Effects of exosomes on tumor immunomodulation and their potential clinical applications (Review)

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Received July 13, 2022; Accepted September 22, 2022

DOI: 10.3892/ijo.2022.5437

Abstract. Exosomes are small extracellular vesicles containing proteins, nucleic acids and lipids, which can transmit information between cells, and can interfere with the epigenetic characteristics and functions of recipient cells. Tumor-derived exosomes play a crucial role as communicators in the tumor microenvironment, and are involved in the occurrence and development of various tumors. The present review article summarizes the biogenesis of exosomes and their communication with local and remote cells, focusing on the function of tumor-derived exosomes in the tumor microenvironment, including the promotion of angiogenesis, the induction of epithelial mesenchymal transformation, and the activation and inhibition of immune cells, as well as the effects of exosomes on the tumor microenvironment during microbial infections. Additionally, the effects of exosomes on tumor immunotherapy and the potential applications of exosomes as biomarkers, delivery vehicles and cancer vaccines in cancer diagnostics and therapeutics are discussed.

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Key words: exosome, tumor immunomodulation, immunotherapy, clinical applications

1. Biogenesis and communication of exosomes

Biogenesis and composition. Exosomes are nanometric vesicles (30-150 nm in diameter) enclosed by a lipid bilayer membrane containing lipids, proteins, DNA [mitochondrial DNA (mtDNA), single-stranded DNA (ssDNA) and double stranded DNA (dsDNA)] and RNA [mRNAs, microRNAs (miRNA/miRs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs)] (1). Exosomes can be produced and secreted by almost all cell types, including hematopoietic, neuronal, fibroblastic and cancer cells, and are commonly found in physical body fluids. The small size and special biofilm composition allow exosomes to cross main biological barriers, and even the blood-brain barrier. Carrying a variety of biomolecules, exosomes can mediate local and distant cellular material transport and information transfer by delivering specific 'cargoes' (2,3).

Exosome formation begins when the plasma membrane invaginates to generate early endosomes, and the endosome membrane then further inverts to form late endosomes containing intraluminal vesicles (ILVs), which are termed multivesicular bodies (MVBs). During this process, signaling molecules derived from the parental plasma membrane, cytoplasmic lysates, as well as common proteins which play a role in membrane fusion and cytoskeletal regulation (Rab family, Alix, GTPase, endosomal sorting complexes required for transport, etc.) are doped into the vesicles, and when the MVBs fuse with the plasma membrane, the ILVs can be released from the parental cell into the extracellular environment as exosomes by cytosolic ejection (4) (Fig. 1).

The endosomal sorting complex required for translocation (ESCRT) is generally considered to be the driving factor for MVB formation (5). ESCRT is composed of five soluble protein complexes [ESCRT-0, ESCRT-I, ESCRT-II, ESCRT-III and auxiliary proteins (Vps4, Vta1 and Alix)]. First, the interaction between the ESCRT-0 subunits and endosomal-enriched phosphatidylinositol 3-phosphate [PtdIns(3)P] enriches ESCRT-0 toward the endosome. The ESCRT-0 complex then recruits

ESCRT-I subunits to recognize and aggregate ubiquitinated 'cargo' on endosome-restricted membrane microdomains. The ESCRT-II subunits then provide a platform that initiates the stepwise assembly of the ESCRT-III complex by coordinating the multiple interactions of ESCRT-I, PtdIns(3)P and ubiquitin to transfer and wrap the ubiquitinated 'cargo', resulting in the formation of 'cargo'-loaded MVBs (6). Alix is an auxiliary protein that binds with ESCRT-III subunits and contributes to the budding and shedding process of ILV generation, which plays a prominent role in exosome formation (3). MVBs can also be generated in an ESCRT-independent manner; however, they require the involvement of neutral sphingomyelinase-dependent ceramide, cholesterol, or tetraspanins (e.g., CD9, CD63 and CD81) (7).

MVB fusion with the plasma membrane is mediated by the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE), which localizes in or is recruited into the docking MVBs and the plasma membrane, and then initiates membrane fusion by forming SNARE complexes, where vesicles within the MVB are released to form exosomes outside the cell. In addition, MVBs are able to fuse with lysosomes and then degrade. The Rab family of GTPases are essential for the regulation of the secretion and degradation of MVBs (Fig. 1). Rab27A and Rab27B are necessary for vesicle transport and fusion during exosome secretion (8); Rab7 is present on late endosomes and lysosomes, and functions by translocating MVBs to lysosomes for degradation (9), whereas active Rab31 can recruit TBC1 structural domain family member 2B to inactivate Rab7, preventing the fusion of MVBs with lysosomes and promoting the secretion of exosomes. Other members of the Rab family, including Rab11, Rab35 and Rab27, are also critical for exosome secretion by regulating the transport of MVBs to the plasma membrane (6,10).

Exosomes are loaded with various proteins, including chaperone proteins, heat shock proteins (HSPs), cytoskeletal proteins (i.e., actin and microtubulin), fusion proteins, mitochondrial proteins and tetraspanins, etc. HSPs and cytoskeletal proteins are present in almost all types of exosomes, while some proteins are cell-specific, such as major histocompatibility complex (MHC) II and MHC I, transferrin receptor and CD3 (11). Exosomes also contain nucleic acid molecules, such as mRNAs and lncRNAs, and exosome RNAs delivered to target cells can alter the epigenetic characteristics of cells and thereby affect their functionality (12).

Although exosomes can be produced by almost all cells, there is evidence to indicate that tumor cells produce significantly more exosomes than other cells, and the level of exosomes in the blood of cancer patients is always higher than that in the blood of healthy individuals (13). It has been proposed that the prevalent hypoxic conditions in the tumor microenvironment (TME) may be responsible for the high secretion of exosomes from tumor cells. Hypoxia may affect key steps of exosome release, such as cargo sorting, MVBs transport and membrane fusion (14). In ovarian cancer cells, hypoxia can stimulate exosome release via the upregulation of Rab27A and the downregulation of Rab7 (15). In addition, the expression of certain four-transmembrane proteins involved in MVB formation, such as CD63 and CD9, is also upregulated due to hypoxia (16). The expression of SNAP-25, a SNARE protein participates in the fusion of MVB with plasma membrane, is also increased under hypoxic conditions (17). However, the exact mechanisms through which hypoxia leads to greater exosome release from tumor cells remain unclear (14).

