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Review Article

Exosome-mediated Crosstalk in the Tumor Immune Microenvironment: Critical Drivers of Hepatocellular Carcinoma Progression

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Abstract

Hepatocellular carcinoma (HCC) is a significant global health issue, ranking as the sixth most prevalent malignancy and the fourth leading cause of cancer-related mortality worldwide. Despite advancements in therapeutic strategies, mortality rates for HCC remain high. The tumor immune microenvironment (TIME) plays a vital role in HCC progression by influencing tumor cell survival and growth. Recent studies highlight the essential role of exosomes in mediating intercellular communication within the TIME, particularly in interactions among tumor cells, immune cells, and fibroblasts. These interactions drive critical aspects of tumor development, including immune escape, angiogenesis, drug resistance, and metastasis. A detailed understanding of the molecular mechanisms by which exosomes modulate the TIME is essential for developing targeted therapies. This review systematically evaluated the roles and regulatory mechanisms of exosomes within the TIME of HCC, examining the impact of both HCC-derived and non-HCC-derived exosomes on various cellular components within the TIME. It emphasized their regulatory effects on cell phenotypes and functions, as well as their roles in HCC progression. The review also explored the potential applications of exosome-based immunotherapies, offering new insights into improving therapeutic strategies for HCC.

Keywords: Exosome; Hepatocellular carcinoma; Tumor immune environment; Cancer therapy; Signal Transduction; Tumor Escape.

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Introduction

Hepatocellular carcinoma (HCC), commonly known as primary liver cancer, is among the most widespread cancers worldwide. According to data, HCC ranks as the sixth most prevalent malignancy and the fourth leading cause of cancer-related mortality globally.[1] By 2025, liver cancer is estimated to affect over one million individuals each year.[2] Current treatment methods for HCC include surgical resection, vascular interventional therapy, radiofrequency ablation, and liver transplantation.[3] However, the lack of early symptoms and specific markers for early detection often results in late diagnosis, leading to advanced stages and poor treatment outcomes.[4] While immunotherapy shows promise, it has not significantly improved survival rates, primarily due to the tumor's ability to evade host immune surveillance, which presents a major challenge to effective cancer therapy.[5] Therefore, it is critically important to clarify the fundamental mechanisms of this disease to advance both diagnosis and treatment strategies.

The tumor immune microenvironment (TIME) constitutes a complex network of interactions among diverse immune cell subtypes, cancer cells, and stromal cells, which collectively play crucial roles in tumor survival and proliferation.[6] As the tumor progresses, the TIME shifts from a state of immune surveillance to one of immune suppression. Initially, immune cells within the TIME attempt to attack the tumor, but as the tumor evolves, it modifies the microenvironment to suppress these immune responses.[7] Exosomes are central

to this transition, facilitating essential intercellular communication within the TIME. They transport bioactive molecules, including proteins, lipids, metabolites, and nucleic acids, thereby modifying the phenotypes of microenvironmental cells and influencing key aspects of tumor development, such as immune escape, proliferation, angiogenesis, metabolism, drug resistance, and metastasis.[8,9] Thus, understanding the specific molecular mechanisms by which exosomes modulate different cellular components of the TIME is essential for developing innovative therapies for HCC. Given their low immunogenicity, minimal toxicity, targeted delivery capabilities, and excellent biocompatibility, exosomes have also gained attention as potential carriers for therapeutic agents, making them particularly appealing for drug delivery systems.[10] Additionally, exosomes have been investigated as cell-free vaccines for cancer treatment, demonstrating promising clinical outcomes.[11] Leveraging exosomes to stimulate antitumor immunity, therefore, represents a viable therapeutic approach.

In this article, we aimed to clarify the role of exosome-mediated regulation within the TIME in the progression of HCC. Initially, we describe the sources and characteristics of exosomes within the TIME. We then focus on the effects of both HCC-derived and non-HCC-derived exosomes on various cellular components in the TIME, emphasizing their impacts on cell phenotypes and functions. Finally, we discuss the potential applications of exosome-based immunotherapies in HCC and explore future research directions for exosome utilization in HCC treatment.

The function and biogenesis of exosomes

Function of exosomes

The concept of extracellular vesicles (EVs) can be traced back to 1946 when Chargaff and West first suggested their existence during research on thromboplastin and platelets.[12] This idea was later confirmed by Wolf in 1967.[13] These early discoveries laid the groundwork for the current understanding of EVs as essential mediators of intercellular communication. In 1996, Raposo *et al*. made a groundbreaking discovery about the function of exosomes in antigen presentation, significantly impacting cancer diagnostics and therapeutics.[14] Consequently, exosomes have become a focal point in tumor research in recent years. Exosomes, the smallest components of EVs, range from 50 to 140 nanometers in size and are encased in a phospholipid bilayer.[15] They are found in various bodily fluids, including blood, plasma, urine, tears, and saliva.[16] Exosomes are synthesized by multiple cell types, such as immune cells, fibroblasts, and tumor cells, and encapsulate bioactive molecules, including proteins, lipids, nucleic acids, and metabolites. Upon release into the extracellular milieu, these bioactive molecules can be absorbed by other cells, allowing them to perform specific functions.[15] In the TIME of HCC, exosomes are synthesized by component cells such as innate and adaptive immune cells, fibroblasts, hepatic stellate cells, and tumor cells. These exosomes are subsequently absorbed by other component cells, where they perform specific functions.[17] Depending on their cargo and the characteristics of the source and recipient cells, exosomes play various roles in modulating the TIME, affecting HCC development through mechanisms such as promoting immune escape, angiogenesis, metabolic reprogramming, drug resistance, proliferation, and metastasis.[8,9]

Biogenesis of exosomes

The biogenesis of exosomes is a complex and tightly regulated process essential for intercellular communication and cellular homeostasis. This process occurs in a series of sequential steps, beginning with the formation of intraluminal vesicles (ILVs) within the lumen of multivesicular bodies (MVBs), which are subsequently transported to the plasma membrane. At the plasma membrane, a critical fusion event releases the ILVs as exosomes into the extracellular environment (Fig. 1).[18]

Initially, a variety of mechanisms drive the inward budding of the plasma membrane, leading to the formation of early endosomes. In the subsequent step, these early endosomes sequester a diverse array of cargo, including proteins, lipids, RNA, and DNA, into ILVs, thereby forming MVBs.[19] The formation of ILVs is predominantly governed by the endosomal sorting complex required for transport machinery, which is instrumental in sorting and directing selective cargoes into the ILVs, ensuring specific molecules are encapsulated for subsequent exosomal release.[20–22] Moreover, MVBs dynamically interact with various cellular organelles and compartments, such as the trans-Golgi network and the endoplasmic reticulum (ER), which regulate MVB generation and influence the molecular contents of ILVs.[19] Following the maturation of MVBs, they are transported to the plasma membrane in a process mediated by Rab27a and Rab27b. These proteins ensure the accurate positioning and anchoring of MVBs at the plasma membrane, preparing them for fusion.[23,24] The final phase of exosome biogenesis is the SNARE-mediated fusion of MVBs with the plasma membrane, leading to the release of exosomes into the surrounding extracellular milieu. Notably, not all MVBs are destined for exosome release; some are redirected to lysosomes for degradation.[25] Once released, exosomes can be taken up by recipient cells through receptor-dependent interactions, endocytosis, or direct fusion with the recipient cell membrane. This process enables the delivery of the exosomes' molecular contents, ultimately modulating the behavior and characteristics of these recipient cells.[26]

Emerging evidence suggests that tumor cells manipulate exosome biogenesis to release exosomes that promote tumor growth. For example, it has been demonstrated that norcholic acid, a compound derived from tumor microenvironments, enhances exosome synthesis and secretion by regulating NSMase and RAB27A in HCC cells.[27] Additionally, lncRNA HOTAIR stimulates exosome release by directing MVB trafficking to the plasma membrane,[28] while GOLM1 facilitates the sorting of PD-L1-containing exosomes by inhibiting Rab27b in the Golgi.[29] These exosome-driven alterations reshape the TIME, shifting immune responses from anti- to pro-tumorigenic, thus promoting tumor progression. Unraveling these mechanisms could inform novel therapies targeting exosome-mediated communication.

HCC-derived exosomes facilitate tumor development via crosstalk in the tumor immune microenvironment

The TIME is composed of a diverse array of immune cell populations that infiltrate tumor tissues, including innate immune cells like macrophages, neutrophils, and dendritic cells, as well as adaptive immune cells including T and B lymphocytes. It also includes other cells such as hepatic stellate cells and cancer-associated fibroblasts. The interactions and functions of these cells collectively influence the role of TIME in cancer progression.[30,31] HCC-derived exosomes further alter the TIME by modulating the polarization and function of these cellular components, thereby shifting immune responses from anti-tumorigenic to pro-tumorigenic, ultimately promoting tumor progression.

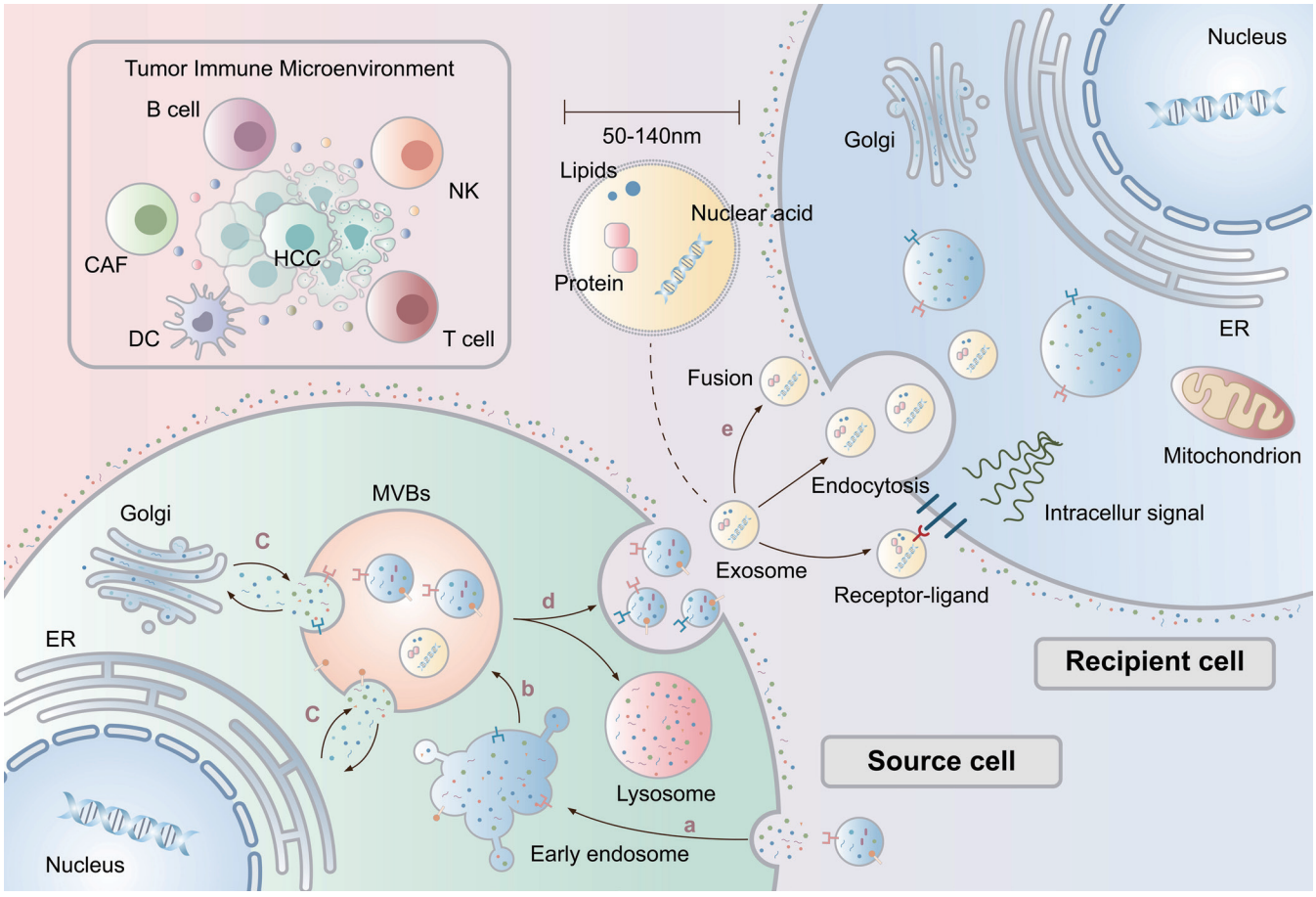

Fig. 1. The process of exosome biogenesis, release, and uptake. The source and recipient cells of exosomes can be any cells within the tumor immune microenvironment. (A) Various mechanisms initiate the inward budding of the plasma membrane, leading to the formation of early endosomes. (B) These early endosomes then sequester a diverse array of cargo, including proteins, lipids, RNA, and DNA, into ILVs, forming MVBs. (C) MVBs dynamically interact with other cellular organelles and compartments, including the TGN and the ER. These interactions regulate the generation of MVBs and influence the molecular contents of ILVs. (D) With the maturation of MVBs, they are capable of either fusing with lysosomes for degradation or with the plasma membrane to release their intraluminal vesicles as exosomes. (E) Following their release, exosomes can impact recipient cells via receptor-dependent interactions, endocytosis, or direct fusion with the recipient cell membrane. ILVs, intraluminal vesicles; MVBs, multivesicular bodies; TGN, trans-Golgi network; ER, endoplasmic reticulum; HCC, hepatocellular carcinoma; CAF, cancer-associated fibroblast; NK, natural killer cell; DC, dendritic cell.

Innate immune cells

Macrophages: Macrophages are a crucial component of the innate immune system, exhibiting the capacity to be polarized by different microenvironment signals, enabling them to switch their phenotypes and functions. The polarization of these cells occurs through two major pathways: the classical pathway, leading to the predominance of M1 macrophages that exert anti-tumor activities, and the alternative pathway, resulting in M2 macrophages known for promoting tumorigenesis and tumor progression.[32] Specifically, M1 macrophages facilitate tumor destruction by secreting cytotoxic molecules, including reactive oxygen species (ROS) and inducible nitric oxide synthase.[33] Additionally, they support Th1 lymphocyte polarization and actively engage in the phagocytosis of tumor cells.[34] In contrast, M2 macrophages suppress anti-tumor immune responses by expressing co-inhibitory molecules like PD-L1 and secreting cytokines with anti-inflammatory properties, such as IL-10, IL-6, and TNF-α,[35,36] as well as by initiating the Th2 immune response. Additionally, M2 macrophages promote angiogenesis in HCC by secreting matrix metalloproteinases (MMPs) and vascular endothelial growth factor, facilitating metastasis through matrix remodeling and invasion.[37] In the context of HCC, tumor-associated macrophages (TAMs) exhibit phenotypic shifts corresponding to different tumor progression stages, with early-stage M1 macrophages gradually giving way to M2 macrophages as the tumor advances, resulting in poorer patient outcomes.[33,38] HCC-derived exosomes are critical in this transition, as they can induce TAMs to shift from M1 to M2 to create a tumor-friendly microenvironment.[39]

By triggering ferroptosis in M1 macrophages via exosomes, HCC cells can bypass surveillance by the immune system (Fig. 2). For example, miR-142-3p within exosomes derived from hepatitis B virus (HBV)-infected HCC cells triggers ferroptosis in M1 macrophages through increased levels of solute carrier family 3 member 2, potentially diminishing the immune response against tumors and aiding in tumor development.[40] Given that HBV infection is a notable risk factor for HCC,[41] this research contributes to understanding the pathogenesis of HBV-related HCC and offers fresh theoretical insights and potential treatment targets.

