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REVIEW ARTICLE

The function of tumor-derived exosomes

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Summary

Exosomes, especially the tumor-derived exosomes (TDEs), are extracellular vesicles released by many kinds of cells, which are involved in several biological and pathological processes. Their contents mainly include DNA, RNA and proteins. The message could be transmitted in neighboring or distant cells by secreting extracellular vesicles (EVs). Exosomes are a main intercellular communication regulator because they are involved and interact with intracellular signaling pathways. Exosomes can be detected in the tumor microenvironment, and there is growing evidence that TDEs are active in tumor growth, angiogenesis, invasion and metastasis, as well as immune responses and drug resistance. All of the functions mentioned above make it clear that exosomes have an important role in tumors. This review focuses on the origin and structure of TDEs and their important biological functions in the environment due to cell-to-cell intercellular communication.

Key words: *exosomes, tumor-derived exosomes (TDEs), cancer*

Introduction

Exosomes are composed of plasma membranes and an intracellular vesicle structure. They are actively secreted by all kinds of cells with a lipid bilayer membrane structure of nanoscale cystic vesicles and have a diameter of approximately 30-100 nm [1]. Exosomes were first discovered when the development of reticulocytes to mature erythrocytes was discovered in 1985. The membrane in the late endosomes of reticular cells is denuded in many places and forms lumen-like vesicles inwardly, which transforms into multicapsular bodies with dynamic subcellular structures. Exosomes can be secreted by many types of cells, such as immune cells, adipocytes, dendritic cells, mast cells and tumor cells, they can be detected in various body fluids, including urine, cerebrospinal fluid and blood [1], and are usually isolated by ultracentrifugation. Exosomes can transport a large number of proteins, lipids, nucleic acids and other components. Furthermore, antigen-presenting cells (APCs) are secreted and released into the extracellular microenvironment and body fluids, and exosomes secreted by APCs can express MHC-I and MHC-II molecules as well as costimulatory protein CD80 [2]. To exert a biological effect, it has been shown that exosomes need to go through several steps from the donor cells into the recipient cells (Figure 1). The exosome cell membrane is invaginated in the late phase of membrane degeneration in the cell cytoplasm, resulting in the inward

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bud formation of the lumen-like vesicles and thus transforming into a dynamic subcellular structure of the multivesicular body (MVB). When MVBs fuse with lysosomes, luminal vesicles degrade. After fusing with the cell membrane, the intraluminal vesicles form small granular vesicles and release into the extracellular environment. However, there is no consensus about the release mechanism of exosomes, which can be roughly divided into three kinds: dependent on the endosomal sorting complex required for transcript (ESCRT) [3] pathway, not dependent on the ESCRT pathway, and the lysophosphatidic acid (LBPA) pathway. The content of the exosomes, mainly transferred from donor cells to recipient cells, plays a vitally important role in intercellular communication, the regulation of angiogenesis, the immune response and fibrosis, among others. More and more emphasis is being placed on the early and accurate diagnosis and treatment of diseases to improve the prognosis of patients. It has been confirmed that exosomes also play an important role in the early stage of accurate treatment, including tumor development, the early diagnosis and precise treatment of cancer, two-way regulation of cellular immunity and targeted medication. This article will focus on the function of tumor-derived exosomes in the development of tumors, invasion and metastasis, diagnosis and treatment.

Tumor-derived exosomes

Numerous studies have shown that exosomes can be released by tumor cells, and the content of TDEs also contain a variety of bioactive molecular components, such as proteins, lipids and nucleic acids, especially nucleic acid components, including noncoding RNA (miRNA, lncRNA, circRNA), mRNA and DNA fragments. These nucleic acid components are involved in intracellular communication, resistance to chemotherapy treatment, microangiogenesis, regulation of the tumor microenvironment and immune reaction, and the promotion of tumor invasion and metastasis. TDEs can also be specifically expressed in membrane proteins, nuclear-related protein Rab family GTPase, and annexin; proteins related biosynthesis transport: Alix, ESCRT; heat shock protein (Hsp70, Hsp90) [4], and the family of Quadruplex cross-linked proteins (CD9, CD53, CD81 and CD82). Among them, CD9, CD63 and CD81 are often used as landmark proteins for the screening of exosomes [5]. In addition, the components of TDEs (especially lncRNA, which can mediate tumor hyperplasia), regulate the signal transmission between donor and recipient cells, and diagnose the progress of tumor development and antitumor activities as a biomarker. Therefore, regulating the level of a particular nucleic acid or protein in TDEs provides a new direc-