Tumor-derived exosomes (TDEs) are known to transport nucleic acids, proteins and metabolites from the maternal tumor cells to other sites to act on recipient cells, and play a role in tumor development and immune regulation (18). Nucleic acids, membrane surface material and other cellular contents derived from maternal tumor cells confer specific molecular characteristics on exosomes, thus leading to the distinction between TDEs and exosomes of non-malignant cell origin, and also between exosomes of different tumor cell origins. As tumor cells are more likely to express and activate a variety of immunosuppressive molecules to block antitumor immune responses, TDEs are often rich in immunosuppressive proteins, including FasL, TNF-related apoptosis-inducing ligand (TRAIL), programmed death-ligand 1 (PD-L1), IL-10, TGF-β1, etc. (4). On the other hand, TDEs also carry tumor-associated antigens (TAAs), MHC molecules and co-stimulatory molecules, enabling them to activate immune system and promote anti-tumor responses (19). Such a complex molecular profile of TDEs confers the dual ability on them to mediate either immunosuppression or immunostimulation under various conditions.

Cell-to-cell communications via exosomes. First discovered in 1981, exosomes were initially considered to be a cellular waste product (20). However, it was later demonstrated that exosomes released extracellularly can be transferred to recipient cells to perform various functions in recipient cells through their membrane molecules and loaded substances, effectively altering the biological responses of recipient cells and therefore enabling intercellular communication (21).

Typically, exosomes can interact with target cells through one or more of the following mechanisms: i) The activation of intracellular signaling pathways by signaling through surface receptor-ligand interactions; ii) fusion with the target cell plasma membrane, and incorporation of its membrane contents into the plasma membrane or the release of cytoplasmic contents into the target cell; iii) the internalization of exosomes by lipid rafts, lattice-protein-dependent giant cell 'drinking' action or phagocytosis; iv) receptor-mediated endocytosis. Exosomes enter target cells by phagocytosis or endocytosis, and the 'cargo' carried within them can be incorporated directly into the cellular machinery to initiate reprogramming, or directed to the lysosome for degradation and removal (22) (Fig. 1).

Studies have demonstrated that different integrins expressed on exosomes determine their specific cell fusion or adhesion to extracellular matrix molecules in selected organs. However, the main components that dictate the targeting specificity of exosomes are currently unknown and warrant further investigation (1,23).

2. Effects of tumor-derived exosomes on the tumor microenvironment

The TME consists of peritumor blood vessels, extracellular matrix and surrounding cells including fibroblasts, adipocytes,

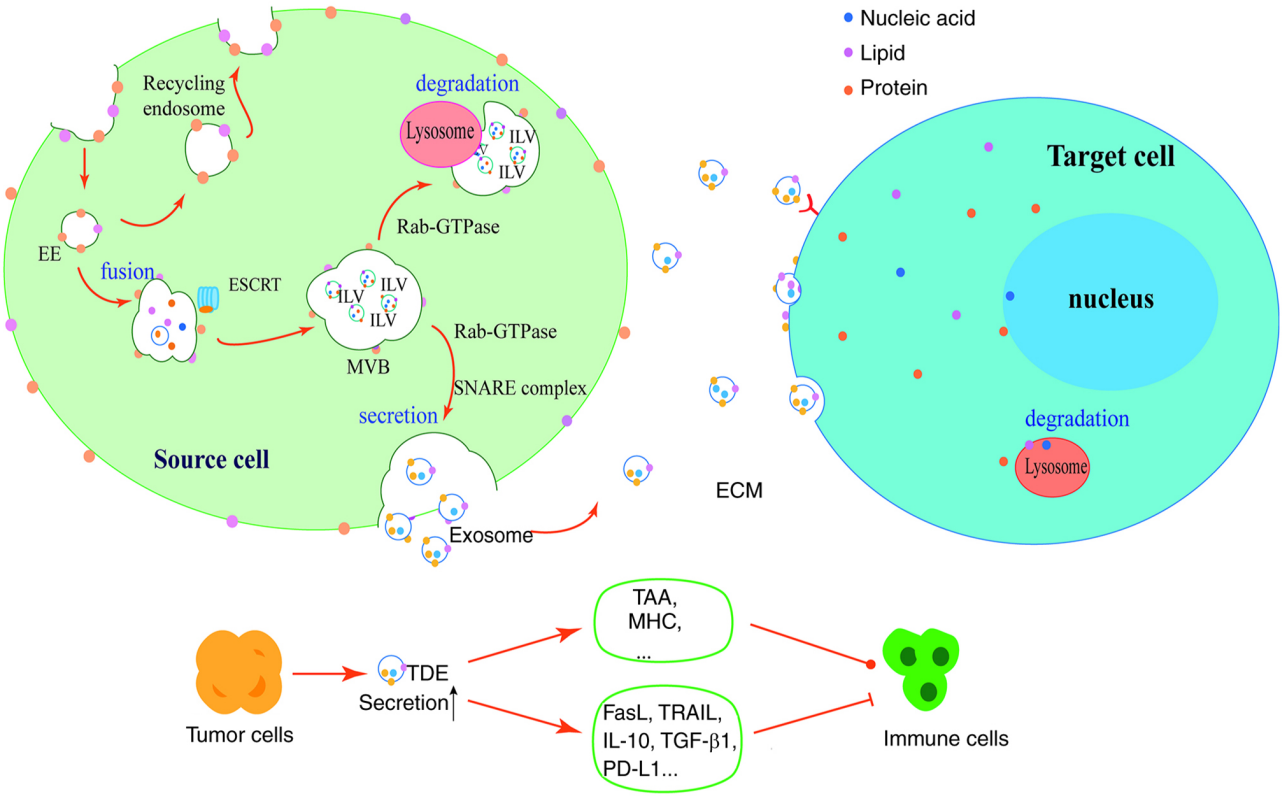

Figure 1. Biogenesis of exosomes and their communications with cells. The production of exosomes begins with the invagination of the cell plasma membrane to form early endosomes, which fuse. As the plasma membrane continues to invaginate and closes to form numerous ILVs, the endosomes are transformed into MVBs containing numerous ILVs, each containing proteins, lipids and nucleic acids, with the assistance of the endosomal sorting complex required for translocation. Under the regulation of Rab-GTPase, MVBs can fuse with lysosomes for degradation, or release ILVs extracellularly to form exosomes via cytosolic exocytosis under the action of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor complex. Exosomes can bind to receptor cells via ligand-receptor form, or fuse directly with target cell membranes, or interact with target cells via endocytosis. Tumor cells can produce more exosomes and carry tumor-associated antigens, major histocompatibility complex molecules or immunosuppressive proteins that activate or inhibit the immune cells. ILVs, intraluminal vesicles; MVBs, multivesicular bodies; EE, early endosomes; ESCRT, endosomal sorting complex required for translocation; ECM, extracellular matrix; TAA, tumor-associated antigen; MHC, major histocompatibility complex; TRAIL, TNF-related apoptosis-inducing ligand; PD-L1, programmed death-ligand 1; TDE, tumor-derived exosome.

immune cells, etc., and plays a key role in the occurrence and progression of tumors (24). TDEs have been shown to be released autonomously by tumor cells and affect the TME via a variety of processes, such as promoting cellular epithelial mesenchymal transition, inducing angiogenesis and inducing various functional changes in immune cells, thus mediating tumor metastasis to proximal or distant tissues and organs (25) (Fig. 2).