Apart from suppressing M1-type macrophages, exosomes originating from HCC dynamically modulate TAM polarization towards an M2 phenotype, thus facilitating tumor advance-

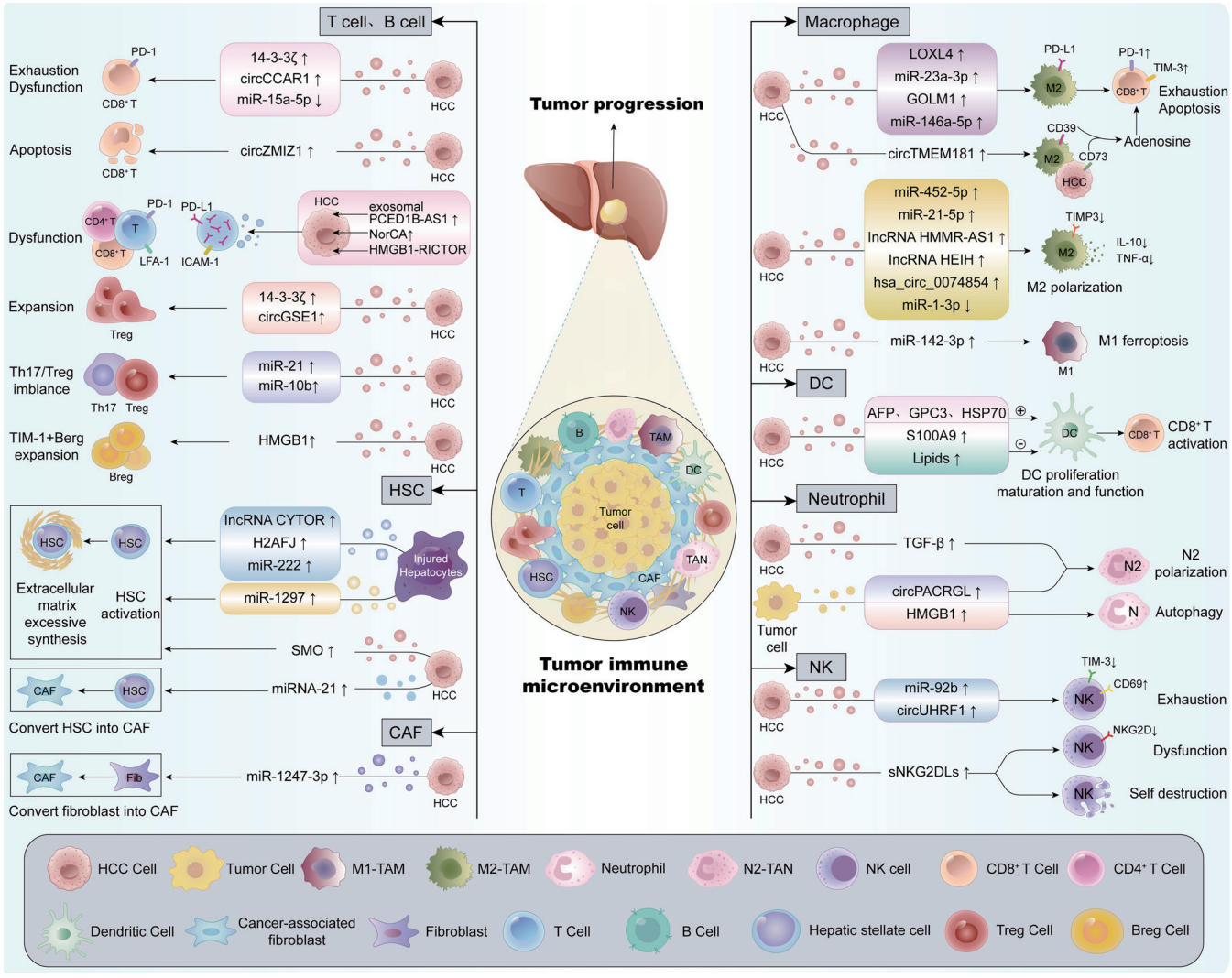

Fig. 2. The role of HCC-derived exosomes in mediating crosstalk within the tumor immune microenvironment and promoting HCC progression. HCC cells secrete diverse exosomes that actively remodel the tumor immune microenvironment, influencing both immune and stromal cell functions. This exosome-mediated crosstalk enables tumor cells to evade immune surveillance, thereby supporting tumor cell proliferation and metastasis. Furthermore, damaged liver cells release exosomes that activate quiescent HSCs, driving excessive extracellular matrix synthesis. This pathway exacerbates the progression of MAFLD and liver fibrosis, establishing a pathological foundation for HCC. HCC, hepatocellular carcinoma; MAFLD, metabolic dysfunction-associated fatty liver disease; HSCs, hepatic stellate cells; DC, dendritic cell; NK, natural killer cell; ↑, upregulation; ↓, downregulation.

ment (Fig. 2). Epigenetic modifications, which alter gene regulation by modifying DNA architecture, are increasingly recognized as key factors in cancer, including HCC. Exosomes carrying miRNAs, lncRNAs, and circRNAs significantly promote TAM differentiation toward the M2 polarized state.[31,42] For instance, elevated levels of exosomal miR-452-5p present in HCC-originated exosomes encourage M2 polarization and HCC advancement by reducing TIMP3 levels, a typical anti-oncogene that prevents M2 macrophage polarization and triggers cell death in HCC cells.[43,44] Similarly, a study by Yu and colleagues illustrated that highly expressed exosomal miR-21-5p originating from HCC attenuates MAPK signaling pathways in HCC cells through its attachment to the 3′-UTR of RhoB, which subsequently leads to an M2-like phenotype transformation in TAMs and promotes HCC progression.[45]

Furthermore, it has been demonstrated that lncRNAs and circRNAs within exosomes from HCC cells function as competitive endogenous RNA, preventing miRNA release from specific genes, thereby enabling macrophages to shift towards the M2 phenotype. Under hypoxic conditions, previous studies have shown that hypoxia-inducible factor (HIF)-1α enhances the transcription of the lncRNA hyaluronan-mediated motility receptor antisense RNA 1 (HMMR-AS1) and promotes exosome release by interacting with the regulatory region of lncRNA HMMR-AS1. The exosomal HMMR-AS1 is then internalized by macrophages, resulting in M2 macrophage polarization and accelerated HCC development through prevention of ARID3A degradation via miR-147a sequestration.[46] Moreover, Ai *et al*. showed that exosome-packaged lncRNA HEIH, which is abundantly expressed in HCC, is transported to macrophages, triggering M2 macrophage polarization and subsequent enhancement of tumor progression through the HEIH/miR-98-5p/STAT3 pathway.[47] Additionally, a study by Wang and colleagues demonstrated that elevated exosomal hsa_circ_0074854 can be internalized by TAMs to promote M2 polarization, leading to increased IL-10 expression and

decreased TNF-α expression, which contributes to HCC progression. The study also found that hsa_circ_0074854 reduces the stability of the protein HuR and decreases ZEB1 expression, further promoting Epithelial-Mesenchymal Transition (EMT) in HCC cells.[48] EMT is a fundamental cellular process in which epithelial cells lose their distinct traits and adopt a mesenchymal state that significantly boosts cancer cells' capacity for migration and invasion.[49]

In contrast, reducing exosomes with growth-inhibiting cargo is a strategy for HCC to maintain proliferation. Gu *et al*. demonstrated that the quantity of exosomal miR-1-3p, which shows a marked reduction in HCC compared to the control group, can enter macrophages and regulate M2 macrophage polarization, thereby facilitating HCC progression. In a xenograft mouse model, tumors treated with miR-1-3p-loaded macrophages were significantly smaller and exhibited a marked increase in apoptosis, indicating the potential of miR-1-3p as a therapeutic target.[50]

Moreover, emerging evidence has confirmed that HCC-derived exosomes suppress T cell functions indirectly by inducing a phenotype shift in macrophages towards the M2 phenotype (Fig. 2). The mechanistic basis for this immunosuppressive effect is driven by increased expression of immune checkpoint proteins (TIM-3, CTLA4, PD-1) on T cells after macrophages are treated with HCC-derived exosomes, leading to T cell exhaustion and immunosuppression.[51,52] Lysyl oxidase-like 4, an enzyme involved in extracellular matrix remodeling, exhibits high expression levels in HCC tissues. Secreted by HCC cells, exosomal lysyl oxidase-like 4 is predominantly internalized by hepatic macrophages, inducing PD-L1 expression by activating interferon (IFN)-mediated, STAT1-dependent pathways. This process leads to reduced cytotoxicity of $CD8^+$ T cells against HCC cells, creating an immunosuppressive environment in HCC.[53,54] Additionally, ER stress activation facilitated by exosomes has been identified in multiple tumor types, including HCC, and plays an essential role in promoting cancer advancement.[55,56] Liu *et al*. discovered that under ER stress, exosomal miR-23a-3p is delivered from HCC cells to macrophages, causing M2-type polarization and PD-L1 expression. This upregulation of PD-L1, driven by PTEN suppression and PI3K/AKT pathway activation, ultimately induces $CD8^+$ T cell apoptosis and reduces IL-2 secretion, thereby lowering the $CD8^+$ T cell ratio.[57] Similarly, elevated levels of GOLM1 have been intricately linked to HCC development and metastasis.[58] Research indicates that overexpression of GOLM1 promotes PD-L1 stability and facilitates its incorporation into exosomes through CSN5-mediated deubiquitination in HCC. These exosomes are then transferred to macrophages, resulting in upregulated PD-L1 on TAMs. The elevated PD-L1 expression on TAMs suppresses $CD8^+$ T cell function, characterized by reduced production of effector cytokines such as IFN-γ and granzyme B, upregulation of inhibitory receptors PD-1 and TIM-3, and a higher rate of apoptosis indicated by activated caspase 3.[29] Furthermore, Sal-like protein 4 (SALL4) is a transcription factor known to play a crucial role in the oncogenesis and progression of various malignancies, including HCC.[59] In a study by Yin and colleagues, it was found that SALL4 overexpression enhances the incorporation of miR-146a-5p into exosomes, which are then delivered to macrophages, promoting their transition to the M2 phenotype via NF-κB pathway stimulation. These exosome-induced M2 macrophages subsequently cause T cell exhaustion and dysfunction by upregulating inhibitory receptors on T cells and reducing cytokine secretion, such as IL-2 and TNF-α. Thus, targeting SALL4 or exosomal miR-146a-5p may serve as a potential therapeutic strategy for HCC.[52]

A recent study reveals that the ATP-adenosine pathway weakens $CD8^+$ T cell function, promotes immunosuppression within the TIME, and induces resistance to PD-1 therapy. Exosomes from HCC cells contain circTMEM181 (circular RNA transmembrane protein 181), which is absorbed by macrophages and sponges miR-488-3p, leading to elevated CD39 expression. CD39 converts extracellular ATP into ADP and AMP, which are further converted into adenosine by CD73 in HCC cells. This interplay between high CD39 levels in macrophages and CD73 in HCC cells activates the ATP-adenosine pathway, resulting in excess adenosine, impairing $CD8^+$ T cell function and promoting PD-1 resistance.[60] Elucidating the specific mechanisms of these exosomes will help assess their potential as therapeutic targets, thereby enhancing anti-tumor immunity and improving patient outcomes.

Dendritic cells: Dendritic cells (DCs) are vital elements of the immune system, named for their distinctive dendritic morphology. Derived from hematopoietic stem cells in the bone marrow and maturing through a complex differentiation process, DCs are competent antigen-presenting cells that effectively recognize, capture, process, and present antigens, contributing significantly to the initiation and modulation of immune responses.[61] Meanwhile, the impact of tumor-derived exosomes (TDEs) on DCs within the TIME exhibits a range of variable outcomes that substantially affect anti-tumor immunity.[62]

On one hand, DCs actively participate in the immune response by efficiently internalizing Tumor-Derived Exosomes (TEXs) carrying a variety of tumor antigens. Once internalized, these antigens are processed by DCs and subsequently presented to T cells, marking an essential step in initiating an immune response (Fig. 2).[63,64] Research conducted by Rao and colleagues demonstrated that, after DCs uptake exosomes derived from HCC cells, there is an increased expression of surface markers including CD11c, MHC classes I and II, alongside costimulatory molecules such as CD80, CD86, and intercellular adhesion molecule-1 (ICAM-1), suggesting that TDEs can induce DC maturation and activation.[64] In addition, HCC-specific antigens such as alpha-fetoprotein, glypican-3, and heat-shock protein 70 are known to be present in these TEXs, enhancing the ability to stimulate T cells and inhibit cancer cell proliferation by stimulating DC proliferation and differentiation.[65] Antigen presentation by TEX-primed DCs is critical for activating T cells, particularly $CD8^+$ T cells. Additionally, TEX-primed DCs help modify the tumor microenvironment to favor immune-mediated tumor suppression, evidenced by increased T-cell infiltration and a shift in cytokine profiles toward higher levels of immunostimulatory cytokines like IFN-γ and lower levels of immune-inhibitory factors like IL-10 and TGF-β.[64]

Conversely, multiple studies have shown that TEXs may also contribute to tumor development by inhibiting the differentiation, maturation, and function of DCs, thereby compromising their ability to mount an effective immune response (Fig. 2).[62] A previous study observed that exosomes derived from breast cancer can target and interact with $CD11b^+$ myeloid precursor cells in the bone marrow. By inducing IL-6 production and activating the STAT3 signaling pathway, these exosomes significantly inhibit the differentiation of myeloid precursor cells into DCs. Even when some precursor cells manage to differentiate into DCs in the presence of these exosomes, they lose their ability to mature properly and fail to effectively activate T cells, significantly enhancing the tumor's ability to evade the immune system and promoting tumor progression.[61] Similarly, Ning *et al*. observed that DCs treated with exosomes derived from lung and breast cancer cells exhibit pronounced immunosuppressive properties, in-

cluding a significant downregulation of surface markers such as CD80, MHC-II, and CD86, alongside upregulation of immunosuppressive markers like PD-L1, and a reduced expression of chemokine receptors such as CCR7, thereby inhibiting their migration to lymph nodes and diminishing their capacity to activate T cells effectively. These combined effects substantially diminish the proliferation, differentiation, and function of T cells, allowing tumor cells to evade immune surveillance.[66] Additionally, TEXs enriched with S100A9 molecules have been shown to impede DC maturation, as indicated by the decreased expression of DC maturation markers.[67] A recent study revealed that exosomes enriched with S100A9 are significantly present in blood specimens of HCC patients, indicating that HCC may inhibit DC maturation via S100A9-rich exosomes, thereby contributing to immune escape.[68]

Moreover, studies have shown that exosomes originating from the HCC cell line (Huh7) are rich in lipids, including glycolipids and fatty acids.[69] These fatty acid-laden TEXs significantly increase cytoplasmic lipid concentrations and activate the metabolic switch peroxisome proliferator-activated receptor α, resulting in the accumulation of lipid droplets and enhanced fatty acid oxidation, which ultimately drives DC metabolism toward mitochondrial oxidative phosphorylation and severely impairs their immune function. Dysfunctional DCs are unable to effectively carry out antigen processing and activation of T cells, thereby weakening their ability to stimulate T cells and leading to immune dysfunction.[70] Additionally, studies have found that bone marrow-derived dendritic cells exposed to antigen-free TDEs display impaired functionality, resulting in the suppression of cytotoxic T cell function and encouraging the development of immunosuppressive regulatory T cells (Tregs).[70] Therefore, targeting peroxisome proliferator-activated receptor α presents a strategic approach to enhance DC-based therapies in cancer treatment.

In conclusion, DCs treated with TDEs exhibit the potential for dual roles in both promoting and suppressing tumors. Initially, TEXs stimulate DC activation and enhance anti-tumor immunity. However, as the tumor progresses, TEXs shift DCs to an immunosuppressive phenotype, reducing antigen presentation and increasing immunosuppressive cytokine secretion, which contributes to tumor immune evasion.[71,72] While HCC exosomes can stimulate DCs, the overall immunosuppressive tumor microenvironment remains a significant challenge. A nuanced approach is needed to balance the therapeutic potential of TEXs with their role in immune escape.

Natural killer cells: Natural killer (NK) cells are a crucial component of the innate immune system, known for their ability to swiftly respond to tumors and virally infected cells without prior sensitization.[73] They distinguish "self" from "non-self" by utilizing a complex system of surface receptors, which include both activating and inhibitory types. When activating receptors, such as NKG2D, encounter stress-induced ligands on tumor cells, they trigger the release of cytotoxic granules containing perforin and granzyme, ultimately leading to cell death.[74,75] On the other hand, inhibitory receptors like KIR and CD94/NKG2A bind to MHC class I molecules on healthy cells, sending inhibitory signals that prevent NK cell activation and protect normal tissues. NK cell activity against cancer is regulated by a balance between activating and inhibitory signals, ensuring selective targeting of threats while preserving normal cells.[74–76]

NK cell function is often compromised by an immunosuppressive microenvironment that alters their phenotype and reduces cytotoxic capabilities. This phenomenon is associated with a decrease in activating receptors like NKG2D and an increase in exhaustion markers, such as PD-1, CD96, Tim-3, and TIGIT.[74,77] Additionally, tumor cells and other cells in the tumor microenvironment, including Tregs, myeloid-derived suppressor cells, and tumor-associated fibroblasts, release soluble factors (such as TGF-β, IL-10, PGE2, and IDO) that further suppress NK cell activity.[74,78] Notably, HCC-derived exosomes can be absorbed by NK cells, potentially compromising their function by modulating activating or inhibitory receptors, thereby enabling cancer cells to evade NK cell detection (Fig. 2).[79,80] For example, exosomal miR-92b from HCC can downregulate CD69 expression on NK cells, decreasing their cytotoxicity and allowing the tumor to evade immune response.[81] Furthermore, exosomal circUHRF1 from HCC cells exacerbates NK cell exhaustion by sponging miR-449c-5p, which raises TIM-3 levels and reduces the secretion of IFN-γ and TNF-α, further contributing to an immunosuppressive microenvironment.[80]

The human NKG2D receptor is a key activating receptor on NK cells, which exerts cytotoxic effects by recognizing specific stress-induced molecules, including MHC class I chain-related molecules A and B (MICA and MICB, collectively referred to as MIC), as well as six cytomegalovirus UL16-binding proteins. In healthy tissues, these ligands are typically absent or expressed at low levels, but their expression significantly increases during tumor transformation. Tumor cells rapidly induce the expression of these ligands in response to stressors such as genetic damage, metabolic abnormalities, and changes in the microenvironment. Elevated levels of MICA, MICB, and ULBP proteins act as "danger signals" that activate NKG2D receptors, initiating the cytotoxic response of NK cells.[82] However, tumor cells can evade immune surveillance by reducing MHC class I molecule expression through proteolytic cleavage or exosome-mediated secretion, thus reducing NK cell recognition.[83,84] Studies indicate that NKG2D receptors on NK cells can be bound by soluble NKG2D ligands, such as sMICA and sMICB, contained within exosomes produced by HCC, which further blocks NK cells from recognizing and destroying tumor cells, promoting immune evasion and impairing NK surveillance (Fig. 2).[85–88] As exosomes accumulate in the tumor microenvironment, high levels of exosomal MICA/B inhibit NKG2D receptor expression and function, diminishing NKG2D-dependent tumor cell destruction, while decreased NKG2DL expression on tumor cells further reduces NK cell-mediated cytotoxic efficiency.[89] Recent studies highlight the dual role of exosome-associated NKG2DLs within the TIME. Initially, exosomes carrying NKG2DLs can activate NK cells after short-term stimulation. However, prolonged exposure to these exosomes leads to a decrease in NKG2D receptor expression and a subsequent impairment in NK cell activity. This effect may result from the continuous release of exosomes within the TIME, which, over time, diminishes the ability of NKG2D to stimulate NK cell activation. Moreover, NK cells marked by exosomal NKG2DLs on their surface are targeted by other NK cells, leading to a perforin- and granzyme-mediated cytotoxic response that promotes self-destructive behavior in NK cells. This mechanism significantly impairs NK cells' antitumor function and provides a novel explanation for tumor immune evasion.[89]

Neutrophils: Neutrophils, critical components of the innate immune system and members of the myeloid family, are pivotal in human immune defense due to their abundance and rapid response.[90] Similar to their myeloid counterparts, macrophages, tumor-associated neutrophils (TANs) exhibit complex and diverse roles, contributing to both anti-tumor activity and tumor progression.[91] The dual functionality of TANs is determined by their phenotype, with N1 TANs exhibiting tumor-suppressing properties and N2 TANs demonstrating tumorigenic effects[7]. The tumor-suppressing effect

of N1 TANs is attributed to two primary mechanisms: direct cytotoxicity via the generation of ROS and the stimulation of various innate and adaptive immune cells.[92] Conversely, N2 TANs enhance tumor proliferation by promoting angiogenesis, remodeling the extracellular matrix, increasing metastasis, and inducing immunosuppression, collectively reshaping the tumor microenvironment into a tumor-promoting state.[93]

TDEs have been observed to alter the TIME by inducing neutrophils to polarize into the N2 phenotype. Research has shown that exosomes originating from tumors increase the number of $CD66b^+$ TANs and facilitate the polarization of TANs into the N2 phenotype, which supports tumor growth across various cancers, including HCC, lung, gastric, colon, and breast cancers. Inhibiting the release of these exosomes has been shown to reduce neutrophil infiltration and limit subsequent tumor cell expansion.[94–97]

Furthermore, upregulation of the TGF-β signaling pathway has been found to induce neutrophils to adopt the N2 phenotype, which is associated with pro-tumorigenic properties.[98] A study by Yang *et al*. revealed a significant presence of TGF-β in exosomes derived from HCC cells, which can be delivered to recipient cells through membrane fusion, regulating the behavior of these cells (Fig. 2).[99] The combined action of TGF-β and Axl induces the secretion of CXCL5, which promotes neutrophil infiltration into HCC tissues and drives the N2 polarization of neutrophils within the TME, thereby accelerating HCC progression.[100] Similarly, studies in colorectal cancer have shown that CRC-derived exosomal circPACRGL is delivered to tumor-associated neutrophils, regulating TGF-β expression by sequestering miRNAs (miR-142-3p and miR-506-3p), which facilitates the transition of neutrophils from the N1 to the N2 subtype, thereby aiding tumor progression.[96]

Autophagy, a critical cellular process that degrades and recycles intracellular components, plays an essential role in maintaining cellular homeostasis and regulating immune responses. In the context of cancer, autophagy has been observed to enhance the survival of neutrophils, promote the production of pro-tumorigenic factors, and influence the tumor microenvironment by regulating various signaling pathways (Fig. 2).[101] Research has demonstrated that tumor-derived exosomes can trigger autophagy, altering neutrophil phenotype and function to promote immune evasion and foster a tumor-promoting microenvironment.[95] In a study by Li *et al*., exosomes from gastric cancer cells were found to contain high-mobility group box 1 (HMGB1), which interacts with TLR4 to activate the NF-κB pathway, triggering autophagy and pro-tumor activity in neutrophils. This activation results in the release of pro-inflammatory cytokines and MMP9, collectively enhancing the migration and invasion capabilities of gastric cancer cells.[95] In HCC tissues, elevated autophagy in neutrophils has been shown to perpetuate their pro-tumorigenic activities, suggesting that investigating the impact of HCC-derived exosomes on neutrophil autophagy could provide valuable insights into the mechanisms underlying HCC progression.[102] A substantial body of clinical evidence indicates that increased neutrophil infiltration is associated with poor prognosis and tumor progression.[90] By elucidating the role of exosomes in mediating the behavior of TANs, researchers may be able to develop new cancer therapies that improve patient outcomes.