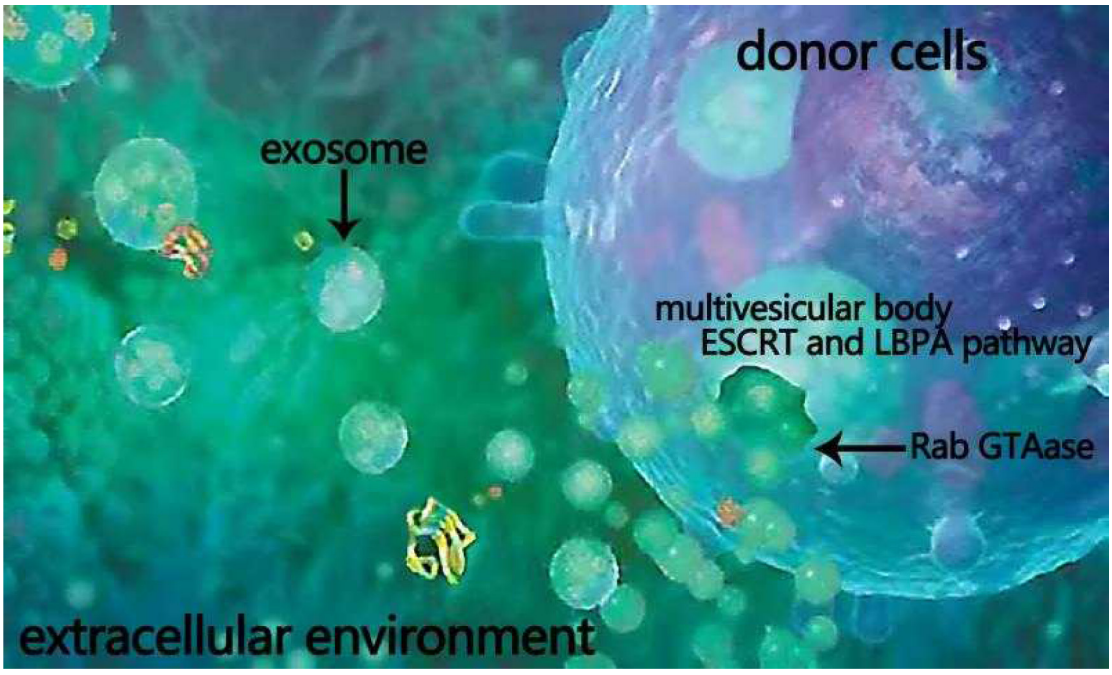

Figure 1. The process of exosome formation and transportation to the extracellular microenvironment. The first step is the inward budding of the endomembrane, which produces multiple vesicles (MVBs) in the cytoplasm of donor cells. Subsequently, the process relies on the endosome sorting complex (ESCRT) or lysophosphatidic acid (LBPA) pathway required for transport. Rab GTPase-dependent fusion of the MVBs with the donor cell membrane releases the produced exosomes to the extracellular microenvironment where they can interact with the recipient cells, completing the exosome load to the recipient cells through ligand-receptor interactions, pinocytosis and cell membrane fusion.

tion and target for the development, diagnosis and treatment of tumors.