TDEs promote epithelial-mesenchymal transition (EMT). Malignant tumors are often aggressive, and tumor epithelial cells need to undergo the EMT process in order to acquire the ability to migrate. Study has confirmed that TDEs are able to enhance the migratory capacity of tumor cells by promoting the conversion of tumor epithelial cells to a mesenchymal phenotype. TGF-β, HIF-1α, IL-6, caveolin-1, vimentin and miRNAs have all been proven to be EMT-promoting factors carried by TDEs (10) (Fig. 2).

EMT usually occurs in the initial stages of tumor metastasis, where tumor cells become invasive by reducing the expression of E-cadherin, the loss of cell polarity, and the increased expression of N-cadherin, imentin and Twist (10). It has been demonstrated that TDEs can transfer EMT-associated RNAs and proteins, such as miR-21 and MMP-13 to recipient cells, mediating calmodulin instability and subsequent EMT. In turn, the exosomal miRNA profile produced following cellular EMT may be altered, which further promotes EMT and tumor cell migration and invasion (26,27).

TGF-β plays a critical role in the maintenance of the tumor stroma and the induction of EMT (28). TGF-β triggers signaling through TGF-βRI and TGF-βRII. Upon binding to TGF-β, TGF-βRII functions as a high-affinity TGF-β receptor to recruit and phosphorylate TGF-βRI, which subsequently activates downstream SMAD proteins, SMAD2 and SMAD3 phosphorylation, and forms a complex with SMAD4 that transfers to the nucleus to bind transcription factors and chromatin proteins to regulate gene transcription (29,30). TDEs have been shown to increase the expression of TGF-βRI and TGF-βRII in recipient cells, and to promote the TGF-β-induced transcription of EMT-related transcription factors (29). For example, an *in vitro* study using cell lines verified that breast cancer-derived exosomes activated TGF-β receptor-mediated signaling pathways in mesenchymal stem cells and promoted their differentiation into fibroblasts, which is a key constituent of the tumor stroma (31).

TDEs promote angiogenesis. Tumor growth is dependent on the construction of the host vascular network, and for this reason, tumor cells can induce a pro-angiogenic environment to build

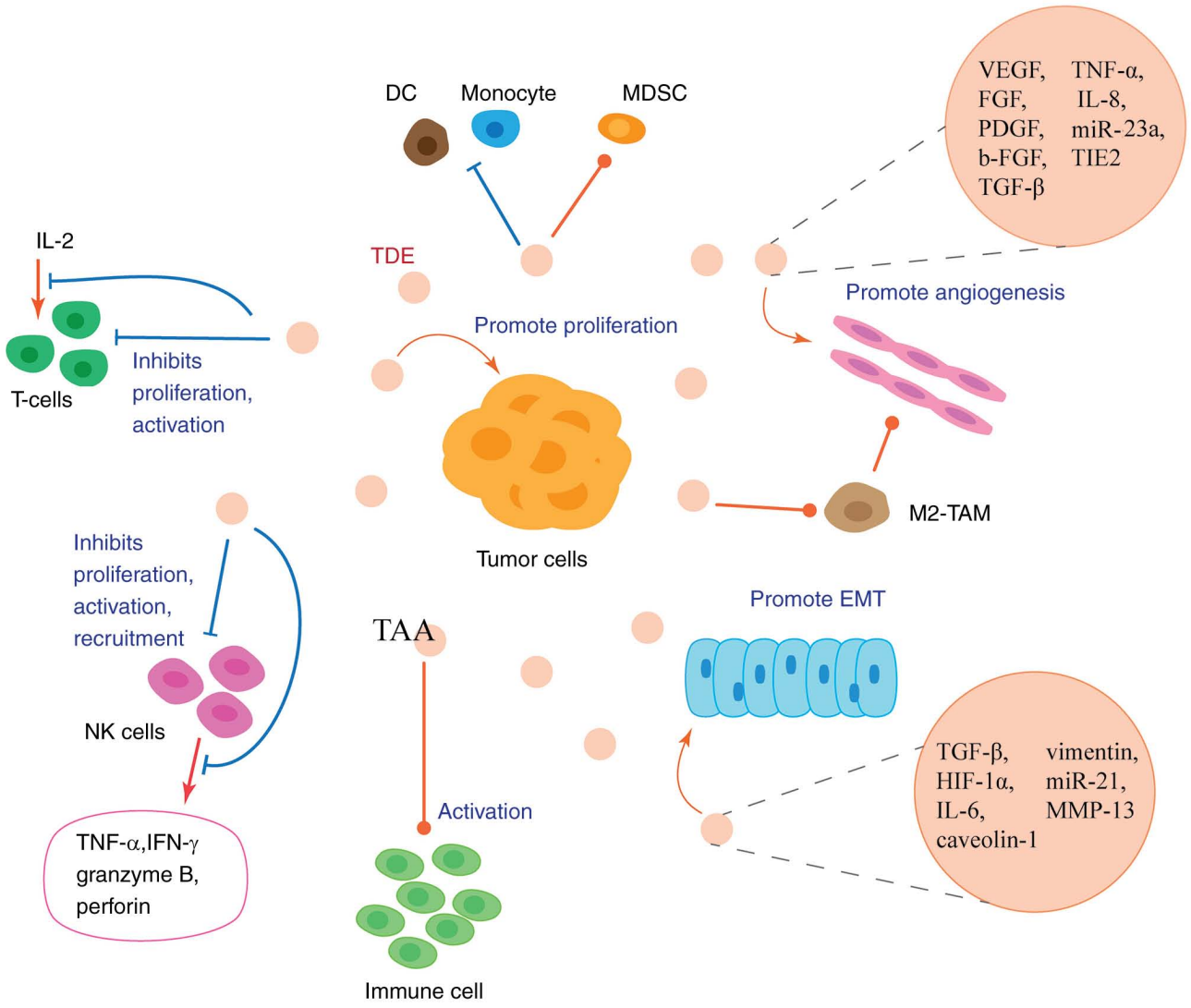

Figure 2. TDEs in the tumor microenvironment. TDEs can be released autonomously by tumor cells and carry EMT-promoting factors and pro-angiogenic factors to promote EMT and angiogenesis. TDEs can also promote the production of M2 phenotype tumor-associated macrophages, and M2-type tumor-associated macrophages secrete pro-angiogenic factors and cytokines to promote angiogenesis. TDEs can carry tumor-associated antigens to activate immune cell functions; however, they mainly exert inhibitory functions on immune cells, including the functions of natural killer cells, T-cells, dendritic cells and monocytes. Ultimately, TDEs can suppress antitumor immunity and induce a microenvironment which promotes tumor proliferation, activation and metastasis. TDEs, tumor-derived exosomes; EMT, epithelial-mesenchymal transition; NK, natural killer; DC, dendritic cell; MDSC, myeloid-derived suppressor cell; TAA, tumor-associated antigen.

a vascular network, and promote tumor growth and spread. TDEs are one of the main mechanisms through which tumor cells induce angiogenesis. VEGF, FGF, PDGF, b-FGF, TGF-β, TNF-α and IL-8 are the key angiogenic stimulating factors carried by TDEs, and TDEs can effectively induce angiogenesis through the transfer and release of these factors (10) (Fig. 2).