Adaptive immune cells

T lymphocytes: T lymphocytes comprise approximately 50% of all lymphocytic cells in a healthy liver and are crucial in mounting an immune response to HCC. These cells are primarily categorized into two subtypes: $CD8^+$ T cells and $CD4^+$ T cells. Known as cytotoxic T lymphocytes (CTLs), $CD8^+$ T cells can effectively inhibit tumor growth by locating and directly destroying tumor cells through cell toxicity. $CD4^+$ T cells support the effectiveness of other immune cells, ensuring a well-coordinated and robust defense against cancer cell proliferation.[103,104] However, numerous tumor cells, including those found in HCC, adopt complex strategies to evade immune surveillance by utilizing exosomes. These exosomes disrupt T lymphocyte function by transferring signaling molecules, thereby providing a protective barrier for tumor cells, allowing them to evade the immune system.

$CD8^+$ T cells. $CD8^+$ T cells are vital in the immune response against malignancy. Despite often becoming dysfunctional in the TIME, the presence of elevated $CD8^+$ T cell levels is associated with higher survival rates in HCC patients.[105] Researchers have postulated that the immunosuppressive tumor microenvironment of established solid tumors induced the dysfunction of these $CD8^+$ T cells in the later stages of cancer progression.[106] In this process, immune checkpoints serve as a primary means of tumors to evade immune responses by upregulating proteins such as PD-1, LAG-3, CTLA-4, and TIM-3.[107] Notably, exosomes from tumor cells significantly impact the anti-tumor capabilities of $CD8^+$ T cells by modulating immune checkpoint protein expression (Fig. 2). Wang *et al*. demonstrated that overexpressed 14-3-3ζ can be transferred from HCC cells to tumor-infiltrating lymphocytes via exosomes, which suppresses T cells' anti-tumor activity and accelerates HCC progression. This suppression is primarily due to the elevated presence of PD-1 and TIM-3 on $CD8^+$ T cells, ultimately leading to $CD8^+$ T cell exhaustion.[108] However, the specific mechanisms through which 14-3-3ζ influences the functionality of tumor-infiltrating lymphocytes are yet to be fully determined. Exosomes carrying epigenetic modifiers may also influence $CD8^+$ T cell function, resulting in impaired immune responses. For instance, exosomal circCCAR1 from HCC can transfer to $CD8^+$ T cells, where it stabilizes PD-1 expression and reduces the secretion of pro-inflammatory cytokines IFN-γ and TNF-α, leading to $CD8^+$ T cell dysfunction and reduced efficacy of PD-1 therapy in HCC. In this process, exosomal circCCAR1 sequesters miR-127-5p and increases the levels of its target, WTAP. The m6A modification mediated by WTAP further stabilizes circCCAR1, creating a regulatory feedback cycle involving the circCCAR1/miR-127-5p/WTAP axis. Additionally, circCCAR1 interacts with the PD-1 protein, preventing its degradation by reducing ubiquitination, thereby further stabilizing PD-1.[109] Zhang *et al*. discovered that elevated levels of circZMIZ1 in the serum of HCC patients promote KCNJ2 expression by sequestering miR-15a-5p, enhancing apoptosis in $CD8^+$ T cells while simultaneously limiting their cytotoxic potential.[110] Conversely, Zhang *et al*. identified that miR-15a-5p, which shows reduced expression in HCC tissues and cell lines, is encapsulated within exosomes and directly targets $CD8^+$ T cells to inhibit PD-1 expression. Further in vitro experiments revealed that overexpressing miR-15a-5p decreased the aggressiveness of HepG2 cells, suggesting a novel target for HCC prevention and treatment.[111]

Moreover, previous research has demonstrated that tumor cells can upregulate PD-Ls, increase the incorporation of PD-L1 into exosomes, and transfer PD-L1 from PD-L1-positive to PD-L1-negative cells. This inhibits $CD8^+$ T cell proliferation and function through the PD-1/PD-L1 interaction, potentially leading to broader immune escape (Fig. 2).[112,113] Fan *et al*. discovered upregulated levels of PCED1B-AS1 in exosomes, which are secreted and absorbed by T cells or other HCC cells. PCED1B-AS1 acts as a microRNA sponge to inhibit the expression of miR-194-5p, leading to increased levels of PD-

L1 and PD-L2 in recipient cells and thus suppressing both recipient T cell and macrophage activity.[114] Wei *et al*. uncovered a sophisticated interplay between "RNA and RNA" in HCC, where HMGB1 enhances RICTOR mRNA expression by sequestering miR-429. This interaction promotes high PD-L1 expression and its incorporation into exosomes via the AKT-mTORC1-P70S6K pathway, which then binds to PD-1 receptors on T cells, impairing $CD8^+$ T cell cytotoxicity and facilitating tumor immune evasion.[115,116]

Beyond the well-known inhibitory ligand PD-L1, cell surface proteins like ICAM-1 may be regulated or carried by tumor-derived exosomes, influencing the function of $CD8^+$ T cells (Fig. 2). ICAM-1, an adhesion molecule produced on immune and endothelial cells, promotes T cell adhesion and motility by binding to lymphocyte function-associated antigen 1 (hereinafter referred to as LFA-1) on T cells.[117] Zhang and colleagues discovered that ICAM-1 is essential for the PD-L1 exosome-mediated suppression of $CD8^+$ T cells. In their research, IFN-γ and other inflammatory molecules greatly increased the co-expression of ICAM-1 and PD-L1 on tumor-derived exosomes. The interaction between exosomal PD-L1 and PD-1 on $CD8^+$ T cells was significantly reduced in the absence of ICAM-1, suggesting that ICAM-1-LFA-1-mediated adhesion is necessary for exosomal PD-L1 to drive $CD8^+$ T cell dysfunction.[118] Furthermore, elevated exosome levels enriched with miR-222 lower ICAM-1 expression on tumor cell surfaces in patients with chronic hepatitis B and HCC,[119,120] reducing the tumor cells' susceptibility to CTL destruction.[121] Blocking key adhesion molecules between tumor-derived exosomes and T cells may improve the efficacy of immune checkpoint therapies and patient outcomes. Further study of these mechanisms will deepen our understanding of HCC-derived exosomes in T cell regulation and their implications for immunotherapy.

$CD4^+$ T cells. There are numerous subtypes of $CD4^+$ T cells, commonly known as "helper T cells," which are categorized based on the cytokines and other secretions they produce during immune responses. Among these, Tregs are considered a crucial subset. Their pivotal role in regulating immune responses is essential, as they promote immune tolerance and maintain immune homeostasis within the body. In the TIME, Tregs exhibit strong immunosuppressive effects by inhibiting the activity of immune effector cells through multiple pathways, thus supporting immune suppression and facilitating cancer progression.[122]

Notably, tumor-secreted exosomes can stimulate the differentiation of immunosuppressive $CD4^+$ T cell subtypes, particularly Tregs, thereby fostering an immunosuppressive tumor microenvironment (Fig. 2).[123] Research has shown that overexpression of 14-3-3ζ inhibits the proliferation and function of $CD3^+$ T cells in peripheral blood. Furthermore, it prompts naive T cells to diverge from becoming effector T cells, instead developing into regulatory T cells.[108] Huang *et al*. made a significant discovery by identifying the transport of HCC-derived exosomal circGSE1 to $CD4^+$ T cells, which promotes Treg proliferation and facilitates immune evasion in HCC by regulating the miR-324-5p/TGFβ receptor 1/SMAD family member 3 axis. In this mechanism, it functions as an absorbing molecule for miR-324-5p, activating the TGFβ receptor 1 and SMAD family member 3 signaling pathways, which, in turn, promote the proliferation of Tregs.[124]

Another distinct subgroup of $CD4^+$ T helper cells is the Th17 cells, characterized by their ability to secrete IL-17. Under certain conditions, IL-17 released by Th17 cells can enhance the immune response against tumors.[125] The imbalance between Th17 and Treg cells induced by TEXs represents another mechanism of immune evasion in HCC (Fig. 2). Guo *et al*. discovered that exosomal heat-shock protein 70 from heat-stressed tumor cells can convert immunosuppressive Tregs into Th17 cells through IL-6 and IL-17 secretion, thereby enhancing their anti-tumor efficacy.[126] In contrast, Tian and colleagues demonstrated that under the acidic conditions of the HCC microenvironment, HIF-1α and HIF-2α are activated and bind to the promoter regions of miR-21 and miR-10b, significantly increasing the expression of these exosomal miRNAs. This elevation in exosomal miRNAs promotes the proliferation, migration, and invasion of HCC cells in both controlled laboratory and real-life settings.[127] This effect likely occurs by suppressing the anti-cancer immune activity of Th17 cells and promoting the differentiation of immunosuppressive Treg cells, disrupting the balance of $CD4^+$ T cell subtypes and establishing an immune-suppressive environment conducive to tumor progression.[128,129]

Moreover, PD-L1 overexpression in exosomes derived from HCC also impairs the functionality of $CD4^+$ T cells (Fig. 2). Gong and colleagues revealed that norcholic acid significantly increases PD-L1 levels on the surface of HCC cells and their secreted exosomes by downregulating the farnesoid X receptor and the small heterodimer partner. This process upregulates the immune checkpoint proteins PD-1 and TIM3 on $CD4^+$ T cells, thereby impairing $CD4^+$ T cell function, facilitating tumor immune escape, and promoting HCC progression.[27]

B lymphocytes: B cells are integral to the adaptive immune system, playing multiple roles in cancer response through various mechanisms, including direct tumor cell killing via granzyme B release, antigen presentation, and cytokine release, such as IFN-γ and IL-12, to activate CTLs.[130] Despite their relatively low abundance in the liver, B cells have a vital function in monitoring and responding to tumors, as well as in developing immunological memory.[131] Nevertheless, B lymphocytes also have a significant function in encouraging tumor growth. Regulatory B (Breg) cells, a subtype of B cells, are closely associated with the progression of hepatocellular carcinoma.[132] They can promote immunosuppression by upregulating cytokines such as IL-10 and PD-L1, which inhibit anti-tumor immune effector cells.[132–134]

Studies have demonstrated that exosomes from HCC can influence the expression and phenotype of Breg cells, thereby contributing to a tumor-supportive microenvironment that protects cancer cells from immune attack (Fig. 2). Ye *et al*. identified a novel regulatory B cell subset, termed $TIM\text{-}1^+$ Breg cells, which is characterized by a distinct phenotype of $CD5^{high}$, $CD24^-$, $CD27^{-/+}$, and $CD38^{+/high}$, setting them apart from traditional peripheral regulatory B cells. Notably, these $TIM\text{-}1^+$ Breg cells exhibit significantly higher expression within tumor tissues compared to surrounding tissues. Their study further demonstrated that HCC-derived exosomal HMGB1 promotes the proliferation of $TIM\text{-}1^+$ Breg cells via the HMGB1-TLR2/4-MAPK signaling pathway. These $TIM\text{-}1^+$ Breg cells secrete large amounts of IL-10 and TGF-β1, which inhibit the expansion and effector functions of $CD8^+$ T cells and downregulate cytokines TNF-α and IFN-γ, thereby fostering an immunosuppressive microenvironment in HCC and promoting tumor progression.[135] Additionally, Xiao *et al*. identified a $PD\text{-}1^{hi}$ B-cell phenotype in advanced HCC, marked by elevated PD-1 expression and a unique $CD5^{hi}CD24^{-/+}CD27^{hi/+}CD38^{dim}$ signature. These cells, upon interaction with PD-L1, secrete substantial amounts of IL-10, impairing $CD8^+$ T cell growth and activity.[136] Although there is no direct evidence showing that exosomes derived from HCC can induce the $PD\text{-}1^{hi}$ B-cell phenotype, studies on esophageal squamous cell carcinoma suggest that exosomes from esophageal squamous cell carcinoma could facilitate the induction of $PD\text{-}1^{hi}$ Bregs.[137] Therefore, it is highly plausible that HCC cells might also induce

the PD-1^{hi} B-cell phenotype through exosomal pathways, a hypothesis that warrants further investigation.

Other cells

Cancer-associated fibroblasts (CAFs): CAFs are fundamental elements of the TIME and are extensively distributed within the stroma. They modulate tumor proliferation, angiogenesis, metastasis, and resistance to therapies.[5,138] These functions are achieved through interactions with tumor-infiltrating immune cells and the release of signaling molecules such as cytokines, growth factors, and exosomes, which create an immunosuppressive environment that promotes immune escape and supports tumor growth.[139]

In HCC, CAFs contribute to immune suppression and tumor progression by producing immunosuppressive molecules such as IDO and IL-6, which impair NK cells,[140] induce regulatory DCs,[141] and promote pro-tumor immune cell polarization.[139] Moreover, CAFs have been shown to upregulate the expression of negative immune regulators, including PD-L1 and PD-L2, leading to immune cell exhaustion and inactivation[142,143] These actions create an environment conducive to cancer progression and resistance to immunotherapy. In addition to modulating immune responses, CAFs produce substantial amounts of extracellular matrix, which not only supports tumor structure and growth but also acts as a physical barrier, impeding immune cell migration and reducing the efficacy of therapeutic drugs.[144–146]

Research has demonstrated that TDEs play a crucial role in transforming normal fibroblasts into CAFs, as observed in various cancers, including head and neck squamous cell carcinoma and HCC (Fig. 2).[147] Studies on head and neck squamous cell carcinoma have shown that TDEs can induce the transformation of normal fibroblasts into CAFs, creating an inflammatory TIME where T-cell proliferation is suppressed, and TAMs shift to an M2 phenotype, thus aiding tumor progression.[148] Fang *et al*. discovered that highly metastatic HCC cells release miR-1247-3p within exosomes to normal fibroblasts, downregulating B4GALT3 levels and transforming them into CAFs through the β1 integrin/NF-κB signaling pathway. The activated CAFs then secrete cytokines such as IL-6 and IL-8, enhancing tumor cell proliferation, stem cell properties, EMT, and angiogenesis, thereby accelerating cancer progression and metastasis. Targeting this pathway or exosomal miR-1247-3p could provide novel strategies for preventing and treating HCC lung metastasis.[149] Nonetheless, research on how exosomes derived from HCC activate CAFs remains sparse. Further exploration of this interaction may offer insights for developing novel therapeutic strategies against HCC.

Hepatic stellate cells: Hepatic stellate cells (HSCs), located within the Disse space of the liver, are crucial nonparenchymal cells known for their remarkable plasticity, enabling them to regulate various pathological processes.[150] During chronic liver injury, HSCs transition from a quiescent state into an activated myofibroblast phenotype with enhanced proliferative and migratory capabilities, accompanied by excessive synthesis of the extracellular matrix.[150] This transformation is a key driver of liver fibrosis, and if uncontrolled, chronic damage can progress to liver cirrhosis and potentially HCC.[151] Within the TIME, activated HSCs also recruit immune-suppressing cells, including myeloid-derived suppressor cells and Tregs, which facilitate immune evasion and advance HCC progression.[152]

Extensive research has shown that exosomes significantly contribute to the development of precancerous liver conditions such as viral hepatitis, metabolism-related fatty liver disease, and liver fibrosis by activating HSCs (Fig. 2). Metabolic-associated fatty liver disease is increasingly recognized as a major risk factor for the development of liver fibrosis and HCC.[153] X *et al*. demonstrated that upregulation of exosomal miR-1297 derived from hepatocytes under lipotoxic stress activates and proliferates HSCs by inhibiting the tumor suppressor gene PTEN, which subsequently activates the PI3K/AKT signaling pathway. Activation of this pathway is a critical driver of fibrogenesis and significantly exacerbates metabolic-associated fatty liver disease, facilitating the progression of the disease toward more severe forms of liver pathology, such as advanced fibrosis, cirrhosis, and HCC.[154] In a similar study, Xu and colleagues showed that elevated expression of lncRNA CYTOR in exosomes derived from damaged liver cells can activate HSCs, leading to liver fibrosis, as evidenced by significantly increased levels of fibrosis-related markers such as α-SMA, type I collagen, and TGF-β. Mechanistically, lncRNA CYTOR functions as a competing endogenous RNA that binds to miR-125, relieving suppression on glial cell line-derived neurotrophic factor, allowing cell line-derived neurotrophic factor to activate LX2 cells—an effective mechanism for HSC activation.[155] Another study revealed that exosomes derived from hepatocytes, following stimulation with carbon tetrachloride to induce liver injury, contain highly expressed H2AFJ, which promotes the migration and invasion of HSCs and exacerbates liver fibrosis through the activation of the MAPK/STMN1 signaling pathway.[156] Moreover, acute viral hepatitis can lead to liver fibrosis, as Zhang *et al*. observed that miR-222 is significantly increased in exosomes from HBV-infected hepatocytes, promoting LX-2 cell activation by inhibiting TFRC and TFRC-induced ferroptosis, thus activating HSCs and promoting liver fibrosis.[157] Based on the aforementioned research, exosomes play a crucial role in the initiation and progression of precancerous liver conditions by influencing HSC activation. This offers new therapeutic options for patients at risk of liver fibrosis and potential targets for the prevention of HCC.