The function of TDEs in cancer

Intercellular signal transduction

Previous research has reported that exosomes can carry RNA as a "communication carrier" for the exchange of genetic material between cells and can exert biological functions in recipient cells, which means that exosomes can serve as a new way to communicate genetic material between cells. Undoubtedly, cancer cells can secrete more variable exosomes than healthy cells, but more importantly, the diverse functions of the contents are remarkable; therefore, cancer cells can act as a vector mediating intercellular signal transduction. TDEs have a close relationship with the cell membrane during cellular communication, and the content of substances can exchange and transmit information. Various nucleic acids (DNA or RNA) and proteins can also serve as a carrier of the information exchanged between cells through the process of cell signaling. It has been confirmed that TDEs contain a unique signal protein, such as small guanosine phosphatase Ras and cell surface receptor tyrosine kinase enzyme epidermal growth factor receptor (EGFR), and different types of RNA regulatory protein expression to stimulate cell growth and survival [6]. Exosomes, the messenger of cell-to-cell information transmission, have high affinity to the tissues. When milk-derived exosomes were combined with paclitaxel as the oral drug, a higher efficiency appeared than the separate application of paclitaxel, which significantly reduced the related side effects [7]. In addition, exosome-derived miR-302b inhibits the growth and metastasis of lung cancer through the extracellular regulated protein kinase (ERK) signaling pathway by transforming growth factor beta receptor 2 (TGFβRII) [8]. Exosomal miRNAs are important vectors for the exchange of information between tumor cells and macrophages. TNF-like weak inducer of apoptosis (TWEAK) increases the number of macrophages and the exosomes secreted and increases the level of miR-7 in ovarian cancer cells. Increasing miR-7 can inhibit the metastasis of ovarian cancer cells by inhibiting the EGFR / AKT / ERK1 / 2 signaling pathway [9]. MiR-302b was amplified *in vitro* and then transferred into the appropriate exosomes, in which it can transport miR-302b to specific sites of lung cancer growth and ultimately achieve the goal of treating lung cancer. Another important research study elaborated that the oncogenic protein cytoplasmic tyrosine kinase (SRC), a core component of many signaling and adhesion molecules, stimulates the secretion of exosomes that carry syntenin and syndecan. This study revealed the function of SRCs in the mechanisms of cellular and exosome biogenesis and activity with potential broad implications for pathophysiology [10]. All in all, TDEs are able to participate in the exchange of information between cells as a carrier of information exchange and have biological functions in regulating tumorigenesis, invasion and metastasis. At the same time, TDEs can be used as a cancer vaccine and drug delivery carrier for the treatment of cancer.

Cell proliferation, invasion and metastasis

In the clinic, it has been shown that the circular exosome vesicles isolated from cancer patients are associated with invasion and metastasis, and most biologically active molecules, such as markers of invasion and metastasis, can guide diagnosis, prognosis and precise treatment. One study found that esophageal cancer cells can decrease the expression of PDCD4 target genes and activate the JNK signaling pathway by secreting exosomes carrying miR-21, which results in promoting tumor cell proliferation [11]. On the one hand, exosomes derived from cancer cells can cause changes in the phenotype and function of stromal cells; on the other hand, exosomes can be secreted by tumor cells, promoting the entry of tumor cells into the blood circulation and metastasis via damaging the vascular endothelial barrier. Interestingly, an important study found that the source of brain astrocyte exosomes containing miRNAs can cause a loss of the PTEN gene in brain metastatic cells [12]. This loss of PTEN permits tumor cells to secrete more of the chemokine CCL2 and facilitate the recruitment of IBAL + / CCR2 + myeloid cells, which can promote the proliferation and inhibit the apoptosis of tumor cells, thus contributing to the growth of tumor cells. TDEs are able to promote the growth and migration of gastric cancer cells by activating the Akt signaling pathway [13]. Breast cancer cells increase their motility by transporting miR-9 to normal mammary fibroblasts through exosomes, whereas fibroblasts can also secrete exosomes that carry miR-9, which are transported to tumor cells for down-regulating the target *E-cadherin* expression, promoting epithelial-mesenchymal transition, and ultimately promoting tumor cell invasion motility [14]. The expression of mesothelial cell adhesive molecules has been induced by TDEs, which may play a key role in the occurrence and development of the peritoneal metastasis of gastric cancer [15]. Pancreatic stellate cells can