It has been reported that exosomal miR-23a derived from lung cancer cells directly inhibits its targets, prolyl hydroxylase (PHD)1 and PHD2, leading to the accumulation of HIF-1α in endothelial cells, thereby enhancing angiogenesis. miR-23a also increases vascular permeability and promotes the migration of tumor cells to the epithelium by inhibiting the tight junction protein, Zonula occludens-1 (32). There is also evidence to indicate that lncRNA-carrying TDEs released from hepatocellular carcinoma (HCC) cells enhance the expression of VEGFR1 in endothelial cells, thereby promoting angiogenesis (33).

Endothelial-specific receptor tyrosine kinase (TIE2), a receptor for angiopoietin, is mainly expressed in endothelial cells and regulates vascular development, thus playing a key role in vascular remodeling for tumor angiogenesis (34). *In vitro* and *in vivo* analyses have demonstrated that TDEs can transfer high levels of TIE2 produced by tumor cells to tumor-associated macrophages (TAMs) and promote angiogenesis by facilitating the conversion of TAMs to TIE2-expressing macrophages (TEMs), which possess a pro-angiogenic phenotype. Exosomes carrying TIE2 can also enter the peripheral blood circulation, induce the conversion of monocytes to TEMs, and eventually interact with endothelial cells to promote angiogenesis (35).

TDEs promote the proliferation and metastasis of tumor cells. The 'cargo' loaded in TDEs can function as critical regulators to induce signal transduction and gene expression, and thus

establish the tumor metastastic niche to promote tumor cell proliferation and migration.

Toll-like receptors (TLRs) are a main class of proteins involved in non-specific immunity, with the ability to monitor and recognize a variety of disease-related molecular patterns. Research using mouse models has demonstrated that TLR3 in lung epithelial cells can be activated by TDEs-RNA, leading to the production of chemokines and the recruitment of neutrophils to the lungs, which induces the formation of the pre-metastatic niche in lung tumors by suppressing antitumor immunity (36). Another study demonstrated that exosomal miRNAs secreted by mouse lung cancer cells could be transferred to macrophages and could bind to TLR7/8, resulting in NF-κB activation and the secretion of the pro-metastatic inflammatory factor, TNF-α (37). Except nucleic acids, proteins such as HSP72 on the surface of TDEs, can also activate NF-κB signaling and induce IL-6 and TNF-α production in myeloid suppressor cells in a TLR2/MYD88-dependent manner. These results suggest that TDEs play a crucial role in the induction of tumor pre-metastatic niches, and that the TLR signaling pathway may be an essential mediator of the action of TDEs by mediating NF-κB activation and pro-inflammatory factor production (38).

TDEs can also transfer oncogenic mutated genes to recipient cells. For example, colon cancer cells expressing mutant K-ras can promote tumor growth and metastasis by transferring the oncogene via exosomes to adjacent normal cells (28).

Activation of immune cells by TDEs. As TDEs carry a number of TAAs and can metastasize to almost any area, they can be uptaken by antigen-presenting cells and can active an effective antitumor immune response in the body. Moreover, exosomes in the TME can also be produced by activated immune cells, including dendritic cells (DCs), natural killer (NK) cells and etc., and can subsequently stimulate the antitumor immune response of the immune cells (4,39).

In a previous study on non-small cell lung cancer (NSCLC), exosomes derived from Rab27a-overexpressing tumor cells were found to significantly promote DC maturation by upregulating the MHC I, CD80 and CD86 levels, and enhancing the proliferation and immune response of $CD4^+$ T-cells (40). It has been demonstrated that radiation therapy at certain doses leads to the accumulation of cytoplasmic dsDNA in tumor cells; TDEs produced by irradiated mouse breast cancer cells can deliver dsDNA to DCs, and DCs can then sense the DNA via cyclic GMP-AMP synthase, stimulate IFN-β production and induce the expression of several interferon-stimulated genes, ultimately leading to DC activation and the antitumor T-cell response (41). There is evidence to indicate that exosomes isolated from patients with non-metastatic primary melanoma have the ability to inhibit tumor lung metastasis. Mechanistically, 'non-metastatic' TDEs can stimulate an intrinsic immune response through the expansion of Ly6Clow patrolling monocytes in bone marrow, and that melanoma cells in pre-metastatic ecological sites are then cleared through NK cell recruitment and TRAIL-dependent macrophage killing (42).

Suppression of immune cells by TDEs. Although TDEs have a certain activating effect on immune cells, they also have an inordinate inhibitory effect, and the majority of the current studies focus on the inhibitory effects of TDEs on immune cells. As tumors grow and develop, tumor cells express a large number of immunosuppressive molecules in order to escape from immune surveillance. They also produce numerous exosomes to carry immunosuppressive 'cargo', which can suppress the body's antitumor immunity by inhibiting the activation of NK cells, suppressing the proliferation and immune response of T-cells, promoting the differentiation of bone marrow progenitor cells and maintaining T-lymphocytes in a quiescent state (43). Since exosomes exist in all types of human bodily fluids, exosomes not only affect immune cells in the TME, but also affect immune cells in the systematic circulation and a variety of lymphoid organs (4).

NK cells. As NK cells do not require prior exposure to antigens to recognize tumor cells, they are considered to be the first responders to the malignant transformation of cells (44). It has been suggested that TDEs can deliver their own loaded 'cargo' to NK cells, thus blocking their antitumor effect (45).

A previous study demonstrated that exosomes isolated from patients with acute myeloid leukemia significantly decreased the migration of NK-92 cells towards tumor cells (46). In a pioneering study, it was also found that pre-treatment with exosomes derived from TS/A cells, a murine breast cancer cell line, significantly reduced the number of NK cells *in vitro*, which indicated that TS/A-exosomes inhibited the proliferation and survival of NK cells (47). Moreover, TDEs can also block NK cell activation. NKG2D and NKp30 are both critical activation receptors on NK cells, and the expression levels of activation receptors determine the antitumor capacity of NK cells (48). TDEs can carry ligands of NKG2D and high levels of membrane-associated TGF-β, which reduces the surface expression of key activation receptors (NKG2D) on NK cells, thus profoundly diminishing the activation of NK cells (48,49).