Additionally, TDEs facilitate intercellular communication between tumor cells and HSCs, influencing the activation of HSCs and driving HCC progression (Fig. 2). Xia *et al*. discovered that when HCC cells are co-cultured with HSCs, the expression level of Smoothened (SMO) in quiescent HSCs is initially low but significantly increases in activated HSCs. Their research indicated that exosomes convey SMO from HCC cells to HSCs, leading to HSC activation, which enhances proliferation, EMT, and stemness, promoting HCC development. Mechanistically, SMO activates the Hedgehog signaling pathway, which enhances the transcriptional activity of Gli1 on MIRLET7BHG in activated HSCs. MIRLET7BHG then sequesters miR330-5p, boosting SMO levels and further activating HSCs and tumor growth in HCC.[158] In addition, under the influence of tumor-derived exosomes, HSCs may serve as another source of CAFs (Fig. 2).[159] Zhou and colleagues identified that the release of exosomal miRNA-21 from HCC cells can trigger the PDK1/AKT signaling pathway by reducing PTEN, transforming HSCs into CAFs. These activated CAFs then release angiogenic factors such as TGF-β, MMP2, bFGF, MMP9, and vascular endothelial growth factor, thereby promoting cancer progression.[160] Understanding exosome-HSC interactions within the immune microenvironment is essential for comprehending the pathogenesis of precancerous liver diseases and HCC. Future research should focus on the mechanisms by which exosomes stimulate HSCs and drive liver disease development, with the goal of developing exosome-based treatments to prevent or reverse liver fibrosis and HCC. We have detailed the functions and pathways mediated by HCC-derived exosomes on immune cells and other cells within the HCC immune microenvironment (Table 1 and Fig. 2).[27,29,40,43,45–48,50,52–54,57,60,64,70,80,81,89,95,96,99,100,108–111,114–116,118,124,127,135,137,149,154–158]

Table 1. The function and pathways regulated by HCC-derived exosomes in the HCC immune microenvironment

Exosome component	Source cell	Recipient cell	Function	Pathway/Mechanism	Ref
miRNA					
miR-142-3p ↑	HCC	Macrophage	Induce ferroptosis in HBV-infected M1-type macrophage	miR-142-3p/SLC3A2 axis	40
miR-452-5p ↑	HCC	Macrophage	Induce M2 polarization of macrophage	miR-452-5p/TIMP3 axis	43
miR-146a-5p ↑	HCC	Macrophage	Inhibit M2 polarization of macrophage	SALL4/miR-146a-5p axis	52
miR-21-5p ↑	HCC	Macrophage	Induce M2 polarization of macrophage	miR-21-5p/RhoB axis	45
miR-1-3p ↓	HCC	Macrophage	Inhibit M2 polarization of macrophage	\	50
miR-23a-3p ↑	HCC	Macrophage	Increase PD-L1 expression, promote M2-type polarization and induce $CD8^+$ T cell apoptosis	miR-23a-3p/PTEN-PI3K-AKT axis	57
miR-146a-5p ↑	HCC	Macrophage	Induce T cell exhaustion	SALL4/miR-146a-5p axis	52
miR-92b ↑	HCC	NK cell	Impair the cytotoxicity of NK cells	miR-92b/CD69 axis	81
miR-15a-5p ↓	HCC	$CD8^+$ T cells	Inhibits PD-1 expression in $CD8^+$ T cells	\	111
miR-21, miR-10b ↑	HCC	$CD4^+$ T cells	Disrupt the balance of $CD4^+$ T cell subtypes	\	127
\	Tumor cells	B cells	Induce PD-1^{hi} B-cell	\	137
miR-1247-3p ↑	HCC	fibroblasts	Activate CAFs and stimulate the release of IL-6 and IL-8	B4GALT3/β1-integrin/NF-κB axis	149
miR-1297 ↑	Hepatocytes (lipotoxic)	HSCs	Promote the activation and proliferation of HSCs, accelerate the progression of MAFLD	PTEN/PI3K/AKT signaling pathway	154
miR-222 ↑	Hepatocytes (infected with HBV)	HSCs	Promote HSC activation and exacerbate liver fibrosis	miR-222/TFRC axis	157
lncRNA					
HMMR-AS1 ↑	HCC	Macrophage	Induce M2 polarization of macrophage	miR-147a/ARID3A axis	46
lncRNA (HEIH) ↑	HCC	Macrophage	Induce M2 polarization of macrophage	HEIH/miR-98-5p/STAT3 axis	47
PCED1B-AS1 ↑	HCC	HCC	Suppress recipient T cell and macrophage activity	Increase PD-Ls expression on T cells and HCC cells	114
lncRNA CYTOR ↑	Hepatocytes (injured)	HSCs	Promote HSC activation and exacerbate liver fibrosis	CYTOR/miR-125/GDNF axis, TGF-β/Smad signaling pathway	155
circRNA					
hsa_circ_0074854 ↑	HCC	Macrophage	Promote M2 polarization of macrophage and EMT in HCC cells	\	48
circTMEM181 ↑	HCC	Macrophage	Suppress the function of $CD8^+$ T cell and enhance resistance to anti-PD-1 therapy	miR-488-3p/CD39/CD73/eATP-adenosine pathway	60
circUHRF1 ↑	HCC	NK cell	Induce NK cell exhaustion and decreases IFN-γ and TNF-α production	miR-449c-5p/TIM-3 axis	80
circPACRGL ↑	Tumor cells	Neutrophils	Promote the polarization of N2 Neutrophils	miR-142-3p, miR-506-3p/TGF-β1 axis	96

(continued)

Table 1. *(continued)*

Exosome component	Source cell	Recipient cell	Function	Pathway/Mechanism	Ref
circCCAR1 ↑	HCC	$CD8^+$ T cells	Suppress the function of $CD8^+$ T cell and enhance resistance to anti-PD-1 therapy	circCCAR1/miR-127-5p/WTAP axis	109
circZMIZ1 ↑	HCC	$CD8^+$ T cells	Induce apoptosis and decrease cytotoxicity in $CD8^+$ T cells	miR-15a-5p/KCNJ2 axis	110
circGSE1 ↑	HCC	$CD4^+$ T cells	Promote the expansion of Tregs	miR-324-5p/TGFBR1/Smad3 axis	124
DNA					
H2AFJ ↑	Hepatocytes (injured)	HSCs	Promote the migration and invasion of HSCs and exacerbate liver fibrosis	H2AFJ/MAPK/STMN1 axis	156
Protein					
LOXL4 ↑	HCC	Macrophage	Enhance the expression of PD-L1 and inhibit the cytotoxicity of $CD8^+$ T cells	IFN-STAT1 (STAT3)/PD-L1 axis	53,54
GOLM1 ↑	HCC	Macrophage	Enhance the expression of PD-L1 and suppress the function of $CD8^+$ T cells	CSN5-mediated deubiquitination	29
AFP, GPC3, HSP70 ↑	HCC	DCs	Promote DC maturation and activation	\	64
NKG2D ligands ↑	HCC	NK cell	Regulate the functionality and induce self-destructive behaviors of NK cells	\	89
TGF-β ↑	HCC	Neutrophils	Promote the phenotypic transition of neutrophils to N2	TGF-β/Axl/CXCL5 axis	99,100
HMGB1 ↑	Tumor cells	Neutrophils	Induce autophagy and N2-like phenotype in neutrophils	HMGB1/TLR4/NF-κB pathway	95
14-3-3ζ ↑	HCC	T cells	Induce $CD8^+$ T cell exhaustion and drive Treg cell differentiation	\	108
PD-L1 ↑	HCC	$CD8^+$ T cells	Suppress the cytotoxicity of $CD8^+$ T cells	Activate the HMGB1/RICTOR axis and AKT-mTORC1-P70S6K pathway	115,116
ICAM-1 ↑	HCC	$CD8^+$ T cells	Prerequisite for PD-L1-induced immune dysfunction in $CD8^+$ T cells	\	118
PD-L1 ↑	HCC	$CD4^+$ T cells	Impair the function of $CD4^+$ T cells and promote the immune escape of HCC	NorCA/FXR/SHP/PD-L1 axis	27
HMGB1 ↑	HCC	B cells	Induce TIM-1^+ Breg cells	HMGB1-TLR2/4-MAPK pathway	135
SMO ↑	HCC	HSCs	Promote activation proliferation, migration, invasion, and EMT in HSCs	MIRLET7BHG/SMO/Hedgehog signaling pathway	158
Lipids					
FAO, LD ↑	Tumor cells	DCs	Cause DC immune dysfunction	FAs/PPARα/FAO axis	70

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HSCs, hematopoietic stem cells; MAFLD, metabolic dysfunction–associated fatty liver disease; EMT, epithelial-mesenchymal transition; ↑, upregulation; ↓, downregulation.

Non-HCC-derived exosomes facilitate tumor development via crosstalk in the tumor immune microenvironment

Immune cell-derived exosomes

It is notable that exosomes derived from M1 macrophages frequently contain molecules that suppress tumor growth and contribute to a more effective immune response against tumors by transmitting anti-tumor signals and modulating the immune microenvironment, indicating their potential as an emerging therapeutic approach (Fig. 3).[161] For instance, exosomes derived from M1 macrophages facilitate the delivery of miR-628-5p to HCC cells, resulting in the suppression of METTL14 expression, which consequently obstructs the m6A

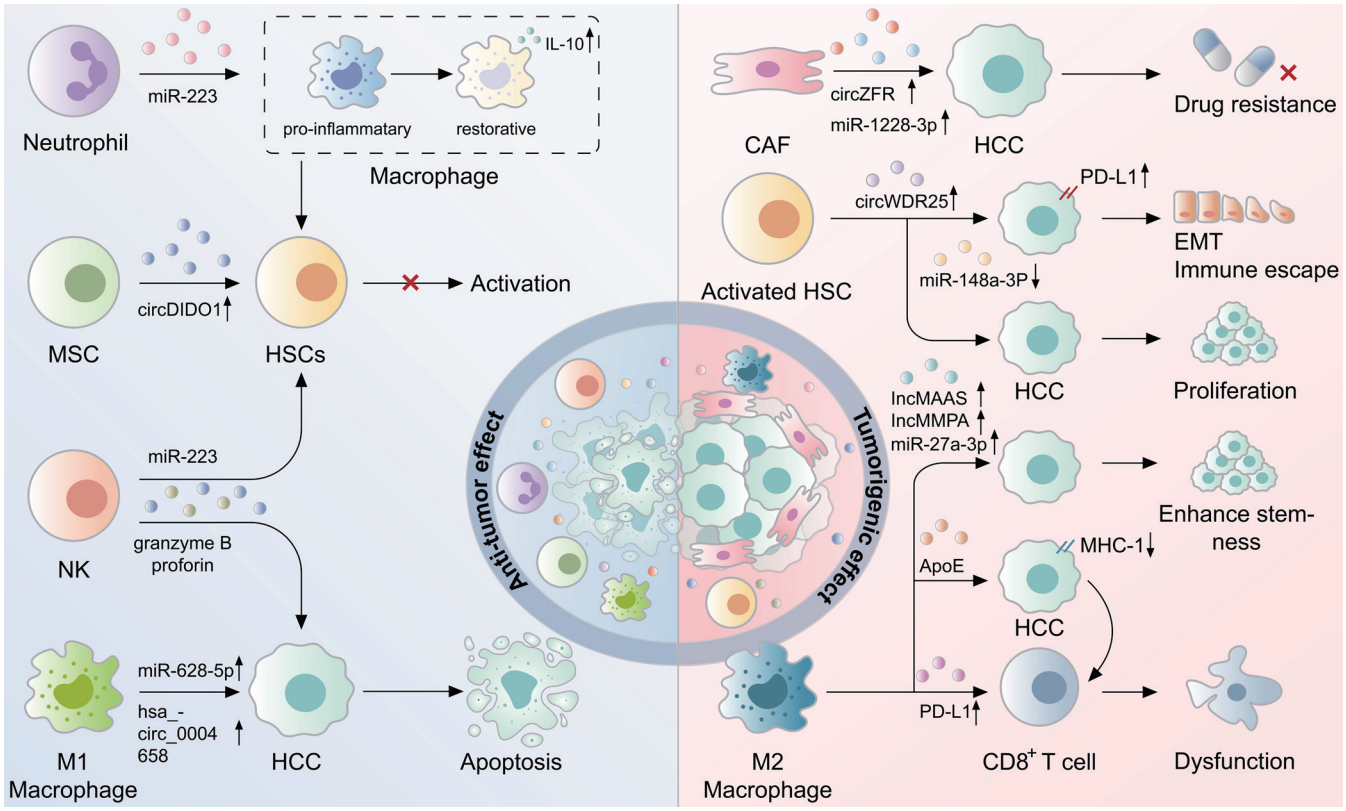

Fig. 3. The roles of non-HCC-derived exosomes in mediating crosstalk within the tumor immune microenvironment and HCC development. HCC, hepatocellular carcinoma. HSCs, Hepatic stellate cells; CAF, cancer-associated fibroblast; MSC, mesenchymal stem cells; ↑, upregulation; ↓, downregulation.

modification of circFUT8. This, in turn, impairs the circFUT8/miR-552-3p/CHMP4B pathway, ultimately inducing apoptosis in HCC cells rather than promoting their proliferation.[162] Furthermore, research by Zhang *et al*. has shown that exosomes derived from RBPJ-overexpressing macrophages deliver hsa_circ_0004658 to HCC cells, where hsa_circ_0004658 functions as a ceRNA for miR-499b-5p, relieving the suppression of JAM3. This, in turn, inhibits proliferation and promotes apoptosis in HCC cells.[163] Consequently, the development of therapies based on increasing the levels of these M1-derived exosomes, or the use of their mimics, provides a theoretical foundation for the effective inhibition of HCC progression.

Additionally, M2 macrophage-derived exosomes significantly exacerbate the malignancy of HCC cells by targeting them within the TIME (Fig. 2). As an illustration, Li *et al*. noted that M2 macrophage-derived exosomal miR-27a-3p directly targets HCC cells, enhancing cancer stemness by downregulating TXNIP.[164] Similarly, Tao *et al*. demonstrated that in HBV-related HCC, HBeAg secreted by HBV$^+$ HCC cells increases lncRNA MAPKAPK5_AS1 (hereinafter referred to as MAAS) expression in M2 macrophages through m6A modification. The elevated lncRNA MAAS is then transferred via exosomes to HBV$^+$ HCC cells, promoting their proliferation by targeting c-Myc. This highlights a crucial molecular mechanism linking HBV infection to HCC progression and suggests potential therapeutic targets.[165] Furthermore, Xu *et al*. discovered that exosomes derived from TAMs facilitate tumor progression through metabolic reprogramming, a characteristic feature of cancers such as HCC.[166] Metabolic reprogramming is a process whereby cellular metabolic pathways are altered to facilitate rapid growth and proliferation, with aerobic glycolysis being one of the most notable features.[167] Their research revealed that exosomes from M2-polarized macrophages transfer lncMMPA to HCC cells, where lncMMPA acts as a microRNA decoy, sequestering miR-548s and resulting in the upregulation of ALDH1A3 expression. Elevated ALDH1A3 levels enhance glucose-related metabolic activities, creating an environment that supports accelerated cell growth and proliferation in HCC.[166] Recent findings also indicate that exosomes from M2 macrophages impair T-cell-mediated tumor killing, thereby reducing the effectiveness of immune checkpoint blockade therapy. Proteomic analysis shows that M2-derived exosomal ApoE decreases the ATPase activity of the binding immunoglobulin protein, resulting in lower MHC-I expression on tumor cells. This reduces tumor immunogenicity and enhances resistance to CD8$^+$ T-cell-mediated cytotoxicity.[168] In addition, M2 macrophages exhibit elevated PD-L1 expression, leading to an increase in PD-L1-carrying exosomes. A molecular mechanism identified by Zhong *et al*. reveals that Akt stimulates exosome release from TAMs via phosphorylation of MADD, which then activates Rab27a. This mechanism is associated with elevated PD-L1 levels on TAM-derived exosomes, which have been shown to significantly inhibit the proliferation and functionality of CD8$^+$ T cells.[169] Finally, it is essential to recognize the mutual promotion between HCC-derived exosomes and M2 macrophages, as they create a feedback loop that mutually reinforces each other's pro-tumorigenic behavior.

Furthermore, neutrophil-derived exosomes have the capacity to modulate other immune cells, thereby decelerating the progression of HCC (Fig. 3). Studies have demonstrated that these exosomes transport miR-223 to hepatic mac-

rophages, inducing a phenotypic shift from pro-inflammatory to restorative macrophages that secrete IL-10 by targeting and inhibiting the NLRP3 gene. IL-10 enhances the expression of anti-inflammatory genes through the activation of the JAK-STAT signaling pathway, while simultaneously inhibiting HSC activation and reducing TGF-β expression. This ultimately decreases collagen production and deposition, alleviating liver fibrosis.[170] Subsequent studies using miR-223-deficient mice have revealed that these mice experience more severe steatohepatitis and HCC when exposed to a high-fat diet, further underscoring the importance of miR-223 as a critical counter-regulatory pathway in limiting HCC progression.[171]

Moreover, it has been demonstrated that exosomal cargos originating from other immune cells within the TIME, including DCs, NK cells, and Tregs, among others, significantly influence cancer progression (Fig. 3). NK cell-derived exosomes, for example, have been shown to carry cytotoxic proteins like perforin and granzyme B, which can trigger apoptosis in tumor cells.[172] Additionally, these exosomes also possess high levels of miR-223, which inhibits autophagy by targeting the autophagy-related gene ATG7. This attenuates the activation of HSCs induced by TGF-β, a prominent driver of HCC.[173] Regulating miR-223 expression could effectively suppress HSC activation, presenting a potential approach for preventing and treating liver fibrosis and related HCC.