also secrete exosomes carrying miR-451a. These exosomes can promote the proliferation and migration of hepatocellular carcinoma cells and upregulate the expression of the chemokine ligands CXCL1 and CXCL2. However, the exosome inhibitor GW4869 can cause the phenomenon of promoting the proliferation and migration of pancreatic cancer cells to cease [16]. Moreover, exosome content affects the signaling pathways involved in the epithelial-mesenchymal transition (EMT) of the recipient cells, promoting the interstitialization of the tumor cells and enhancing their ability to migrate. At the same time, the exosomes can be secreted by exosome-specific membrane proteins that are transferred into the receptor organs, creating a transfer "niche" and waiting for tumor cells to form metastases. Compared with normal fibroblast-derived exosomes, the level of miR-320a in exosomes secreted by tumor-associated fibroblasts was significantly reduced [17]. However, *in vivo* and *in vitro* experiments have found that miR-320a has a tumor suppressor effect, that is, overexpression of miR-320a significantly downregulates the level of the target gene *PBX3*, and eventually the proliferation of hepatoma cells, invasion and tumor metastasis can be inhibited by curbing the activation of the MAPK signaling pathway and downregulating the expression levels of CDK2 and MMP2 [18]. It has been reported that TDEs can stimulate EMT in the surrounding tissues of tumors to accelerate tumor invasion and metastasis. When human normal bronchial epithelial cells were cocultured with lung cancer cell-derived exosomes of patients with highly metastatic lung cancer, these lung cancer cell-derived exosomes were found to induce the expression of vimentin in human normal bronchial epithelial cells and cause a gradual malignant transformation by prompting the EMT process in normal bronchial epithelial cells [19]. Therefore, TDEs can promote the proliferation, invasion and metastasis of tumor cells by different ways.

Regulation of tumor microenvironment

In the physiological process, exosomes can serve as a means of microenvironment communication among cells and play an important role in mediating the local microenvironment, in addition to acting as a mediator of the cell-to-cell communication effect in cancer. Numerous studies have shown that the excretory secretion of functional substances into the tumor microenvironment (TEM) is mainly involved in tumorigenesis, development and metastasis, such as exosome secretion by fibroblasts through the PCP signal pathway to promote cancer metastasis. TDEs can induce the EMT signal in the TEM through paracrine or autocrine processes. A critical element in cancer progression is the regulation of the conditions of the TEM, especially hypoxia and acidosis, which can better optimize the condition for tumor progression and metastasis. Moreover, rapid growth is a major feature of tumors, and the rapid growth of tumor cells is accompanied by an increase in tumor volume and the number of tumor cells, leading to an insufficient blood supply and an increased demand for blood supply within the tumor. When the oxygen supply cannot meet the needs of the growth of tumor cells, hypoxia occurs within the tumor cells. Compared with normal body tissues, oxygen partial pressure in most parts of the tumor is significantly lower. When the PO_2 level in the center of the tumor is below 10 mmHg (1 mmHg=0.1333 kPa), the central part of the tumor can develop anoxia, which is one of the basic features of the central tumor microenvironment. The hypoxic microenvironment is of great significance in the evolution and metastasis of tumors. On the one hand, it can promote cell differentiation, inhibit cell proliferation and induce cell necrosis and apoptosis. However, when hypoxia occurs in tumor cells, the adaptability of some intraepithelial cells changes, and the expression of HIF-1α, AP-1, NF-κB and other related genes are also changed, resulting in a more aggressive phenotype. Increased cell proliferation and antiapoptosis and invasion lead to local or distant metastases and an increased resistance to treatment. Researchers have also found that oral squamous cell carcinoma overexpresses miR-21 in exosomes secreted in hypoxia and promotes the invasion and migration of cancer cells by relying on HIF-1α and HIF-2α [20]. The tumor hypoxia microenvironment is closely related to the growth, development, invasion, metastasis and prognosis of patients, as well as the therapeutic effect. Therefore, regulating the microenvironment of tumors through different mechanisms may become a new way of treating tumors in the future.

Exosomes as biomarkers in cancer diagnostics and treatment

Due to the lack of appropriate clinical indicators, clinical treatment is stagnant in certain diseases. Exosomes can be released into body fluids such as urine and blood, which are readily available and detectable and can therefore be a valuable source of medical testing. Currently, exosomes are a thriving research hotspot in the field of cancer, and they may be very useful biomarkers for the diagnosis and prognosis of malignant tumors. Although tissue biopsies are the gold standard for