Apart from reducing the number of NK cells and interfering with NK cell recruitment and activation, TDEs have also been demonstrated to suppress activated NK cells by inhibiting the production of TNF-α and IFN-γ, the two main cytokines involved in the cytotoxic effects of NK cells (24). In addition, the cytotoxic effects of activated NK cells are also largely dependent on the release of perforin and granzyme B, and it has been shown that TDEs can significantly reduce the expression of perforin and granzyme B at the protein level in a concentration-dependent manner (50). The aforementioned effects of TDEs result in the attenuation of the toxic effects of NK cells from various aspects.

Macrophages. Exosomes have been proven to alter the phenotype of macrophages. They can convert the macrophage phenotype to either the M1- or M2-type. M1 macrophages are in a pro-inflammatory phenotype and increase the secretion of pro-inflammatory cytokines and chemotactic molecules, inducing immune stimulation and the effective clearance of pathogens and infections; M2 macrophages are anti-inflammatory and play a central role in stimulating angiogenesis, as well as promoting tumor progression (1).

Exosome-activated macrophages are considered to play a key role in tumor progression, as macrophages activate paracrine signaling pathways to promote tumor growth, angiogenesis and invasion, while blocking inflammation and immune remodeling. In co-culture studies, tumor cells have

been shown to secrete chemokines, such as CCL2 and CSF1, which recruit monocytes from the peripheral circulating blood to the TME and induce them to differentiate into TAMs, which exhibit the M2 phenotype, and can secrete pro-angiogenic factors and cytokines that promote angiogenesis, tumor growth and metastasis (51,52).

It has also been proposed that HCC cell-derived exosomes containing high levels of lncRNA TUC339 can regulate the development of neighboring macrophages toward the M2 phenotype, ultimately creating an immunosuppressive environment conducive to tumor proliferation and progression (53). Under tumor characteristic hypoxic conditions, lactate-rich exosomes secreted by prostate cancer cells can induce VEGF and Arginase 1 (Arg1) expression in macrophages via HIF1α. VEGF mediates tumor neovascularization; Arg1 is involved in regulating cell proliferation and promoting tumor growth. In addition, an increased Arg1 expression leads to a diminished cytotoxic response of macrophages to growing tumor cells (54).

While M1 macrophages are pro-inflammatory and anti-tumor phenotypes, TDEs have also been shown to have the potential to polarize macrophages to the M1 phenotype. Therefore, promoting the conversion of macrophages to the M1 phenotype through exosomes may be a developable direction for tumor immunotherapy (52).

T-lymphocytes. T lymphocytes play a central role in the immune response. $CD8^+$ T-cells are cytotoxic and can directly kill pathogen-infected cells or cancer cells, while $CD4^+$ T-cells mainly play regulatory and paracrine roles. It has been demonstrated that TDEs can induce immunosuppression by promoting the apoptosis of $CD8^+$ T-cells and enhancing the suppressive activity of $CD4^+$ regulatory T-cells, thereby facilitating tumor immune escape (55).

TDEs carry a variety of surface ligands which can be delivered to T-cell surface receptors to regulate T-cell gene expression and function. It has also been shown that exosomes from tumor cells carry higher levels of PD-L1, which can directly interact with PD-1 on the surface of CD8+ T-cells, and inhibit their proliferation and activation, thereby promoting tumor immune escape (56), and that TDEs can transfer PD-L1 to PD-L1-negative tumor cells and confer them the ability to inhibit T-cell function (57). In addition, TDEs also induce immunosuppressive monocytes, thus indirectly inhibiting T-cell proliferation and activation (58). Since exosomes can be released into bodily fluids, TDEs carrying PD-L1 can also enter lymph nodes with lymphatic drainage, as well as other remote tissues and organs, such as the spleen, via the blood circulation to inhibit the proliferation and function of local T-cells (59).

Additionally, exosomes can be internalized into cells and release proteins, miRNAs and other inclusions that interfere with T-cell function, as demonstrated by previous studies: Exosomes derived from several head and neck cancers have been found to be loaded with an immunomodulatory protein galectin-1, inducing $CD8^+$ T-cells to differentiate towards a suppressive phenotype (60); TDEs deliver high levels of TGF-β secreted by tumor cells to T-cells to inhibit their proliferation and differentiation, and TGF-β1-rich exosomes also exert immunosuppressive effects by suppressing lymphocyte responses to IL-2 (28); in addition, it has been reported that TDEs can function as long-distance transport carriers of Arg1 and deliver it to peripheral T-cells to inhibit their proliferation, thus attenuating the body's antitumor immune response (61).

Furthermore, TDEs have been shown to carry CD39/CD73, the most critical extracellular enzyme for adenosine (ADO) production, contributing to the upregulation of ADO in recipient cells (62). Subsequently, ADO inhibits the function and proliferation of both $CD4^+$ T-helper cells and $CD8^+$ cytotoxic T-cells via G protein-coupled receptors, facilitating tumor cell escape from the host immune system (63).

Other immune cells. DCs are antigen-presenting cells that function as messengers between intrinsic and adaptive immunity. Exosomes from breast cancer or Lewis lung cancer cells have been shown to inhibit bone marrow progenitor cell differentiation into DC and induce apoptosis (64). TDEs also transfer miRNAs to DCs, leading to the downregulation of TLR4 expression, and subsequently resulting in the decreased production of cytokines involved in the immune response in DCs (1). In addition, TDEs can block the migration of DCs to secondary lymphoid organs by inhibiting the expression of chemokine receptors, such as CCR6, CCR7 and CXCR3 (65).

Monocytes are a critical part of the body's defense system and can differentiate into macrophages and DCs in the peripheral area, while TDEs suppress the immune response by affecting the maturation and differentiation of monocytes (66). For example, TDEs have been reported to inhibit the differentiation of monocyte precursor cells into DCs or promote the monocytes to differentiate into TGF-β-expressing DCs interfering with T-lymphocyte proliferation; TDEs can also drive monocytes to differentiate towards a pro-tumor phenotype that releases tumor-supporting cytokines and leads them to express the immunosuppressive molecule, PD-L1 (1).

Myeloid-derived suppressor cells (MDSCs) are immature bone marrow cells with immunosuppressive activity that produce numerous immunosuppressive factors and suppress antitumor immune responses; TDEs have been shown to play a critical role in MDSC expansion and activation (24). A previous *in vitro* study demonstrated that miR-10a and miR-21 expression in exosomes produced by glioblastoma enhanced MDSC expansion and immunosuppressive factor levels (67). TDEs can also induce the conversion of bone marrow cells into MDSCs through the delivery of prostaglandin E2 (PGE2) and TGF-β; the blocking of exosomal PGE2 and TGF-β can eliminate the induction of MDSCs and diminish the MDSC-mediated immunosuppressive effects (68).

Effect of exosomes on the TME during microbial infections. An increasing number of studies have demonstrated that exosomes can not only be produced by a variety of mammalian cells, but are also found in bacteria, viruses and fungi (69). Since the infection of certain microorganisms is closely related to tumor development, exosomes may also have a potential effect on their interaction.

