to express a well-characterized exosomal membrane protein (Lamp2b) fused to αv integrin-specific iRGD peptide (CRGDKGPDC) to facilitate tumor targeting. The purified exosomes from imDCs were loaded with Dox via electroporation with an encapsulation efficiency of up to 20%. iRGD exosomes were highly efficient for the targeted delivery Dox to αv integrin-positive breast cancer cells *in vitro* and *in vivo*. These studies demonstrate the potential of exosomes for anti-tumor drug delivery. However, there are limited studies on exosome-based drug delivery to liver cancer. Future studies must examine exosomal chemotaxis to lay the foundation for the application of exosome-directed drug delivery to the liver, which can improve tumor characterization and optimize personalized treatment for patients with HCC.

Conclusions and future perspectives

Immunotherapies, such as nivolumab, pembrolizumab, and ipilimumab, have been used for the clinical treatment of cancers.[106] However, the objective response rate of anti-PD1 immunotherapy is only 15%~20%.[107] The unique immune response in the liver is reported to promote drug tolerance, which is a major challenge for the application of conventional immunotherapy in patients with HCC.[108] The liver, which is a major immunological organ, is exposed to antigen-enriched blood from the gut via the portal vein.[109] Therefore, the uninflamed liver provides a tolerogenic microenvironment and suppresses both innate and adaptive immunity under homeostasic conditions to prevent prolonged inflammation and tissue damage.[110] This underscores the need to develope novel therapeutic strategies for HCC. Exosomes, which serve a pivotal role in intercellular commnication and TME, are a prospective therapeutic target for HCC. The cargos, including functional proteins, RNAs, and anti-tumor drugs, in the exosomes can serve as diagnostic markers and regulate various physiological and pathological processes.[65,111] Recent studies have improved our understanding of the role of exosomes in cancers, such as gastrointestinal and liver cancers.[112] Additionally, exosomes can serve as a potential therapeutic target for cancer. Exosomes can also be potentially used as drug carriers for cancer treatments.[113] The modification of the exosomal membrane can increase the chemotaxis of exosomes to specific lesions.[114,115] Thus, exosomes can deliver anti-tumor drugs directly and effectively to the HCC tissues and prevent the progression of HCC. However, further studies are needed for the clinical application of exosomes for the diagnosis and treatment of HCC.

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