the diagnosis of tumors, they are inconvenient and have disadvantages for many patients; however, noninvasive biomarkers are emerging as an alternative, using the detection of exosomes for the early diagnosis of disease, effective monitoring and accurate treatment. The diversity and specificity of TDEs (miRNA, lncRNA, circRNA and mRNA) enable their use in the diagnosis of tumors and in the monitoring of swollen tumors. A large amount of RNA and mRNA constitute the content of TDEs, with microRNA accounting for a large proportion. MicroRNAs (miRNAs) are a kind of small noncoding RNAs 20-40 nucleotides long, and when entering the recipient cells, they can bind to target mRNA sequences and inhibit translation. It is known that miRNAs can regulate more than 50% of the encoded proteins that are expressed by genes. The miRNAs bind to the specific 3'UTR of the target gene mRNA and play an extremely important role in regulating the receptor cells by regulating the transcription level of the target gene. The expression of miRNAs has been found to be disordered in most cancers but plays a negative regulatory role in the translation process. There is a significant difference in the miRNA content of exosomes between normal and lung cancer patients in body fluids. For example, the contents of let-7f, miR-20b, miR-30e-3p, miR-25 and miR-223 in the body fluid of lung cancer patients were significantly different from those in normal subjects. Among them, the levels of miR-25 and miR-223 in the plasma of lung cancer patients were significantly higher than those in normal subjects, while the contents of let-7f, miR-20b and miR-30e-3p were significantly lower than those in normal subjects. Therefore, the detection of tumor-derived miRNAs and other components in different body fluids can serve as a tumor marker for lung cancer, providing a more scientific basis for the early diagnosis and prognosis assessment of lung cancer patients. Serum-derived exosomes from cancer patients play a crucial role in promoting tumor invasiveness but have limited effects on tumor cell survival and proliferation [21]. The expression levels of the TDEs were significantly higher than those of healthy people, and the same result was obtained through experimental verification; therefore, the combination of miRNAs can be used to diagnose colorectal cancer (CRC). Dou et al. [22] found that tumor cells and extracellular microvesicles contain not only miRNAs but also circRNAs, which can significantly reduce the expression levels in cell lines through KRAS mutations. Compared with healthy human tissue, the levels of circRNAs in tumor tissues of patients with cancer were significantly downregulated; thus, circRNAs may be related to the occurrence and development of tumors. In addition to diagnostics, the body of miR-19a can be used as a standard prognostic marker for CRC patients with disease recurrence [23]. The serum of prostate cancer patients in castrated patients was collected before the second-line hormone therapy, and the excretion of serum AR-V7 RNA was detected by microtiter PCR. Median progression-free survival analysis and overall survival analysis demonstrated that exosome AR-V7 could be used as a biomarker to predict the drug sensitivity and efficacy of hormone therapy in patients with prostate cancer [24]. A clinical laboratory report pointed out that using both exosomal RNA and circulating tumor cell DNA (ctDNA) methods for detection are more sensitive than those using ctDNA alone, owing to the mutations of EGFR in the patients with non-small cell lung cancer (NSCLC) [25]. This means that the combined detection of exoRNA and ctDNA increases the sensitivity of detecting EGFR mutations in plasma, and exosomes can be used as biomarkers in cancer diagnostics. Although the RNA characteristics of exosomes from different cell sources are different, many RNAs are tumor-specific; therefore, TDEs can be used as diagnostic and prognostic biomarkers for various cancers. The analysis and detection of tumor-derived exosomes contribute to the early diagnosis of tumors and to provide new treatments.

Participation in the regulation of tumor immunity

Exosomes derived from tumor cells can not only inhibit the host immune response and promote tumor metastasis but also exert immunity against tumors under certain conditions. Therefore, exploring the effect of TDEs on the immune response and related mechanisms is of great significance for tumor immunotherapy.

TDEs are a double-edged sword that can regulate the reactions of tumor immunity in the microenvironment. On the one hand, TDEs contain tumor cell antigens and information that can stimulate immune cell responses and kill tumor cells; on the other hand, TDEs have the ability to affect the differentiation and activation of immune cells, inducing T cell apoptosis, and can help tumor cell immune escape [26]. The study also found that TDEs have an effect on the function of natural killer (NK) cells. NK cells, a component of classical innate immunity in immune cells, is the first line of defense against cancer. The NK cell surface activating receptors are mainly NKG2D, NKP30 and NKP46, and they can combine with the antigens of tumor cells to stimulate NK cell activity. However, TDEs are able to inhibit the expression of these receptors,