Helicobacter pylori (*H. pylori*) infection. Studies have proposed that Gram-negative bacteria can release 'cargo'-loaded exosomes that can spread infection by activating the transcription of genes which promote bacterial infection (70). Exosomes produced by infected gastric epithelial cells are capable of transferring virulence factors to modulate host immune responses and assist bacterial invasion (71).

H. pylori is a Gram-negative bacterium that colonizes the gastric epithelium and damages the gastric mucosa; it has a high infection rate and is strongly associated with various gastric mucosal diseases, including gastric cancer (GC) (72). Previous research has revealed the impact of *H. pylori* infection on the treatment outcomes of tumors in sites beyond the gastrointestinal tract (73). However, due to the particular survival and growth environment of *H. pylori* and the gastric tissue barrier, *H. pylori* itself does not enter the blood circulation or reach other tissues and organs (72); presumably there may be an exosomal influence during this action.

A previous study demonstrated that the protein levels of mesenchymal-epithelial transition (MET) factors were significantly decreased in GC cells following *H. pylori* infection, while their mRNA levels remained unchanged. However, the phosphorylated active form of MET factors was increased in exosomes released from *H. pylori*-infected GC cells, which were delivered to tumor-infiltrating macrophages and internalized. This induced macrophages to convert into a pro-tumorigenic phenotype and stimulating the expression of the pro-inflammatory factor, IL-1β, and the activation of its downstream signaling pathways, thereby promoting tumor growth and progression (74). Cytotoxin-associated gene A (cagA) positive strains of *H. pylori* is one of the most virulent strains. CagA-positive *H. pylori*-infected GC cells secrete CagA-containing exosomes that induce morphological changes in gastric epithelial cells and GC cells, and transmit functional CagA into cells that may be involved in the development of extragastric diseases associated with CagA-positive *H. pylori* infection (2).

Fusobacterium nucleatum (Fn) infection. Infection of Fn, a specialized anaerobic bacterium, is the most important microbial-related risk factor in the development of colorectal cancer (CRC) (75). Fn chronic infection involved in the development of CRC is achieved by interacting with immune cells and stromal cells by the surface molecules of Fn and then inducing immune escape and immunosuppression (76). Fn infection has been shown to increase the secretion of exosomes from CRC cells, and that proteins and miRNAs involved in cell migration are enriched in the secreted exosomes, which are delivered from Fn-infected CRC cells to uninfected cells to increase their migration capacity and promote tumor metastasis. The levels of miRNAs and proteins in circulating exosomes associated with CRC cell migration are also closely related to Fn abundance and the tumor stage of patients with CRC (77).

Hepatitis B virus (HBV) infection. HBV is considered an important pathogenic factor in the development of HCC. HBV-infected hepatocytes secrete exosomes (HBx) containing numerous HBV DNA, RNA and protein components, that can be delivered to uninfected hepatocytes to regulate cell function and phenotype, thereby shaping a microenvironment conducive to viral replication (78). HBx contain significantly higher levels of immunosuppressive miRNAs, and these miRNAs can inhibit the body's antiviral immune response by downregulating IL-12 expression to inhibit NK cell activity (79). In addition, exosomes with HBV replication secreted from HBV-induced HepAD38 cells can significantly upregulate PD-L1 expression in monocytes, which can bind to PD-1 on T-cells to induce T-cell failure, thereby inhibiting T-cell function to promote HBV infection (80). TDEs from HCC can also transport interferon induced transmembrane protein 2 to DCs, thereby inhibiting IFN-α secretion and blocking the antiviral effects (81). All these effects of exosomes contribute to the development of HBV infection and HCC.

3. Impact of exosomes on immunotherapy

Since the suppressive effects of TDEs on the body's immunity far exceeds the activating effect, and immunotherapy mostly promotes antitumor immunity by regulating the body's immune system, the presence of TDEs inevitably has several adverse effects on immunotherapy. TDEs carry TAAs, which effectively bind to tumor-reactive antibodies used in immunotherapy, and significantly inhibit the binding of these antibodies to tumor cells, as well as the antibody-dependent cell-mediated cytotoxic effect, leading to the reduced effectiveness of tumor immunotherapy drugs (66).

Anti-PD-1/PD-L1 immunotherapy is currently one of the most commonly used types of immunotherapy in the clinical practice; however, its effectiveness remains limited. Exosomal PD-L1 from tumor cells is considered to play a key role in mediating resistance to anti-PD-1/PD-L1 immunotherapy. A possible mechanism involved in drug resistance has been suggested to be the high expression level of exosomal PD-L1 and its competitive binding to anti-PD-L1 antibodies results in the failure to inhibit PD-L1 function on the surface of tumor cells (82). It has also been shown that miR-21 overexpression is associated with acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) in NSCLC. In EGFR-TKI-resistant NSCLC cells, miR-21 is overexpressed and exosomes can transfer miR-21 into EGFR-TKI-sensitive NSCLC cells, reducing the sensitivity of cancer cells to EGFR-TKI, and thus inducing drug resistance (83,84).

Cancer stem cells (CSCs) are a small subpopulation of malignant tumor cells with an extremely potent capacity for self-renewal and metastatic spread; they are crucial for tumor progression and treatment resistance (85). Under the stimulation of a hypoxic environment, the expression levels of survival and growth factors in CSCs within the TME increase, and CSC-derived exosomes can act on recipient cells by transferring these factors. This induces genetic instability and malignant transformation, thus promoting CSC survival, differentiation, self-renewal and enhances their resistance to various cancer therapies (86). Currently, targeting CSCs by exosomes is also considered a highly promising novel tumor immunotherapy (87).

4. Clinical applications of exosomes in tumor therapy

Diagnostic and monitoring potential. Exosomes carry genetic materials, proteins and other molecules that can reflect their cellular origin and disease state, and these 'cargoes' are encapsulated by the plasma membrane, and can be relatively stable in blood and other body fluids. For these reasons, exosome-based liquid biopsies have the potential to function as biomarkers for cancer diagnosis and prognosis, as well as for the monitoring of disease progression and the immunotherapeutic response (4).

Exosomal miRNAs are key regulators of gene expression in recipient cells and are involved in intercellular communications in the TME, which affects tumor development. Therefore,

exosomal miRNAs have been shown promise as biomarkers for various tumors and have significant clinical value in the early diagnosis of tumor metastasis (26,38). It has also been shown that exosomal mRNAs have potential clinical applications. TDEs have been reported to contain ~10,000 different mRNA species (88). In previous a retrospective vaccination study, the mRNA levels of four immunomodulatory genes (*IL-8, ZAP70, TGFB* and *TIMP1*) were significantly decreased in TDEs isolated from the plasma of patients with recurrent gliomas, and this change only occurred in patients who exhibited a clinical response to the vaccine (89). That study indicated that the analysis of mRNAs in TDEs from plasma of cancer patients receiving immunotherapy may be helpful in predicting reactivity and determining prognosis (89).