Furthermore, Tregs exert their influence on the immune response not only by regulating the activity of effector T cells but also by modulating the function of other immune cells through the secretion of exosomes.[174] Tung *et al*. made a pioneering discovery showing that Treg-derived exosomes deliver miR-150-5p and miR-142-3p to DCs, inducing a tolerogenic phenotype with higher IL-10 levels and lower IL-6 levels, thus enhancing the suppression of antitumor immune responses.[175] Another study by Xie *et al*. reported that natural $CD8^+$ $CD25^+$ Treg-derived exosomes markedly reduced $CD8^+$ T cell responses initiated by DCs and antitumor immunity in vivo.[176] While these mechanisms have not been directly verified in HCC, they represent a potential mechanism and a direction for future research.

Non-immune cell-derived exosomes

Non-immune cells, such as CAFs and HSCs, are crucial in HCC progression through exosome-mediated bidirectional signaling within the TIME. Multiple studies have demonstrated that exosomes released by CAFs contain various signaling molecules that can significantly modulate the TIME, thereby enhancing tumor growth, facilitating immune escape, and contributing to drug resistance (Fig. 3). For instance, Dou *et al*. discovered that exosomes secreted by CAFs transport miR-92 to breast cancer cells, where YAP1 signaling is activated and subsequently translocated from the cytoplasm to the nucleus. This nuclear translocation results in the upregulation of PD-L1 expression, which impairs the cancer-killing capacity of the immune system through the PD-1/PD-L1 interaction, thereby facilitating immune evasion.[177] Additionally, CAF-derived exosomes have been linked to promoting chemoresistance in HCC. Zhou and colleagues identified that exosomal circZFR, highly expressed in exosomes from CAFs, is transferred to HCC cells, where it promotes HCC cell proliferation and reduces sensitivity to cisplatin by inhibiting the STAT3 and NF-κB signaling pathways.[178] Moreover, Zhang and others found that CAF-derived exosomes carrying miR-1228-3p enhance HCC's resistance to sorafenib through the activation of the PLAC8-mediated PI3K/AKT signaling pathway.[179] These findings suggest that targeting exosome-mediated communication could be a promising strategy for overcoming chemoresistance in HCC and developing effective exosome-based therapies.

Activated HSCs also impact the behavior of HCC cells through exosome-mediated pathways (Fig. 3). Specifically, exosomes from HCC-activated HSCs exhibit a notable upregulation of circWDR25, which triggers the EMT in HCC cells by modulating the circWDR25/miR-4474-3p/ALOX15 pathway. This process boosts HCC cell proliferation and invasiveness, while concurrently elevating CTLA-4 expression in HSCs and PD-L1 expression in HCC cells, which supports immune evasion.[180] Liu's research demonstrated that the depletion of miR-148a-3p in exosomes from activated HSCs facilitates the progression of HCC through the ITGA5/PI3K/Akt signaling axis. Increasing miR-148a-3p in these exosomes has been shown to suppress HCC cell proliferation, highlighting a potential target for therapeutic intervention.[181] Furthermore, exosomes produced by activated HSCs can be reabsorbed by quiescent HSCs, establishing a self-reinforcing loop that intensifies their activation and advances HCC progression.[149] Beyond CAFs and HSCs, exosomes from mesenchymal stem cells containing circDIDO1 have been proven to effectively inhibit HSC activation and reduce liver fibrosis by targeting miR-141-3p and modulating the PTEN/AKT signaling pathway (Fig. 3).[182] It is crucial to understand the intercellular interactions between non-immune and tumor cells through exosomal communication to facilitate the development of targeted therapies capable of disrupting signaling pathways and impeding HCC progression. While much research has been conducted on the effects of exosomes from tumor cells on their microenvironment, exosomes from non-tumor sources offer valuable insights for developing exosome-based therapeutic strategies for cancer progression.

The functions and pathways mediated by non-HCC-derived exosomes in immune cells and other cells within the HCC immune microenvironment are detailed in Figure 3 and Table 2.[162–166,168,170,173,175,177–182]

Application of exosome-mediated crosstalk in HCC immunotherapy

Despite advancements in conventional therapies like surgery, radiotherapy, and chemotherapy, the prognosis for HCC remains poor, with persistently high mortality rates. This underscores the urgent need for novel treatments that are safe, effective, and precisely targeted. Given their high biocompatibility, low immunogenicity, and robust capacity for targeted drug delivery, exosomes have emerged as promising tools in cancer immunotherapy, particularly in applications that enhance immune modulation and targeting specificity.[10,183] Engineering modifications further enhance exosome targeting and therapeutic efficacy, reducing adverse effects and improving treatment safety.[184] With these properties, exosomes enable the precise delivery of therapeutic proteins or nucleic acids directly to target cells. For instance, exosomes can be modified to deliver specific miRNAs directly to HCC cells, effectively disrupting oncogenic signaling pathways and curbing tumor growth.[185] Exosomes also offer innovative approaches by activating immune surveillance mechanisms, thus bolstering anti-tumor immune responses.[183,186]

A promising HCC strategy involves reprogramming macrophages towards an anti-tumor M1 phenotype using M1 macrophage-derived exosomes (M1-MEXs). Research shows that iron oxide nanoparticles promote M1 polarization in macrophages, significantly increasing pro-inflammatory factors such as TNF-α and IL-12 to suppress tumor growth.[187] Building on this, Chen and colleagues employed exosome-mediated delivery of PIONs@E6 to macrophages, amplifying M1 polarization, as evidenced by higher levels of IL-12,

Table 2. The function and pathways mediated by non-HCC-derived exosomes in the HCC immune microenvironment

Exosome component	Source cell	Recipient cell	Function	Pathway/Mechanism	Ref
miRNA					
miR-628-5p ↑	Macrophage	HCC	Induce the apoptosis of HCC cells	miR-628-5p/METTL14 axis, circFUT8/miR-552-3p/CHMP4B pathway	162
miR-27a-3p ↑	Macrophage	HCC	Enhance the stemness of HCC cells	miR-27a-3p/TXNIP axis	164
miR-223	Neutrophil	Macrophage	Regulate the activation state of macrophage and HSCs	miR-223/NLRP3 axis	170
miR-223	NK cells	HSCs	Inhibit autophagy and reducing activation in HSCs	miR-223/ATG7 axis	173
miR-150-5p and miR-142-3p ↑	Tregs	DCs	Induce a tolerogenic phenotype of DCs	\	175
miR-92 ↑	CAFs	Tumor cells	Upregulate PD-L1 expression	miR-92/LATS2/YAP1/PD-L1 axis	177
miR-1228-3p ↑	CAFs	HCC	Enhance HCC's resistance to sorafenib	PLAC8/PI3K/AKT signaling pathway	179
miR-148a-3p ↓	HSCs	HCC	Suppress the proliferation of HCC cells	ITGA5/PI3K/Akt pathway	181
lncRNA					
lncRNA MAAS ↑	Macrophage	HCC	Enhance the proliferation of HCC cells	MAAS/c-Myc axis	165
lncMMPA ↑	Macrophage	HCC	Promote the proliferation of HCC cells	lncMMPA/miR-548s/ALDH1A3 axis	166
circRNA					
hsa_circ_0004658 ↑	Macrophage	HCC	Induce the apoptosis of HCC cells	hsa_circ_0004658/miR-499b-5p/JAM3 axis	163
circZFR ↑	CAFs	HCC	Promote HCC cell proliferation and reduce sensitivity to cisplatin	STAT3 and NF-κB pathways	178
circWDR25 ↑	HSCs	HCC	Promote the proliferation and invasiveness of HCC cells	miR-4474-3p/ALOX15 axis	180
circDIDO1 ↑	MSCs	HCC	Inhibit the activation of HSC	PTEN/AKT pathway	182
Protein					
ApoE ↑	Macrophage	Tumor cells	Lower the MHC-I expression on tumor cells	\	168

HCC, hepatocellular carcinoma; HSCs, hematopoietic stem cells; CAF, cancer-associated fibroblasts; MSCs, mesenchymal stem cells; ↑, upregulation; ↓, downregulation.

TNF-α, and ROS, which effectively suppressed tumor growth in an HCC mouse model.[188] Another study engineered M1-MEXs to carry NF-κB p50 siRNA and miR-511-3p, with IL4R-targeting peptides for selective M2 macrophage targeting. These modified M1-MEXs downregulated NF-κB p50 and ROCK2 upon uptake by M2 macrophages, inhibited tumor cell proliferation, and boosted M1 markers.[189] Although MEXs are still in the early clinical stages, their potential as drug carriers and immune modulators is gaining traction, particularly with PTX-loaded MEXs showing reduced chemotherapy toxicity alongside significant tumor suppression.[190]

DEXs represent another promising avenue in cancer immunotherapy. DEXs possess innate antigen-presenting capabilities, allowing them to carry tumor antigens and activate specific T cells to induce a robust CTL response.[191] The presence of CCR7 on DEXs aids in their migration to the spleen, thereby enhancing targeting efficiency.[192,193] Additionally, molecules like IL-15Rα, TNF family ligands, and NKG2D on DEXs directly activate NK cells, further strengthening the anti-tumor response.[194,195] Research in mouse models has demonstrated that DEXs stimulate mature DCs, significantly enhancing antigen-specific T cell activity.[196] In HCC models, alpha-fetoprotein-modified DEXs reduced immunosuppressive factors such as IL-10 and TGF-β within the TME and increased IFN-γ expression in $CD8^+$ T cells.[64] Chen *et al*. developed a multifunctional DEX vaccine (DEXP&A2&N) incorporating targeting ligands, antigens, and peptide adjuvants, which effectively recruited and activated DCs. This activation stimulated both innate and adaptive immunity, achieving complete tumor regression in HCC mouse models.[197] DEXs generated from tumor-specific antigens have shown significant anti-tumor effects across various tumor models by activating T and B cells and enhancing CTL responses.[198] In a Phase I clinical trial, DEXs as vaccines showed good tolerance and generated immune responses in cancers such as lung cancer and melanoma, with some patients experiencing

notable tumor reduction, though effectiveness in advanced cases with weak immune activation remains limited.[191,199,200]

Despite innovations in exosome engineering, challenges remain in clinical application. Technologies like electroporation, nanotechnology, and environment-sensitive materials have improved drug loading and release control. Yet, exosomes still face standardization challenges in extraction, purification, and quality control. These inconsistencies can lead to variable results across experiments and clinical trials, limiting scalability.[201] Furthermore, common delivery methods—such as subcutaneous and intravenous injections—often suffer from low absorption, rapid clearance, and nonspecific distribution.[202,203]

Thus, advancing high-efficiency exosome extraction and purification methods, promoting standardized protocols, and optimizing delivery strategies remain essential.[25] Microfluidic technology, which allows for precise physical filtration, is increasingly applied in exosome isolation to enhance quality.[204] Further investigation into exosome metabolism and biodistribution will be critical in refining clinical applications of exosome-based therapies for cancer.

Conclusions

This review provides a comprehensive investigation of the latest functions and mechanisms of both HCC-derived and non-HCC-derived exosomes in the regulation of TIME. We have discussed how exosomes contribute to tumor growth by creating an immunosuppressive environment. The therapeutic potential of exosomes in the context of HCC is considerable. They have the potential to be utilized as targeted drug delivery systems, to modulate the immune system, and even to serve as vaccines to enhance anti-cancer immunity.

Nevertheless, several challenges remain, particularly those related to the heterogeneity of exosomes, the effectiveness of exosome isolation and delivery, and the possibility that exosomes may promote rather than inhibit tumor growth. Future research needs to focus on exploring the specific molecular mechanisms by which exosomes influence the interactions and functional regulation of different cellular components within the TIME. The development of models incorporating various cell types within the TIME is essential for better understanding the synergistic effects. Such approaches will allow researchers to study the collective effects of cell interactions in the tumor immune microenvironment, uncover the intricate processes of exosome-tumor-immune interactions, and identify new therapeutic targets. To fully exploit exosomes as a therapeutic tool, it is essential to develop advanced techniques for their isolation and characterization. Moreover, clinical research is necessary to ascertain the safety and efficacy of exosome-based therapies in patients with HCC.

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Conflict of interest

JWPY has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

Author contributions

Writing—original draft preparation (YG, LJ), writing—review and editing (QD, JWPY, YX, XZ), and supervision (XZ). All authors have read and agreed to the published version of the manuscript.

References

[1] Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. J Hepatol 2020;72(2):250–261. doi:10.1016/j.jhep.2019.08.025, PMID:31954490.
[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71(3):209–249. doi:10.3322/caac.21660, PMID:33538338.
[3] Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, *et al*. Hepatocellular carcinoma. Nat Rev Dis Primers 2021;7(1):6. doi:10.1038/s41572-020-00240-3, PMID:33479224.
[4] Hollebecque A, Malka D, Ferté C, Ducreux M, Boige V. Systemic treatment of advanced hepatocellular carcinoma: from disillusions to new horizons. Eur J Cancer 2015;51(3):327–339. doi:10.1016/j.ejca.2014.12.005, PMID:25559615.
[5] De Jaeghere EA, Denys HG, De Wever O. Fibroblasts Fuel Immune Escape in the Tumor Microenvironment. Trends Cancer 2019;5(11):704–723. doi:10.1016/j.trecan.2019.09.009, PMID:31735289.
[6] Li X, Ramadori P, Pfister D, Seehawer M, Zender L, Heikenwalder M. The immunological and metabolic landscape in primary and metastatic liver cancer. Nat Rev Cancer 2021;21(9):541–557. doi:10.1038/s41568-021-00383-9, PMID:34326518.
[7] Tie Y, Tang F, Wei YQ, Wei XW. Immunosuppressive cells in cancer: mechanisms and potential therapeutic targets. J Hematol Oncol 2022;15(1):61. doi:10.1186/s13045-022-01282-8, PMID:35585567.
[8] Lian X, Yang K, Li R, Li M, Zuo J, Zheng B, *et al*. Immunometabolic rewiring in tumorigenesis and anti-tumor immunotherapy. Mol Cancer 2022;21(1):27. doi:10.1186/s12943-021-01486-5, PMID:35062950.
[9] He G, Peng X, Wei S, Yang S, Li X, Huang M, *et al*. Exosomes in the hypoxic TME: from release, uptake and biofunctions to clinical applications. Mol Cancer 2022;21(1):19. doi:10.1186/s12943-021-01440-5, PMID:35039054.
[10] Liang Y, Duan L, Lu J, Xia J. Engineering exosomes for targeted drug delivery. Theranostics 2021;11(7):3183–3195. doi:10.7150/thno.52570, PMID:33537081.
[11] Zitvogel L, Regnault A, Lozier A, Wolfers J, Flament C, Tenza D, *et al*. Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell-derived exosomes. Nat Med 1998;4(5):594–600. doi:10.1038/nm0598-594, PMID:9585234.
[12] CHARGAFF E, WEST R. The biological significance of the thromboplastic protein of blood. J Biol Chem 1946;166(1):189–197. PMID:20273687.
[13] Wolf P. The nature and significance of platelet products in human plasma. Br J Haematol 1967;13(3):269–288. doi:10.1111/j.1365-2141.1967.tb08741.x, PMID:6025241.
[14] Raposo G, Nijman HW, Stoorvogel W, Liejendekker R, Harding CV, Melief CJ, *et al*. B lymphocytes secrete antigen-presenting vesicles. J Exp Med 1996;183(3):1161–1172. doi:10.1084/jem.183.3.1161, PMID:8642258.
[15] Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science 2020;367:6478. doi:10.1126/science.aau6977, PMID:32029601.
[16] Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol 2013;200(4):373–383. doi:10.1083/jcb.201211138, PMID:23420871.
[17] Li X, Li C, Zhang L, Wu M, Cao K, Jiang F, *et al*. The significance of exosomes in the development and treatment of hepatocellular carcinoma. Mol Cancer 2020;19(1):1. doi:10.1186/s12943-019-1085-0, PMID:31901224.
[18] Huang M, Peng X, Yang L, Yang S, Li X, Tang S, *et al*. Non-coding RNA derived from extracellular vesicles in cancer immune escape: Biological functions and potential clinical applications. Cancer Lett 2021;501:234–246. doi:10.1016/j.canlet.2020.11.005, PMID:33186654.
[19] Han QF, Li WJ, Hu KS, Gao J, Zhai WL, Yang JH, *et al*. Exosome biogenesis:

machinery, regulation, and therapeutic implications in cancer. Mol Cancer 2022;21(1):207. doi:10.1186/s12943-022-01671-0, PMID:36320056.
[20] Cardona-López X, Cuyas L, Marín E, Rajulu C, Irigoyen ML, Gil E, *et al*. ESCRT-III-Associated Protein ALIX Mediates High-Affinity Phosphate Transporter Trafficking to Maintain Phosphate Homeostasis in Arabidopsis. Plant Cell 2015;27(9):2560–2581. doi:10.1105/tpc.15.00393, PMID:26342016.
[21] Hurley JH, Hanson PI. Membrane budding and scission by the ESCRT machinery: it's all in the neck. Nat Rev Mol Cell Biol 2010;11(8):556–566. doi:10.1038/nrm2937, PMID:20588296.
[22] Henne WM, Buchkovich NJ, Emr SD. The ESCRT pathway. Dev Cell 2011;21(1):77–91. doi:10.1016/j.devcel.2011.05.015, PMID:21763610.
[23] Théry C. Exosomes: secreted vesicles and intercellular communications. F1000 Biol Rep 2011;3:15. doi:10.3410/B3-15, PMID:21876726.
[24] Piper RC, Katzmann DJ. Biogenesis and function of multivesicular bodies. Annu Rev Cell Dev Biol 2007;23:519–547. doi:10.1146/annurev.cellbio.23.090506.123319, PMID:17506697.
[25] van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol 2018;19(4):213–228. doi:10.1038/nrm.2017.125, PMID:29339798.
[26] Ginini L, Billan S, Fridman E, Gil Z. Insight into Extracellular Vesicle-Cell Communication: From Cell Recognition to Intracellular Fate. Cells 2022;11(9):1375. doi:10.3390/cells11091375, PMID:35563681.
[27] Gong Y, Li K, Qin Y, Zeng K, Liu J, Huang S, *et al*. Norcholic Acid Promotes Tumor Progression and Immune Escape by Regulating Farnesoid X Receptor in Hepatocellular Carcinoma. Front Oncol 2021;11:711448. doi:10.3389/fonc.2021.711448, PMID:34888230.
[28] Yang L, Peng X, Li Y, Zhang X, Ma Y, Wu C, *et al*. Long non-coding RNA HOTAIR promotes exosome secretion by regulating RAB35 and SNAP23 in hepatocellular carcinoma. Mol Cancer 2019;18(1):78. doi:10.1186/s12943-019-0990-6, PMID:30943982.
[29] Chen J, Lin Z, Liu L, Zhang R, Geng Y, Fan M, *et al*. GOLM1 exacerbates CD8(+) T cell suppression in hepatocellular carcinoma by promoting exosomal PD-L1 transport into tumor-associated macrophages. Signal Transduct Target Ther 2021;6(1):397. doi:10.1038/s41392-021-00784-0, PMID:34795203.
[30] Fu T, Dai LJ, Wu SY, Xiao Y, Ma D, Jiang YZ, *et al*. Spatial architecture of the immune microenvironment orchestrates tumor immunity and therapeutic response. J Hematol Oncol 2021;14(1):98. doi:10.1186/s13045-021-01103-4, PMID:34172088.
[31] Tien FM, Lu HH, Lin SY, Tsai HC. Epigenetic remodeling of the immune landscape in cancer: therapeutic hurdles and opportunities. J Biomed Sci 2023;30(1):3. doi:10.1186/s12929-022-00893-0, PMID:36627707.
[32] Zhou D, Huang C, Lin Z, Zhan S, Kong L, Fang C, *et al*. Macrophage polarization and function with emphasis on the evolving roles of coordinated regulation of cellular signaling pathways. Cell Signal 2014;26(2):192–197. doi:10.1016/j.cellsig.2013.11.004, PMID:24219909.
[33] Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. J Clin Invest 2012;122(3):787–795. doi:10.1172/JCI59643, PMID:22378047.
[34] Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. Nat Immunol 2010;11(10):889–896. doi:10.1038/ni.1937, PMID:20856220.
[35] Hartley GP, Chow L, Ammons DT, Wheat WH, Dow SW. Programmed Cell Death Ligand 1 (PD-L1) Signaling Regulates Macrophage Proliferation and Activation. Cancer Immunol Res 2018;6(10):1260–1273. doi:10.1158/2326-6066.CIR-17-0537, PMID:30012633.
[36] Maeda S, Kamata H, Luo JL, Leffert H, Karin M. IKKbeta couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis. Cell 2005;121(7):977–990. doi:10.1016/j.cell.2005.04.014, PMID:15989949.
[37] Wan S, Kuo N, Kryczek I, Zou W, Welling TH. Myeloid cells in hepatocellular carcinoma. Hepatology 2015;62(4):1304–1312. doi:10.1002/hep.27867, PMID:25914264.
[38] Lu Y, Han G, Zhang Y, Zhang L, Li Z, Wang Q, *et al*. M2 macrophage-secreted exosomes promote metastasis and increase vascular permeability in hepatocellular carcinoma. Cell Commun Signal 2023;21(1):299. doi:10.1186/s12964-022-00872-w, PMID:37904170.
[39] Choi JY, Seok HJ, Lee DH, Lee E, Kim TJ, Bae S, *et al*. Tumor-derived miR-6794-5p enhances cancer growth by promoting M2 macrophage polarization. Cell Commun Signal 2024;22(1):190. doi:10.1186/s12964-024-01570-5, PMID:38521953.
[40] Hu Z, Yin Y, Jiang J, Yan C, Wang Y, Wang D, *et al*. Exosomal miR-142-3p secreted by hepatitis B virus (HBV)-hepatocellular carcinoma (HCC) cells promotes ferroptosis of M1-type macrophages through SLC3A2 and the mechanism of HCC progression. J Gastrointest Oncol 2022;13(2):754–767. doi:10.21037/jgo-21-916, PMID:35557596.
[41] Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 2019;16(10):589–604. doi:10.1038/s41575-019-0186-y, PMID:31439937.
[42] Niu Y, Chen J, Qiao Y. Epigenetic Modifications in Tumor-Associated Macrophages: A New Perspective for an Old Foe. Front Immunol 2022;13:836223. doi:10.3389/fimmu.2022.836223, PMID:35140725.
[43] Zongqiang H, Jiapeng C, Yingpeng Z, Chuntao Y, Yiting W, Jiashun Z, *et al*. Exosomal miR-452-5p Induce M2 Macrophage Polarization to Accelerate Hepatocellular Carcinoma Progression by Targeting TIMP3. J Immunol Res 2022;2022:1032106. doi:10.1155/2022/1032106, PMID:36164322.
[44] Cheng Y, Cheng T, Qu Y. TIMP-3 suppression induces choroidal neovascularization by moderating the polarization of macrophages in age-related macular degeneration. Mol Immunol 2019;106:119–126. doi:10.1016/j.molimm.2018.12.026, PMID:30594674.
[45] Yu H, Pan J, Zheng S, Cai D, Luo A, Xia Z, *et al*. Hepatocellular Carcinoma Cell-Derived Exosomal miR-21-5p Induces Macrophage M2 Polarization by Targeting RhoB. Int J Mol Sci 2023;24(5):4593. doi:10.3390/ijms24054593, PMID:36902024.
[46] Wang X, Zhou Y, Dong K, Zhang H, Gong J, Wang S. Exosomal lncRNA HMMR-AS1 mediates macrophage polarization through miR-147a/ARID3A axis under hypoxia and affects the progression of hepatocellular carcinoma. Environ Toxicol 2022;37(6):1357–1372. doi:10.1002/tox.23489, PMID:35179300.
[47] Ai JH, Wen YZ, Dai SJ, Zhang LD, Huang ZJ, Shi J. Exosomal lncRNA HEIH, an essential communicator for hepatocellular carcinoma cells and macrophage M2 polarization through the miR-98-5p/STAT3 axis. J Biochem Mol Toxicol 2024;38(4):e23686. doi:10.1002/jbt.23686, PMID:38549433.
[48] Wang Y, Gao R, Li J, Tang S, Li S, Tong Q, *et al*. Downregulation of hsa_circ_0074854 Suppresses the Migration and Invasion in Hepatocellular Carcinoma via Interacting with HuR and via Suppressing Exosomes-Mediated Macrophage M2 Polarization. Int J Nanomedicine 2021;16:2803–2818. doi:10.2147/IJN.S284560, PMID:33880025.
[49] Blackwell RH, Foreman KE, Gupta GN. The Role of Cancer-Derived Exosomes in Tumorigenicity & Epithelial-to-Mesenchymal Transition. Cancers (Basel) 2017;9(8):105. doi:10.3390/cancers9080105, PMID:28796150.
[50] Gu W, Yang Y, Liu J, Xue J, Zhao H, Mao L, *et al*. Tumor-derived exosomes promote macrophages M2 polarization through miR-1-3p and regulate the progression of liver cancer. Mol Immunol 2023;162:64–73. doi:10.1016/j.molimm.2023.08.006, PMID:37657187.
[51] Jiang X, Liu G, Li Y, Pan Y. Immune checkpoint: The novel target for antitumor therapy. Genes Dis 2021;8(1):25–37. doi:10.1016/j.gendis.2019.12.004, PMID:33569511.
[52] Yin C, Han Q, Xu D, Zheng B, Zhao X, Zhang J. SALL4-mediated upregulation of exosomal miR-146a-5p drives T-cell exhaustion by M2 tumor-associated macrophages in HCC. Oncoimmunology 2019;8(7):1601479. doi:10.1080/2162402X.2019.1601479, PMID:31143524.
[53] Tan HY, Wang N, Zhang C, Chan YT, Yuen MF, Feng Y. Lysyl Oxidase-Like 4 Fosters an Immunosuppressive Microenvironment During Hepatocarcinogenesis. Hepatology 2021;73(6):2326–2341. doi:10.1002/hep.31600, PMID:33068461.
[54] Zhao L, Pei R, Ding Y, Su Z, Li D, Zhu S, *et al*. LOXL4 Shuttled by Tumor Cells-derived Extracellular Vesicles Promotes Immune Escape in Hepatocellular Carcinoma by Activating the STAT1/PD-L1 Axis. J Immunother 2024;47(2):64–76. doi:10.1097/CJI.0000000000000496, PMID:38047403.
[55] Clarke HJ, Chambers JE, Liniker E, Marciniak SJ. Endoplasmic reticulum stress in malignancy. Cancer Cell 2014;25(5):563–573. doi:10.1016/j.ccr.2014.03.015, PMID:24823636.
[56] Yao X, Tu Y, Xu Y, Guo Y, Yao F, Zhang X. Endoplasmic reticulum stress-induced exosomal miR-27a-3p promotes immune escape in breast cancer via regulating PD-L1 expression in macrophages. J Cell Mol Med 2020;24(17):9560–9573. doi:10.1111/jcmm.15367, PMID:32672418.
[57] Liu J, Fan L, Yu H, Zhang J, He Y, Feng D, *et al*. Endoplasmic Reticulum Stress Causes Liver Cancer Cells to Release Exosomal miR-23a-3p and Up-regulate Programmed Death Ligand 1 Expression in Macrophages. Hepatology 2019;70(1):241–258. doi:10.1002/hep.30607, PMID:30854665.
[58] Gai X, Tang B, Liu F, Wu Y, Wang F, Jing Y, *et al*. mTOR/miR-145-regulated exosomal GOLM1 promotes hepatocellular carcinoma through augmented GSK-3β/MMPs. J Genet Genomics 2019;46(5):235–245. doi:10.1016/j.jgg.2019.03.013, PMID:31186161.
[59] Sun C, Lan P, Han Q, Huang M, Zhang Z, Xu G, *et al*. Oncofetal gene SALL4 reactivation by hepatitis B virus counteracts miR-200c in PD-L1-induced T cell exhaustion. Nat Commun 2018;9(1):1241. doi:10.1038/s41467-018-03584-3, PMID:29593314.
[60] Lu JC, Zhang PF, Huang XY, Guo XJ, Gao C, Zeng HY, *et al*. Amplification of spatially isolated adenosine pathway by tumor-macrophage interaction induces anti-PD1 resistance in hepatocellular carcinoma. J Hematol Oncol 2021;14(1):200. doi:10.1186/s13045-021-01207-x, PMID:34838121.
[61] Yu S, Liu C, Su K, Wang J, Liu Y, Zhang L, *et al*. Tumor exosomes inhibit differentiation of bone marrow dendritic cells. J Immunol 2007;178(11):6867–6875. doi:10.4049/jimmunol.178.11.6867, PMID:17513735.
[62] Hosseini R, Asef-Kabiri L, Yousefi H, Sarvnaz H, Salehi M, Akbari ME, *et al*. The roles of tumor-derived exosomes in altered differentiation, maturation and function of dendritic cells. Mol Cancer 2021;20(1):83. doi:10.1186/s12943-021-01376-w, PMID:34078376.
[63] Robbins PD, Morelli AE. Regulation of immune responses by extracellular vesicles. Nat Rev Immunol 2014;14(3):195–208. doi:10.1038/nri3622, PMID:24566916.
[64] Rao Q, Zuo B, Lu Z, Gao X, You A, Wu C, *et al*. Tumor-derived exosomes elicit tumor suppression in murine hepatocellular carcinoma models and humans in vitro. Hepatology 2016;64(2):456–472. doi:10.1002/hep.28549, PMID:26990897.
[65] Shi S, Wang L, Wang C, Xu J, Niu Z. Serum-derived exosomes function as tumor antigens in patients with advanced hepatocellular carcinoma. Mol Immunol 2021;134:210–217. doi:10.1016/j.molimm.2021.03.017, PMID:33819783.
[66] Ning Y, Shen K, Wu Q, Sun X, Bai Y, Xie Y, *et al*. Tumor exosomes block dendritic cells maturation to decrease the T cell immune response. Immunol Lett 2018;199:36–43. doi:10.1016/j.imlet.2018.05.002, PMID:29800589.
[67] Maus RLG, Jakub JW, Hieken TJ, Nevala WK, Christensen TA, Sutor SL, *et al*. Identification of novel, immune-mediating extracellular vesicles in human lymphatic effluent draining primary cutaneous melanoma. Oncoimmunology 2019;8(12):e1667742. doi:10.1080/2162402X.2019.1667742, PMID:31741769.
[68] Zhu L, Lou Y, Xiao Q, Wang L, Chen G, Yang W, *et al*. Establishment and