Exosomes also contain various proteins that reflect the characteristics of parental cells. Proteins that are aberrantly expressed in tumor cells can be expressed in exosomes; thus, exosomal proteins may also serve as potential biomarkers for tumor diagnosis, as well as for the monitoring of disease progression and the immunotherapeutic response.

An example of this is the extensively studied PD-1/PD-L1. It has been demonstrated that higher levels of exosomal PD-L1 (ExoPD-L1) are present in the circulation of cancer patients compared to healthy individuals (59), and appear to be consistent with the expression levels of PD-L1 in their parental tumor cells (90). However, in another study on prostate cancer, it was found that cancer cells expressed high mRNA levels of PD-L1 and produced high levels of ExoPD-L1, whereas no PD-L1 was present on the surface of the cancer cells (91); this suggests that exosome-based tumor marker detection can be used to screen some patients with a normal histology. Furthermore, high levels of circulating ExoPD-L1 have been shown to be associated with the poor prognosis of patients with various tumors, including metastatic melanoma, and pancreatic and metastatic gastric cancer (59,92). It also has been shown that a quantitative increase in circulating ExoPD-L1 levels in patients with melanoma during early treatment can distinguish the clinical responders from non-responders (93). A previous prospective study on melanoma also suggested that monitoring circulating ExoPD-L1 levels may help to predict treatment efficacy and clinical outcomes (94). From the aforementioned findings, it can be concluded that circulating ExoPD-L1 has potential for use as an effective biomarker for tumor diagnosis, and for the determination of tumor progression, prognosis and immunotherapy efficacy. It can also be used as a complement to tumor tissue PD-L1 expression levels to improve accuracy.

Therapeutic potential

Exosomes as delivery vehicles. The lipid bilayer membrane of exosomes protects the delivered substances from biodegradation, and exosomes carrying 'cargo' also have a low immunogenicity and a long half-life in the body, which endow them with the high stability in the circulation and the ability to cross biological barriers. Thus, exosomes can be modified to deliver a wide range of substances, including therapeutic RNAs, antitumor drugs, functional proteins, immunomodulators, etc., in a specific manner to the target cells of the body to exert their effects (10,83). For example, siRNA targeting RAD51 (a DNA repair protein) can be delivered by exosomes to HeLa cells, leading to the death of a large proportion of proliferating cells (95). A previous study on lung cancer also reported that exosomes loaded with paclitaxel could be targeted to lung cancer cells and exerted superior antitumor effects compared to direct treatment with paclitaxel (96).

Exosomes can facilitate drugs or antigenic substances to specific cells by modifying their own lipids, and glycosylation has been shown to protect exosomes from protein hydrolysis and to direct exosomes to specific destinations *in vivo* (97). The modification of exosome membranes with certain markers also allows them to target specific recipient cells; for example, loading exosome membranes with unique markers for CSCs (e.g., CD44, CD24, CD133 and CD200) allows exosomes to target CSCs (10), exerting an inhibitory effect on tumor progression by targeting CSCs.

Exosomes as cancer vaccines. As exosomes can induce tumor-specific immunity, their use in cancer treatments has received increasing attention, and several studies have revealed the potential of exosomes as a cancer vaccine (98). A previous study on melanoma found that NK cell-derived exosomes enriched in perforin and FasL exerted cytotoxic effects on melanoma cells, and that NK cell-derived exosomes secreted TNF-α, which affected cell proliferation signaling pathways; the results of that study demonstrated that NK cell-derived exosomes exerted antitumor effects against aggressive melanoma both *in vitro* and *in vivo* (99). Another study demonstrated that exosomes from class II trans-activator gene-modified mouse melanoma cells expressed MHC II and the tumor antigen TRP2, and when injected into mice as a vaccine, they were found to induce a Th1 polarized immune response and stimulated the production of Th1 IgG2a antibody and IFN-γ, as well as the upregulation of TRP2-specific $CD8^+$ T-cells, therefore attenuating tumor growth (100).

DC-derived exosomes (DEX) are enriched in MHC I, MHC II and CD86, which can stimulate the activation of $CD4^+$ T and $CD8^+$ T-cells, induce $CD8^+$ T-cell proliferation, and exert potent antitumor effects *in vivo* (101). There have been two phase I clinical trials and one phase II clinical trial analyzing the feasibility of DEX as a cancer vaccine (102-104). In these clinical trials, some patients achieved disease stabilization, and a small number of patients observed a mild response, indicating that DEX as a vaccine was well-tolerated and safe. However, it is worth noting that in all three trials, the results of low clinical efficacy and insufficient antigen-specific T-cell response are presented; thus, further research is required in order to identify strategies with which to enhance the DEX-induced T-cell function the antitumor effect (105).

Targeted inhibition of TDEs to improve immunotherapy efficacy. As TDEs are involved in several immunomodulatory processes related to tumorigenesis and tumor development, the targeted inhibition of the biosynthesis or secretion of TDEs may prove to be beneficial for the treatment of tumors (59).

Current immunosuppressive therapies and immune checkpoint blockade mainly focus on the PD-1/PD-L1 pathway; however, there are certain disadvantages, such as individual variations in the drug response, differences in efficacy against various tumors and drug resistance. Targeting exosomal PD-L1 may be a potentially effective approach to address these issues (82). Previous studies have demonstrated that anti-PD-L1 antibody therapy has a higher therapeutic efficacy when combined with inhibitors targeting exosome

Table I. Frontier research advances in exosomes.

Authors	Date of publication	Type of study	Exosome research methods	Conclusions of the study	Exosome potential applications	(Refs.)
Li *et al*	July, 2022	Clinical study	Transmission electron microscopy, Western blot analysis and ELISA	The plasma NCAM/ ABCA1 dual-labeled exosomal Aβ42/40 and miR-384 had potential advantages in the diagnosis of subjective cognitive decline	Diagnosis of subjective cognitive decline	(108)
Wang *et al*	May, 2022	*In vitro* cell lines and mouse model	BCA protein assay, dynamic light scattering, transmission electron microscopy, nanosight tracking analysis and nanoparticle tracking analysis	Engineering a 293T exosome-based delivery platform for efficient tumor-targeting chemotherapy and internal irradiation combination therapy	Medication delivery	(110)
Huang *et al*	February, 2022	Mouse and model organoid model	Transmission electron microscopy, nanoscale flow cytometry and western blot analysis	HeLa-Exos exhibit potent antitumor activity by promoting the activation of cDC1s *in situ* and thus improving the subsequent tumor-reactive $CD8^+$ T-cell responses	Tumor treatment	(109)
Bai *et al*	February, 2022	*In vitro* cell lines	Transmission electron microscopy and nanoparticle tracking analysis	Human placental exosomes suppress the adaptive immune system by promoting the expression of PD-L1, down-regulating phosphatase and tension protein homologs in monocytes	Immunomodulatory	(111)
Song *et al*	January, 2022	Clinical study and mouse model	BCA protein assay, nanoparticle tracking analysis, transmission electron microscopy and western blot analysis	miR-155-3p-loaded M2 macrophages-derived exosomes enhances the growth of medulloblastoma cells by downregulating WDR82	Tumor immunomodulation	(112)
Gao *et al*	January, 2022	*In vitro* cell lines and mouse model	Nanoparticle tracking analysis, BCA protein assay, transmission electron microscopy and western blot analysis	Hepatocellular carcinoma cells with high expression levels of GOLPH3 can promote angiogenesis and sorafenib resistance by enhancing exosomal miR-494-3p secretion	Tumor microenvironment modulates and mediates drug resistance	(113)

Table I. Continued.

Authors	Date of publication	Type of study	Exosome research methods	Conclusions of the study	Exosome potential applications	(Refs.)
Zhang *et al*	January, 2022	Mouse model	Nanosight tracking analysis, transmission electron microscopy and western blot analysis	Delivery of platelet-rich plasma-derived exosomes incorporated in thermosensitive hydrogel provides a novel approach of cell-free therapy and has therapeutic effect on subtalar osteoarthritis	Arthritis treatment	(114)
Qin *et al*	August, 2021	Clinical study	Nanoscale liquid chromatography coupled to tandem mass spectrometry	Patients with RA have different plasma exosome protein profiles. These proteins not only take important parts in the vicious circle in the pathogenic process of RA, but also serve as novel biomarkers in RA diagnosis and prognosis	Diagnosis and prognostic determination of RA	(115)
Du *et al*	April, 2021	Clinical study	Ultra-performance liquid chromatography-tandem mass spectrometry	Exosomal metabolites have the potential to function as biomarkers for schizophrenia diagnostics	Diagnosis of schizophrenia	(116)
Kohaar *et al*	February, 2021	Clinical study	Nanoparticle tracking analysis and transmission electron microscopy	Expression levels of urine exosome-specific genes (PCA3 and PCGEM1) contribute to the prediction of high-grade prostate cancer	Adjunctive diagnosis of prostate cancer	(117)
Xia *et al*	March, 2020	Clinical study and mouse model	BCA protein assay, transmission electron microscopy, particle and molecular size analyzer and western blot analysis	*Helicobacter pylori* infection impaired endothelial function in patients and mice through exosome-medicated mechanisms	Involved in the endothelial damage caused by *Helicobacter pylori* infection	(72)

RA, rheumatoid arthritis; Exos, exosomes; cDC1s, type one conventional dendritic cells.

biosynthesis (57,91). In addition, researchers have found that blocking ExoPD-L1 exerts synergistic antitumor effects by inhibiting not only local tumor growth, but also distant tumor growth. Furthermore, as previously demonstrated, when tumor cells previously treated with ExoPD-L1 blockade therapy were re-injected into the tumor site, the cells did not grow and were rapidly destroyed, which suggested that the T-cells developed an antitumor immune memory following ExoPD-L1 blockade (91). Therefore, anti-PD-L1 combined with targeted TDE inhibition may prove to be a novel approach with which to improve the efficacy of conventional immunotherapy.

5. Frontier research advances in exosomes

Due to the wide distribution of exosomes *in vivo* and their special biological properties, exosomes have become a new research hotspot, particularly in the fields of cancer diagnosis and treatment, targeted drug delivery. In recent years,

a number of studies have also elaborated on the role and mechanisms of exosomes in neoplastic, neurodegenerative and cardiovascular diseases, providing several new avenues for the diagnosis and treatment of these diseases (106). For example, previous multicenter studies using transmission electron microscopy to analyze exosomes confirmed the value of exosomes in the diagnosis of pancreatic cancer and subjective cognitive decline (107,108). Other studies using mouse models and human breast cancer organoid models have used transmission electron microscopy and nanoscale flow cytometry to analyze exosomes, revealing that engineered exosomes can enhance the antitumor immunity of the body by promoting the activation of type one conventional DCs *in situ* (109). The findings of recent studies on exosomes are presented in Table I (72,108-117).

6. Conclusions and future perspectives

Exosomes, as intercellular message carriers, are critical mediators of cellular communications, both locally and systematically. Exosomes produced by tumor cells have been shown to play an essential connective role among various cells in the TME, and are closely associated with tumorigenesis, tumor progression and therapeutic resistance (118). TDEs construct a pro-tumor metastatic microenvironment by promoting EMT and angiogenesis, as well as by inducing a pre-metastatic ecological niche. More importantly, TDEs can inhibit the function of immune cells via multiple mechanisms, facilitate tumor immune escape, and even impair the efficacy of immunotherapy. In cancers associated with microbial infections, exosomes are also involved in infection factor-associated immune responses, and play a role in promoting infection and tumor development (119). In addition, due to the biological properties of exosomes, their potential application in clinical practice is also highly noteworthy. Compared to conventional biopsy methods, exosomes based on bodily fluid sample detection may prove to be superior biomarkers for tumor diagnosis and monitoring (120). Furthermore, due to their low immunogenicity and molecule delivery function, exosomes exhibit immense potential for use in tumor immunotherapy, particularly as cancer vaccines and targeted carriers for antigens and drugs (106). As nanoscale particles of lipid components, exosomes are also able to across biological barriers, even the blood-brain barrier, an effect which is difficult to achieve with several drugs (121). Nevertheless, the complex crosstalk between TDEs and the TME is not yet fully understood and thus further investigations into this matter are warranted. Another unresolved issue is the identification of mechanisms with which to obtain intact and stable exosomes, and to modify and package them for clinical treatment (122). The current research progress regarding the u se of exosomes in tumor therapy also appears to be limited to animal studies and *in vitro* experiments; thus further clinical trials are required for verification (123). Providing a more in-depth understanding of the characteristics of exosomes and their functional role in tumorigenesis may provide novel insight and may further improve antitumor therapeutics and cancer diagnostics in the future.

Acknowledgements

Not applicable.

Funding

The present study was funded by the National Natural Science Foundation of China (grant nos. 81700496 and 32000923), the Peking University Medicine Fund of Fostering Young Scholars' Scientific and Technological Innovation (grant no. BMU2021PY002), and the Beijing Municipal Natural Science Foundation (grant no. 7214304).

Availability of data and materials

Not applicable.

Authors' contributions

ML searched the literature and wrote the manuscript. HC and RD re-examined the literature. YS designed the study. YS and JC revised the manuscript. All authors contributed to the article and have read and approved the final manuscript. Data authentication is not applicable.

Ethical approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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