Evaluation of Exosomes-Related Gene Risk Model in Hepatocellular Carcinoma. Biochem Genet 2024;62(2):698–717. doi:10.1007/s10528-023-10441-6, PMID:37405532.
[69] Haraszti RA, Didiot MC, Sapp E, Leszyk J, Shaffer SA, Rockwell HE, *et al*. High-resolution proteomic and lipidomic analysis of exosomes and microvesicles from different cell sources. J Extracell Vesicles 2016;5:32570. doi:10.3402/jev.v5.32570, PMID:27863537.
[70] Yin X, Zeng W, Wu B, Wang L, Wang Z, Tian H, *et al*. PPARα Inhibition Overcomes Tumor-Derived Exosomal Lipid-Induced Dendritic Cell Dysfunction. Cell Rep 2020;33(3):108278. doi:10.1016/j.celrep.2020.108278, PMID:33086073.
[71] Scarlett UK, Rutkowski MR, Rauwerdink AM, Fields J, Escovar-Fadul X, Baird J, *et al*. Ovarian cancer progression is controlled by phenotypic changes in dendritic cells. J Exp Med 2012;209(3):495–506. doi:10.1084/jem.20111413, PMID:22351930.
[72] Laoui D, Keirsse J, Morias Y, Van Overmeire E, Geeraerts X, Elkrim Y, *et al*. The tumour microenvironment harbours ontogenically distinct dendritic cell populations with opposing effects on tumour immunity. Nat Commun 2016;7:13720. doi:10.1038/ncomms13720, PMID:28008905.
[73] Ran GH, Lin YQ, Tian L, Zhang T, Yan DM, Yu JH, *et al*. Natural killer cell homing and trafficking in tissues and tumors: from biology to application. Signal Transduct Target Ther 2022;7(1):205. doi:10.1038/s41392-022-01058-z, PMID:35768424.
[74] Hu Z, Xu X, Wei H. The Adverse Impact of Tumor Microenvironment on NK-Cell. Front Immunol 2021;12:633361. doi:10.3389/fimmu.2021.633361, PMID:34177887.
[75] Dębska-Zielkowska J, Moszkowska G, Zieliński M, Zielińska H, Dukat-Mazurek A, Trzonkowski P, *et al*. KIR Receptors as Key Regulators of NK Cells Activity in Health and Disease. Cells 2021;10(7):1777. doi:10.3390/cells10071777, PMID:34359951.
[76] Cheng M, Chen Y, Xiao W, Sun R, Tian Z. NK cell-based immunotherapy for malignant diseases. Cell Mol Immunol 2013;10(3):230–252. doi:10.1038/cmi.2013.10, PMID:23604045.
[77] Dong W, Wu X, Ma S, Wang Y, Nalin AP, Zhu Z, *et al*. The Mechanism of Anti-PD-L1 Antibody Efficacy against PD-L1-Negative Tumors Identifies NK Cells Expressing PD-L1 as a Cytolytic Effector. Cancer Discov 2019;9(10):1422–1437. doi:10.1158/2159-8290.CD-18-1259, PMID:31340937.
[78] Melaiu O, Lucarini V, Cifaldi L, Fruci D. Influence of the Tumor Microenvironment on NK Cell Function in Solid Tumors. Front Immunol 2019;10:3038. doi:10.3389/fimmu.2019.03038, PMID:32038612.
[79] Liu Z, You Y, Chen Q, Li G, Pan W, Yang Q, *et al*. Extracellular vesicle-mediated communication between hepatocytes and natural killer cells promotes hepatocellular tumorigenesis. Mol Ther 2022;30(2):606–620. doi:10.1016/j.ymthe.2021.07.015, PMID:34601133.
[80] Zhang PF, Gao C, Huang XY, Lu JC, Guo XJ, Shi GM, *et al*. Cancer cell-derived exosomal circUHRF1 induces natural killer cell exhaustion and may cause resistance to anti-PD1 therapy in hepatocellular carcinoma. Mol Cancer 2020;19(1):110. doi:10.1186/s12943-020-01222-5, PMID:32593303.
[81] Nakano T, Chen IH, Wang CC, Chen PJ, Tseng HP, Huang KT, *et al*. Circulating exosomal miR-92b: Its role for cancer immunoediting and clinical value for prediction of posttransplant hepatocellular carcinoma recurrence. Am J Transplant 2019;19(12):3250–3262. doi:10.1111/ajt.15490, PMID:31162867.
[82] Le Bert N, Gasser S. Advances in NKG2D ligand recognition and responses by NK cells. Immunol Cell Biol 2014;92(3):230–236. doi:10.1038/icb.2013.111, PMID:24445601.
[83] Dhar P, Wu JD. NKG2D and its ligands in cancer. Curr Opin Immunol 2018;51:55–61. doi:10.1016/j.coi.2018.02.004, PMID:29525346.
[84] Mincheva-Nilsson L, Baranov V. Cancer exosomes and NKG2D receptor-ligand interactions: impairing NKG2D-mediated cytotoxicity and anti-tumour immune surveillance. Semin Cancer Biol 2014;28:24–30. doi:10.1016/j.semcancer.2014.02.010, PMID:24602822.
[85] Schmiedel D, Mandelboim O. NKG2D Ligands-Critical Targets for Cancer Immune Escape and Therapy. Front Immunol 2018;9:2040. doi:10.3389/fimmu.2018.02040, PMID:30254634.
[86] Ashiru O, Boutet P, Fernández-Messina L, Agüera-González S, Skepper JN, Valés-Gómez M, *et al*. Natural killer cell cytotoxicity is suppressed by exposure to the human NKG2D ligand MICA*008 that is shed by tumor cells in exosomes. Cancer Res 2010;70(2):481–489. doi:10.1158/0008-5472.CAN-09-1688, PMID:20068167.
[87] Hedlund M, Nagaeva O, Kargl D, Baranov V, Mincheva-Nilsson L. Thermal- and oxidative stress causes enhanced release of NKG2D ligand-bearing immunosuppressive exosomes in leukemia/lymphoma T and B cells. PLoS One 2011;6(2):e16899. doi:10.1371/journal.pone.0016899, PMID:21364924.
[88] Xiao W, Dong W, Zhang C, Saren G, Geng P, Zhao H, *et al*. Effects of the epigenetic drug MS-275 on the release and function of exosome-related immune molecules in hepatocellular carcinoma cells. Eur J Med Res 2013;18(1):61. doi:10.1186/2047-783X-18-61, PMID:24359553.
[89] Vulpis E, Loconte L, Peri A, Molfetta R, Caracciolo G, Masuelli L, *et al*. Impact on NK cell functions of acute versus chronic exposure to extracellular vesicle-associated MICA: Dual role in cancer immunosurveillance. J Extracell Vesicles 2022;11(1):e12176. doi:10.1002/jev2.12176, PMID:34973063.
[90] Sionov RV, Fridlender ZG, Granot Z. The Multifaceted Roles Neutrophils Play in the Tumor Microenvironment. Cancer Microenviron 2015;8(3):125–158. doi:10.1007/s12307-014-0147-5, PMID:24895166.
[91] Yu X, Li C, Wang Z, Xu Y, Shao S, Shao F, *et al*. Neutrophils in cancer: dual roles through intercellular interactions. Oncogene 2024;43(16):1163–1177. doi:10.1038/s41388-024-03004-5, PMID:38472320.
[92] Jaillon S, Galdiero MR, Del Prete D, Cassatella MA, Garlanda C, Mantovani A. Neutrophils in innate and adaptive immunity. Semin Immunopathol 2013;35(4):377–394. doi:10.1007/s00281-013-0374-8, PMID:23553214.
[93] Jaillon S, Ponzetta A, Di Mitri D, Santoni A, Bonecchi R, Mantovani A. Neutrophil diversity and plasticity in tumour progression and therapy. Nat Rev Cancer 2020;20(9):485–503. doi:10.1038/s41568-020-0281-y, PMID:32694624.
[94] Qi M, Xia Y, Wu Y, Zhang Z, Wang X, Lu L, *et al*. Lin28B-high breast cancer cells promote immune suppression in the lung pre-metastatic niche via exosomes and support cancer progression. Nat Commun 2022;13(1):897. doi:10.1038/s41467-022-28438-x, PMID:35173168.
[95] Zhang X, Shi H, Yuan X, Jiang P, Qian H, Xu W. Tumor-derived exosomes induce N2 polarization of neutrophils to promote gastric cancer cell migration. Mol Cancer 2018;17(1):146. doi:10.1186/s12943-018-0898-6, PMID:30292233.
[96] Shang A, Gu C, Wang W, Wang X, Sun J, Zeng B, *et al*. Exosomal circPACRGL promotes progression of colorectal cancer via the miR-142-3p/miR-506-3p- TGF-β1 axis. Mol Cancer 2020;19(1):117. doi:10.1186/s12943-020-01235-0, PMID:32713345.
[97] Liu Y, Gu Y, Han Y, Zhang Q, Jiang Z, Zhang X, *et al*. Tumor Exosomal RNAs Promote Lung Pre-metastatic Niche Formation by Activating Alveolar Epithelial TLR3 to Recruit Neutrophils. Cancer Cell 2016;30(2):243–256. doi:10.1016/j.ccell.2016.06.021, PMID:27505671.
[98] Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, Ling L, *et al*. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. Cancer Cell 2009;16(3):183–194. doi:10.1016/j.ccr.2009.06.017, PMID:19732719.
[99] Yang N, Li S, Li G, Zhang S, Tang X, Ni S, *et al*. The role of extracellular vesicles in mediating progression, metastasis and potential treatment of hepatocellular carcinoma. Oncotarget 2017;8(2):3683–3695. doi:10.18632/oncotarget.12465, PMID:27713136.
[100] Haider C, Hnat J, Wagner R, Huber H, Timelthaler G, Grubinger M, *et al*. Transforming Growth Factor-β and Axl Induce CXCL5 and Neutrophil Recruitment in Hepatocellular Carcinoma. Hepatology 2019;69(1):222–236. doi:10.1002/hep.30166, PMID:30014484.
[101] Furumaya C, Martinez-Sanz P, Bouti P, Kuijpers TW, Matlung HL. Plasticity in Pro- and Anti-tumor Activity of Neutrophils: Shifting the Balance. Front Immunol 2020;11:2100. doi:10.3389/fimmu.2020.02100, PMID:32983165.
[102] Li XF, Chen DP, Ouyang FZ, Chen MM, Wu Y, Kuang DM, *et al*. Increased autophagy sustains the survival and pro-tumourigenic effects of neutrophils in human hepatocellular carcinoma. J Hepatol 2015;62(1):131–139. doi:10.1016/j.jhep.2014.08.023, PMID:25152203.
[103] Shuai Z, Leung MW, He X, Zhang W, Yang G, Leung PS, *et al*. Adaptive immunity in the liver. Cell Mol Immunol 2016;13(3):354–368. doi:10.1038/cmi.2016.4, PMID:26996069.
[104] Ringelhan M, Pfister D, O'Connor T, Pikarsky E, Heikenwalder M. The immunology of hepatocellular carcinoma. Nat Immunol 2018;19(3):222–232. doi:10.1038/s41590-018-0044-z, PMID:29379119.
[105] Hellström I, Hellström KE, Pierce GE, Yang JP. Cellular and humoral immunity to different types of human neoplasms. Nature 1968;220(5174):1352–1354. doi:10.1038/2201352a0, PMID:4302696.
[106] Anderson KG, Stromnes IM, Greenberg PD. Obstacles Posed by the Tumor Microenvironment to T cell Activity: A Case for Synergistic Therapies. Cancer Cell 2017;31(3):311–325. doi:10.1016/j.ccell.2017.02.008, PMID:28292435.
[107] Philip M, Schietinger A. CD8(+) T cell differentiation and dysfunction in cancer. Nat Rev Immunol 2022;22(4):209–223. doi:10.1038/s41577-021-00574-3, PMID:34253904.
[108] Wang X, Shen H, Zhangyuan G, Huang R, Zhang W, He Q, *et al*. 14-3-3ζ delivered by hepatocellular carcinoma-derived exosomes impaired anti-tumor function of tumor-infiltrating T lymphocytes. Cell Death Dis 2018;9(2):159. doi:10.1038/s41419-017-0180-7, PMID:29415983.
[109] Hu Z, Chen G, Zhao Y, Gao H, Li L, Yin Y, *et al*. Exosome-derived circCCAR1 promotes CD8 + T-cell dysfunction and anti-PD1 resistance in hepatocellular carcinoma. Mol Cancer 2023;22(1):55. doi:10.1186/s12943-023-01759-1, PMID:36932387.
[110] Li X, Wu A, Wang Y, Li D, Wu M. Knockdown of circZMIZ1 enhances the anti-tumor activity of CD8(+) T cells to alleviate hepatocellular carcinoma. Funct Integr Genomics 2024;24(1):27. doi:10.1007/s10142-024-01302-5, PMID:38332346.
[111] Zhang HY, Liang HX, Wu SH, Jiang HQ, Wang Q, Yu ZJ. Overexpressed Tumor Suppressor Exosomal miR-15a-5p in Cancer Cells Inhibits PD1 Expression in CD8+T Cells and Suppresses the Hepatocellular Carcinoma Progression. Front Oncol 2021;11:622263. doi:10.3389/fonc.2021.622263, PMID:33816255.
[112] Xie F, Xu M, Lu J, Mao L, Wang S. The role of exosomal PD-L1 in tumor progression and immunotherapy. Mol Cancer 2019;18(1):146. doi:10.1186/s12943-019-1074-3, PMID:31647023.
[113] Yang Y, Li CW, Chan LC, Wei Y, Hsu JM, Xia W, *et al*. Exosomal PD-L1 harbors active defense function to suppress T cell killing of breast cancer cells and promote tumor growth. Cell Res 2018;28(8):862–864. doi:10.1038/s41422-018-0060-4, PMID:29959401.
[114] Fan F, Chen K, Lu X, Li A, Liu C, Wu B. Dual targeting of PD-L1 and PD-L2 by PCED1B-AS1 via sponging hsa-miR-194-5p induces immunosuppression in hepatocellular carcinoma. Hepatol Int 2021;15(2):444–458. doi:10.1007/s12072-020-10101-6, PMID:33219943.
[115] Wei Y, Tang X, Ren Y, Yang Y, Song F, Fu J, *et al*. An RNA-RNA crosstalk network involving HMGB1 and RICTOR facilitates hepatocellular carcinoma tumorigenesis by promoting glutamine metabolism and impedes immunotherapy by PD-L1+ exosomes activity. Signal Transduct Target Ther 2021;6(1):421. doi:10.1038/s41392-021-00801-2, PMID:34916485.

[116] Chen G, Huang AC, Zhang W, Zhang G, Wu M, Xu W, *et al*. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. Nature 2018;560(7718):382–386. doi:10.1038/s41586-018-0392-8, PMID:30089911.
[117] Walling BL, Kim M. LFA-1 in T Cell Migration and Differentiation. Front Immunol 2018;9:952. doi:10.3389/fimmu.2018.00952, PMID:29774029.
[118] Zhang W, Zhong W, Wang B, Yang J, Yang J, Yu Z, *et al*. ICAM-1-mediated adhesion is a prerequisite for exosome-induced T cell suppression. Dev Cell 2022;57(3):329–343.e7. doi:10.1016/j.devcel.2022.01.002, PMID:35085484.
[119] Elghoroury EA, Abdelghaffar EE, Awadallah E, Kamel SA, Kandil D, Hassan EM, *et al*. Detection of exosomal miR-18a and miR-222 levels in Egyptian patients with hepatic cirrhosis and hepatocellular carcinoma. Int J Immunopathol Pharmacol 2022;36:3946320221097832. doi:10.1177/03946320221097832, PMID:35467432.
[120] Sohn W, Kim J, Kang SH, Yang SR, Cho JY, Cho HC, *et al*. Serum exosomal microRNAs as novel biomarkers for hepatocellular carcinoma. Exp Mol Med 2015;47(9):e184. doi:10.1038/emm.2015.68, PMID:26380927.
[121] Ueda R, Kohanbash G, Sasaki K, Fujita M, Zhu X, Kastenhuber ER, *et al*. Dicer-regulated microRNAs 222 and 339 promote resistance of cancer cells to cytotoxic T-lymphocytes by down-regulation of ICAM-1. Proc Natl Acad Sci U S A 2009;106(26):10746–10751. doi:10.1073/pnas.0811817106, PMID:19520829.
[122] Li C, Jiang P, Wei S, Xu X, Wang J. Regulatory T cells in tumor microenvironment: new mechanisms, potential therapeutic strategies and future prospects. Mol Cancer 2020;19(1):116. doi:10.1186/s12943-020-01234-1, PMID:32680511.
[123] Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations (*). Annu Rev Immunol 2010;28:445–489. doi:10.1146/annurev-immunol-030409-101212, PMID:20192806.
[124] Huang M, Huang X, Huang N. Exosomal circGSE1 promotes immune escape of hepatocellular carcinoma by inducing the expansion of regulatory T cells. Cancer Sci 2022;113(6):1968–1983. doi:10.1111/cas.15365, PMID:35396771.
[125] Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. Annu Rev Immunol 2007;25:821–852. doi:10.1146/annurev.immunol.25.022106.141557, PMID:17201677.
[126] Guo D, Chen Y, Wang S, Yu L, Shen Y, Zhong H, *et al*. Exosomes from heat-stressed tumour cells inhibit tumour growth by converting regulatory T cells to Th17 cells via IL-6. Immunology 2018;154(1):132–143. doi:10.1111/imm.12874, PMID:29197065.
[127] Tian XP, Wang CY, Jin XH, Li M, Wang FW, Huang WJ, *et al*. Acidic Microenvironment Up-Regulates Exosomal miR-21 and miR-10b in Early-Stage Hepatocellular Carcinoma to Promote Cancer Cell Proliferation and Metastasis. Theranostics 2019;9(7):1965–1979. doi:10.7150/thno.30958, PMID:31037150.
[128] Tu J, Han D, Fang Y, Jiang H, Tan X, Xu Z, *et al*. MicroRNA-10b promotes arthritis development by disrupting CD4(+) T cell subtypes. Mol Ther Nucleic Acids 2022;27:733–750. doi:10.1016/j.omtn.2021.12.022, PMID:35317281.
[129] Yao SX, Zhang GS, Cao HX, Song G, Li ZT, Zhang WT. Correlation between microRNA-21 and expression of Th17 and Treg cells in microenvironment of rats with hepatocellular carcinoma. Asian Pac J Trop Med 2015;8(9):762–765. doi:10.1016/j.apjtm.2015.07.021, PMID:26433664.
[130] Tsou P, Katayama H, Ostrin EJ, Hanash SM. The Emerging Role of B Cells in Tumor Immunity. Cancer Res 2016;76(19):5597–5601. doi:10.1158/0008-5472.CAN-16-0431, PMID:27634765.
[131] Shang J, Zha H, Sun Y. Phenotypes, Functions, and Clinical Relevance of Regulatory B Cells in Cancer. Front Immunol 2020;11:582657. doi:10.3389/fimmu.2020.582657, PMID:33193391.
[132] Shao Y, Lo CM, Ling CC, Liu XB, Ng KT, Chu AC, *et al*. Regulatory B cells accelerate hepatocellular carcinoma progression via CD40/CD154 signaling pathway. Cancer Lett 2014;355(2):264–272. doi:10.1016/j.canlet.2014.09.026, PMID:25301451.
[133] Carter NA, Rosser EC, Mauri C. Interleukin-10 produced by B cells is crucial for the suppression of Th17/Th1 responses, induction of T regulatory type 1 cells and reduction of collagen-induced arthritis. Arthritis Res Ther 2012;14(1):R32. doi:10.1186/ar3736, PMID:22315945.
[134] Khan AR, Hams E, Floudas A, Sparwasser T, Weaver CT, Fallon PG. PD-L1hi B cells are critical regulators of humoral immunity. Nat Commun 2015;6:5997. doi:10.1038/ncomms6997, PMID:25609381.
[135] Ye L, Zhang Q, Cheng Y, Chen X, Wang G, Shi M, *et al*. Tumor-derived exosomal HMGB1 fosters hepatocellular carcinoma immune evasion by promoting TIM-1(+) regulatory B cell expansion. J Immunother Cancer 2018;6(1):145. doi:10.1186/s40425-018-0451-6, PMID:30526680.
[136] Xiao X, Lao XM, Chen MM, Liu RX, Wei Y, Ouyang FZ, *et al*. PD-1hi Identifies a Novel Regulatory B-cell Population in Human Hepatoma That Promotes Disease Progression. Cancer Discov 2016;6(5):546–559. doi:10.1158/2159-8290.CD-15-1408, PMID:26928313.
[137] Mao Y, Wang Y, Dong L, Zhang Q, Wang C, Zhang Y, *et al*. Circulating exosomes from esophageal squamous cell carcinoma mediate the generation of B10 and PD-1(high) Breg cells. Cancer Sci 2019;110(9):2700–2710. doi:10.1111/cas.14122, PMID:31276257.
[138] Bu L, Yonemura A, Yasuda-Yoshihara N, Uchihara T, Ismagulov G, Takasugi S, *et al*. Tumor microenvironmental 15-PGDH depletion promotes fibrotic tumor formation and angiogenesis in pancreatic cancer. Cancer Sci 2022;113(10):3579–3592. doi:10.1111/cas.15495, PMID:35848891.
[139] Mao X, Xu J, Wang W, Liang C, Hua J, Liu J, *et al*. Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: new findings and future perspectives. Mol Cancer 2021;20(1):131. doi:10.1186/s12943-021-01428-1, PMID:34635121.
[140] Li T, Yang Y, Hua X, Wang G, Liu W, Jia C, *et al*. Hepatocellular carcinoma-associated fibroblasts trigger NK cell dysfunction via PGE2 and IDO. Cancer Lett 2012;318(2):154–161. doi:10.1016/j.canlet.2011.12.020, PMID:22182446.
[141] Cheng JT, Deng YN, Yi HM, Wang GY, Fu BS, Chen WJ, *et al*. Hepatic carcinoma-associated fibroblasts induce IDO-producing regulatory dendritic cells through IL-6-mediated STAT3 activation. Oncogenesis 2016;5(2):e198. doi:10.1038/oncsis.2016.7, PMID:26900950.
[142] Yi M, Zheng X, Niu M, Zhu S, Ge H, Wu K. Combination strategies with PD-1/PD-L1 blockade: current advances and future directions. Mol Cancer 2022;21(1):28. doi:10.1186/s12943-021-01489-2, PMID:35062949.
[143] Wang B, Han Y, Zhang Y, Zhao Q, Wang H, Wei J, *et al*. Overcoming acquired resistance to cancer immune checkpoint therapy: potential strategies based on molecular mechanisms. Cell Biosci 2023;13(1):120. doi:10.1186/s13578-023-01073-9, PMID:37386520.
[144] Eble JA, Niland S. The extracellular matrix in tumor progression and metastasis. Clin Exp Metastasis 2019;36(3):171–198. doi:10.1007/s10585-019-09966-1, PMID:30972526.
[145] Sorokin L. The impact of the extracellular matrix on inflammation. Nat Rev Immunol 2010;10(10):712–723. doi:10.1038/nri2852, PMID:20865019.
[146] Yuan Z, Li Y, Zhang S, Wang X, Dou H, Yu X, *et al*. Extracellular matrix remodeling in tumor progression and immune escape: from mechanisms to treatments. Mol Cancer 2023;22(1):48. doi:10.1186/s12943-023-01744-8, PMID:36906534.
[147] Nagao Y, Yokoi A, Yoshida K, Kitagawa M, Asano-Inami E, Kato T, *et al*. Uterine leiomyosarcoma cell-derived extracellular vesicles induce the formation of cancer-associated fibroblasts. Biochim Biophys Acta Mol Basis Dis 2024;1870(4):167103. doi:10.1016/j.bbadis.2024.167103, PMID:38417460.
[148] Mito I, Takahashi H, Kawabata-Iwakawa R, Horikawa M, Ida S, Tada H, *et al*. Tumor-derived exosomes elicit cancer-associated fibroblasts shaping inflammatory tumor microenvironment in head and neck squamous cell carcinoma. Oral Oncol 2023;136:106270. doi:10.1016/j.oraloncology.2022.106270, PMID:36462328.
[149] Fang T, Lv H, Lv G, Li T, Wang C, Han Q, *et al*. Tumor-derived exosomal miR-1247-3p induces cancer-associated fibroblast activation to foster lung metastasis of liver cancer. Nat Commun 2018;9(1):191. doi:10.1038/s41467-017-02583-0, PMID:29335551.
[150] Trivedi P, Wang S, Friedman SL. The Power of Plasticity-Metabolic Regulation of Hepatic Stellate Cells. Cell Metab 2021;33(2):242–257. doi:10.1016/j.cmet.2020.10.026, PMID:33232666.
[151] Yan Y, Zeng J, Xing L, Li C. Extra- and Intra-Cellular Mechanisms of Hepatic Stellate Cell Activation. Biomedicines 2021;9(8):1014. doi:10.3390/biomedicines9081014, PMID:34440218.
[152] Zhao W, Zhang L, Xu Y, Zhang Z, Ren G, Tang K, *et al*. Hepatic stellate cells promote tumor progression by enhancement of immunosuppressive cells in an orthotopic liver tumor mouse model. Lab Invest 2014;94(2):182–191. doi:10.1038/labinvest.2013.139, PMID:24296878.
[153] Johira Y, Nakahara T, Kinami T, Yamasaki S, Kosaka M, Shirane Y, *et al*. Impact and usefulness of the transition to the new MAFLD classification for non-B, non-C HCC: a retrospective cohort study. BMC Gastroenterol 2023;23(1):222. doi:10.1186/s12876-023-02851-y, PMID:37380950.
[154] Luo X, Luo SZ, Xu ZX, Zhou C, Li ZH, Zhou XY, *et al*. Lipotoxic hepatocyte-derived exosomal miR-1297 promotes hepatic stellate cell activation through the PTEN signaling pathway in metabolic-associated fatty liver disease. World J Gastroenterol 2021;27(14):1419–1434. doi:10.3748/wjg.v27.i14.1419, PMID:33911465.
[155] Xu W, Mo W, Han D, Dai W, Xu X, Li J, *et al*. Hepatocyte-derived exosomes deliver the lncRNA CYTOR to hepatic stellate cells and promote liver fibrosis. J Cell Mol Med 2024;28(8):e18234. doi:10.1111/jcmm.18234, PMID:38520214.
[156] Liu B, Wang J, Wang G, Jiang W, Li Z, Shi Y, *et al*. Hepatocyte-derived exosomes deliver H2AFJ to hepatic stellate cells and promote liver fibrosis via the MAPK/STMN1 axis activation. Int Immunopharmacol 2023;115:109605. doi:10.1016/j.intimp.2022.109605, PMID:36608439.
[157] Zhang Q, Qu Y, Zhang Q, Li F, Li B, Li Z, *et al*. Exosomes derived from hepatitis B virus-infected hepatocytes promote liver fibrosis via miR-222/TFRC axis. Cell Biol Toxicol 2023;39(2):467–481. doi:10.1007/s10565-021-09684-z, PMID:34978008.
[158] Xia Y, Zhen L, Li H, Wang S, Chen S, Wang C, *et al*. MIRLET7BHG promotes hepatocellular carcinoma progression by activating hepatic stellate cells through exosomal SMO to trigger Hedgehog pathway. Cell Death Dis 2021;12(4):326. doi:10.1038/s41419-021-03494-1, PMID:33771969.
[159] Yin C, Evason KJ, Asahina K, Stainier DY. Hepatic stellate cells in liver development, regeneration, and cancer. J Clin Invest 2013;123(5):1902–1910. doi:10.1172/JCI66369, PMID:23635788.
[160] Zhou Y, Ren H, Dai B, Li J, Shang L, Huang J, *et al*. Hepatocellular carcinoma-derived exosomal miRNA-21 contributes to tumor progression by converting hepatocyte stellate cells to cancer-associated fibroblasts. J Exp Clin Cancer Res 2018;37(1):324. doi:10.1186/s13046-018-0965-2, PMID:30591064.
[161] Zhou M, He X, Mei C, Ou C. Exosome derived from tumor-associated macrophages: biogenesis, functions, and therapeutic implications in human cancers. Biomark Res 2023;11(1):100. doi:10.1186/s40364-023-00538-w, PMID:37981718.
[162] Wang L, Yi X, Xiao X, Zheng Q, Ma L, Li B. Exosomal miR-628-5p from M1 polarized macrophages hinders m6A modification of circFUT8 to suppress hepatocellular carcinoma progression. Cell Mol Biol Lett 2022;27(1):106. doi:10.1186/s11658-022-00406-9, PMID:36474147.
[163] Zhang L, Zhang J, Li P, Li T, Zhou Z, Wu H. Exosomal hsa_circ_0004658

derived from RBPJ overexpressed-macrophages inhibits hepatocellular carcinoma progression via miR-499b-5p/JAM3. Cell Death Dis 2022;13(1):32. doi:10.1038/s41419-021-04345-9, PMID:35013102.
[164] Li W, Xin X, Li X, Geng J, Sun Y. Exosomes secreted by M2 macrophages promote cancer stemness of hepatocellular carcinoma via the miR-27a-3p/TXNIP pathways. Int Immunopharmacol 2021;101(Pt A):107585. doi:10.1016/j.intimp.2021.107585, PMID:34601333.
[165] Tao L, Li D, Mu S, Tian G, Yan G. LncRNA MAPKAPK5_AS1 facilitates cell proliferation in hepatitis B virus -related hepatocellular carcinoma. Lab Invest 2022;102(5):494–504. doi:10.1038/s41374-022-00731-9, PMID:35264707.
[166] Xu M, Zhou C, Weng J, Chen Z, Zhou Q, Gao J, *et al*. Tumor associated macrophages-derived exosomes facilitate hepatocellular carcinoma malignance by transferring lncMMPA to tumor cells and activating glycolysis pathway. J Exp Clin Cancer Res 2022;41(1):253. doi:10.1186/s13046-022-02458-3, PMID:35986343.
[167] Liu MX, Jin L, Sun SJ, Liu P, Feng X, Cheng ZL, *et al*. Metabolic reprogramming by PCK1 promotes TCA cataplerosis, oxidative stress and apoptosis in liver cancer cells and suppresses hepatocellular carcinoma. Oncogene 2018;37(12):1637–1653. doi:10.1038/s41388-017-0070-6, PMID:29335519.
[168] Zheng N, Wang T, Luo Q, Liu Y, Yang J, Zhou Y, *et al*. M2 macrophage-derived exosomes suppress tumor intrinsic immunogenicity to confer immunotherapy resistance. Oncoimmunology 2023;12(1):2210959. doi:10.1080/2162402X.2023.2210959, PMID:37197441.
[169] Zhong W, Lu Y, Han X, Yang J, Qin Z, Zhang W, *et al*. Upregulation of exosome secretion from tumor-associated macrophages plays a key role in the suppression of anti-tumor immunity. Cell Rep 2023;42(10):113224. doi:10.1016/j.celrep.2023.113224, PMID:37805922.
[170] Calvente CJ, Tameda M, Johnson CD, Del Pilar H, Lin YC, Adronikou N, *et al*. Neutrophils contribute to spontaneous resolution of liver inflammation and fibrosis via microRNA-223. J Clin Invest 2019;129(10):4091–4109. doi:10.1172/JCI122258, PMID:31295147.
[171] He Y, Hwang S, Cai Y, Kim SJ, Xu M, Yang D, *et al*. MicroRNA-223 Ameliorates Nonalcoholic Steatohepatitis and Cancer by Targeting Multiple Inflammatory and Oncogenic Genes in Hepatocytes. Hepatology 2019;70(4):1150–1167. doi:10.1002/hep.30645, PMID:30964207.
[172] Kim HY, Min HK, Song HW, Yoo A, Lee S, Kim KP, *et al*. Delivery of human natural killer cell-derived exosomes for liver cancer therapy: an in vivo study in subcutaneous and orthotopic animal models. Drug Deliv 2022;29(1):2897–2911. doi:10.1080/10717544.2022.2118898, PMID:36068970.
[173] Wang L, Wang Y, Quan J. Exosomal miR-223 derived from natural killer cells inhibits hepatic stellate cell activation by suppressing autophagy. Mol Med 2020;26(1):81. doi:10.1186/s10020-020-00207-w, PMID:32873229.
[174] Okoye IS, Coomes SM, Pelly VS, Czieso S, Papayannopoulos V, Tolmachova T, *et al*. MicroRNA-containing T-regulatory-cell-derived exosomes suppress pathogenic T helper 1 cells. Immunity 2014;41(1):89–103. doi:10.1016/j.immuni.2014.05.019, PMID:25035954.
[175] Tung SL, Boardman DA, Sen M, Letizia M, Peng Q, Cianci N, *et al*. Regulatory T cell-derived extracellular vesicles modify dendritic cell function. Sci Rep 2018;8(1):6065. doi:10.1038/s41598-018-24531-8, PMID:29666503.
[176] Xie Y, Zhang X, Zhao T, Li W, Xiang J. Natural $CD8^+25^+$ regulatory T cell-secreted exosomes capable of suppressing cytotoxic T lymphocyte-mediated immunity against B16 melanoma. Biochem Biophys Res Commun 2013;438(1):152–155. doi:10.1016/j.bbrc.2013.07.044, PMID:23876314.
[177] Dou D, Ren X, Han M, Xu X, Ge X, Gu Y, *et al*. Cancer-Associated Fibroblasts-Derived Exosomes Suppress Immune Cell Function in Breast Cancer via the miR-92/PD-L1 Pathway. Front Immunol 2020;11:2026. doi:10.3389/fimmu.2020.02026, PMID:33162971.
[178] Zhou Y, Tang W, Zhuo H, Zhu D, Rong D, Sun J, *et al*. Cancer-associated fibroblast exosomes promote chemoresistance to cisplatin in hepatocellular carcinoma through circZFR targeting signal transducers and activators of transcription (STAT3)/nuclear factor -kappa B (NF-κB) pathway. Bioengineered 2022;13(3):4786–4797. doi:10.1080/21655979.2022.2032972, PMID:35139763.
[179] Zhang Y, Pan Q, Shao Z. Extracellular vesicles derived from cancer-associated fibroblasts carry tumor-promotive microRNA-1228-3p to enhance the resistance of hepatocellular carcinoma cells to sorafenib. Hum Cell 2023;36(1):296–311. doi:10.1007/s13577-022-00800-7, PMID:36424471.
[180] Liu L, Liao R, Wu Z, Du C, You Y, Que K, *et al*. Hepatic stellate cell exosome-derived circWDR25 promotes the progression of hepatocellular carcinoma via the miRNA-4474-3P-ALOX-15 and EMT axes. Biosci Trends 2022;16(4):267–281. doi:10.5582/bst.2022.01281, PMID:35934785.
[181] Zhang X, Chen F, Huang P, Wang X, Zhou K, Zhou C, *et al*. Exosome-depleted MiR-148a-3p derived from Hepatic Stellate Cells Promotes Tumor Progression via ITGA5/PI3K/Akt Axis in Hepatocellular Carcinoma. Int J Biol Sci 2022;18(6):2249–2260. doi:10.7150/ijbs.66184, PMID:35414782.
[182] Ma L, Wei J, Zeng Y, Liu J, Xiao E, Kang Y, *et al*. Mesenchymal stem cell-originated exosomal circDIDO1 suppresses hepatic stellate cell activation by miR-141-3p/PTEN/AKT pathway in human liver fibrosis. Drug Deliv 2022;29(1):440–453. doi:10.1080/10717544.2022.2030428, PMID:35099348.
[183] Yue M, Hu S, Sun H, Tuo B, Jia B, Chen C, *et al*. Extracellular vesicles remodel tumor environment for cancer immunotherapy. Mol Cancer 2023;22(1):203. doi:10.1186/s12943-023-01898-5, PMID:38087360.
[184] Sadeghi S, Tehrani FR, Tahmasebi S, Shafiee A, Hashemi SM. Exosome engineering in cell therapy and drug delivery. Inflammopharmacology 2023;31(1):145–169. doi:10.1007/s10787-022-01115-7, PMID:36609717.
[185] Liu M, Lai Z, Yuan X, Jin Q, Shen H, Rao D, *et al*. Role of exosomes in the development, diagnosis, prognosis and treatment of hepatocellular carcinoma. Mol Med 2023;29(1):136. doi:10.1186/s10020-023-00731-5, PMID:37848835.
[186] Xu Z, Zeng S, Gong Z, Yan Y. Exosome-based immunotherapy: a promising approach for cancer treatment. Mol Cancer 2020;19(1):160. doi:10.1186/s12943-020-01278-3, PMID:33183286.
[187] Zanganeh S, Hutter G, Spitler R, Lenkov O, Mahmoudi M, Shaw A, *et al*. Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues. Nat Nanotechnol 2016;11(11):986–994. doi:10.1038/nnano.2016.168, PMID:27668795.
[188] Chen H, Jiang S, Zhang P, Ren Z, Wen J. Exosomes synergized with PIONs@E6 enhance their immunity against hepatocellular carcinoma via promoting M1 macrophages polarization. Int Immunopharmacol 2021;99:107960. doi:10.1016/j.intimp.2021.107960, PMID:34284286.
[189] Gunassekaran GR, Poongkavithai Vadevoo SM, Baek MC, Lee B. M1 macrophage exosomes engineered to foster M1 polarization and target the IL-4 receptor inhibit tumor growth by reprogramming tumor-associated macrophages into M1-like macrophages. Biomaterials 2021;278:121137. doi:10.1016/j.biomaterials.2021.121137, PMID:34560422.
[190] Jung I, Shin S, Baek MC, Yea K. Modification of immune cell-derived exosomes for enhanced cancer immunotherapy: current advances and therapeutic applications. Exp Mol Med 2024;56(1):19–31. doi:10.1038/s12276-023-01132-8, PMID:38172594.
[191] Lindenbergh MFS, Wubbolts R, Borg EGF, van 't Veld EM, Boes M, Stoorvogel W. Dendritic cells release exosomes together with phagocytosed pathogen; potential implications for the role of exosomes in antigen presentation. J Extracell Vesicles 2020;9(1):1798606. doi:10.1080/20013078.2020.1798606, PMID:32944186.
[192] Wei G, Jie Y, Haibo L, Chaoneng W, Dong H, Jianbing Z, *et al*. Dendritic cells derived exosomes migration to spleen and induction of inflammation are regulated by CCR7. Sci Rep 2017;7:42996. doi:10.1038/srep42996, PMID:28223684.
[193] Lindenbergh MFS, Stoorvogel W. Antigen Presentation by Extracellular Vesicles from Professional Antigen-Presenting Cells. Annu Rev Immunol 2018;36:435–459. doi:10.1146/annurev-immunol-041015-055700, PMID:29400984.
[194] Viaud S, Terme M, Flament C, Taieb J, André F, Novault S, *et al*. Dendritic cell-derived exosomes promote natural killer cell activation and proliferation: a role for NKG2D ligands and IL-15Ralpha. PLoS One 2009;4(3):e4942. doi:10.1371/journal.pone.0004942, PMID:19319200.
[195] Munich S, Sobo-Vujanovic A, Buchser WJ, Beer-Stolz D, Vujanovic NL. Dendritic cell exosomes directly kill tumor cells and activate natural killer cells via TNF superfamily ligands. Oncoimmunology 2012;1(7):1074–1083. doi:10.4161/onci.20897, PMID:23170255.
[196] Segura E, Nicco C, Lombard B, Véron P, Raposo G, Batteux F, *et al*. ICAM-1 on exosomes from mature dendritic cells is critical for efficient naive T-cell priming. Blood 2005;106(1):216–223. doi:10.1182/blood-2005-01-0220, PMID:15790784.
[197] Lu Z, Zuo B, Jing R, Gao X, Rao Q, Liu Z, *et al*. Dendritic cell-derived exosomes elicit tumor regression in autochthonous hepatocellular carcinoma mouse models. J Hepatol 2017;67(4):739–748. doi:10.1016/j.jhep.2017.05.019, PMID:28549917.
[198] Näslund TI, Gehrmann U, Qazi KR, Karlsson MC, Gabrielsson S. Dendritic cell-derived exosomes need to activate both T and B cells to induce antitumor immunity. J Immunol 2013;190(6):2712–2719. doi:10.4049/jimmunol.1203082, PMID:23418627.
[199] Morse MA, Garst J, Osada T, Khan S, Hobeika A, Clay TM, *et al*. A phase I study of dexosome immunotherapy in patients with advanced non-small cell lung cancer. J Transl Med 2005;3(1):9. doi:10.1186/1479-5876-3-9, PMID:15723705.
[200] Escudier B, Dorval T, Chaput N, André F, Caby MP, Novault S, *et al*. Vaccination of metastatic melanoma patients with autologous dendritic cell (DC) derived-exosomes: results of thefirst phase I clinical trial. J Transl Med 2005;3(1):10. doi:10.1186/1479-5876-3-10, PMID:15740633.
[201] Tan F, Li X, Wang Z, Li J, Shahzad K, Zheng J. Clinical applications of stem cell-derived exosomes. Signal Transduct Target Ther 2024;9(1):17. doi:10.1038/s41392-023-01704-0, PMID:38212307.
[202] Pegtel DM, Gould SJ. Exosomes. Annu Rev Biochem 2019;88:487–514. doi:10.1146/annurev-biochem-013118-111902, PMID:31220978.
[203] Luan X, Sansanaphongpricha K, Myers I, Chen H, Yuan H, Sun D. Engineering exosomes as refined biological nanoplatforms for drug delivery. Acta Pharmacol Sin 2017;38(6):754–763. doi:10.1038/aps.2017.12, PMID:28392567.
[204] Ding L, Yang X, Gao Z, Effah CY, Zhang X, Wu Y, *et al*. A Holistic Review of the State-of-the-Art Microfluidics for Exosome Separation: An Overview of the Current Status, Existing Obstacles, and Future Outlook. Small 2021;17(29):e2007174. doi:10.1002/smll.202007174, PMID:34047052.