especially NKG2D, thereby reducing the cytotoxic effect of NK cells [27]. Tumor cells can also alter the tumor microenvironment through the phenotype of exosomes derived from the immune cell, thereby inhibiting the normal function of immune cells. For instance, exosomes derived from dendritic cells promote targeted allogeneic immune responses and indicate the important role of exosomes in antigen presentation during immunization [28]. TDEs are closely related to tumorigenesis, development and immune status. The regulatory role of exosomes derived from tumor cells is a mechanism by which tumor cells inhibit antitumor responses. Colorectal cancer-derived exosomes induce a phenotypic conversion of T cells to Treg cells by activating the TGF-β/Smad pathway and blocking the SAPK pathway [29]. *In vitro* and *in vivo* experiments showed that Treg cells induced by colorectal cancer exosomes had a more pronounced effect on promoting tumor growth. TDEs also regulate immunity and promote immune escape [26]. Thus, TDEs and tumor immune response are closely related in regulating different mechanisms of the body's immune response, thereby inhibiting the growth of tumor cells to achieve the purpose of cancer treatment.

Resistance to drug therapy

Numerous studies have demonstrated that noncoding RNAs (ncRNAs) and proteins play important roles in chemoresistance. It is known that the content of TDEs, including ncRNA, DNA and proteins (especially ncRNA), can alter the effectiveness of chemotherapy on recipient cells. In the study of breast cancer MDA-MB-231 cells and drug-resistant subfamilies, the expression levels of miRNA from secreted exosomes were different, which suggested that these differences in gene resistance mechanisms may have an important function [30]. Some researchers also found that epirubicin-resistant breast cancer cells can make sensitive cells acquire resistance, resulting in chemoresistance through the function of exosomes secreting miR-222 [31]. Due to the heterogeneity of tumor cells in the same tumor, the sensitivity of different tumor cells to chemotherapeutic drugs can be divided into drug-resistant and drug-sensitive cells. Many studies found that such resistance can be obtained by the signal transduction between drug-resistant cells and sensitive cells. Exosomes can induce tumor cells to develop resistance and adversely affect the efficacy of chemotherapy by expelling chemotherapeutic drugs into tumor cells. In renal cell carcinoma (RCC), exosomes can mediate the switch of a factor from resistant cells to sensitive cells with its AXL and c-MET by competing for endogenous miR-34 and miR-449 expression to increase so that it can promote drug resistance [32]. Gemcitabine (GEM) is an anticancer drug known to be an antimetabolite of difluoro nucleosides that can disrupt DNA replication and is used to treat pancreatic cancer, non-small cell lung cancer, breast cancer, and ovarian cancer. GEM treatment causes elevated levels of miR-155 in pancreatic cancer cells and is transported to other pancreatic cancer cells via the exosome secretion pathway miR-155, further by enhancing antiapoptotic capacity and inducing resistance to gemcitabine [33]. Since exosomes are resistant to drugs, removing some drug-resistant exosomes from the tumor may improve the therapeutic effect of the tumor. Cancer-associated fibroblasts (CAFs) account for the major components of pancreatic ductal adenocarcinomas (PDAC). Studies have found that the CAFs of PDAC are not sensitive to the standard treatment of GEM, and the level of CAF exosomes released is significantly increased in the presence of GEM. When using drugs that inhibit the release of exosomes by CAFs, the survival of cocultured epithelial cells was significantly reduced. This experiment demonstrated that CAF exosomes are the key regulators of chemoresistance in PDAC cells. Blocking the secretion of CAF exosomes can reduce the survival rate of PDAC cells and effectively avoid chemotherapy resistance and improve the effect of tumor treatment [34]. In addition, in the process of tumor development, due to its own and environmental influences, different degrees of heterogeneity are produced. The heterogeneity of different cells in the same tumor on chemotherapeutic drug sensitivity is inconsistent. Chemosensitivity in tumor cell classification can be divided into drug-resistant cells and sensitive cells. Studies have shown that this inconsistency in the sensitivity of chemotherapeutic drugs to tumor cells can be transmitted between cells so that susceptible cells acquire resistance. TDEs can translocate a drug-resistant overexpressed lncRNA, acting as an endogenous competition RNA in the tumor, causing tumor cells to mutate and resist, thereby mediating tumor resistance. Inhibiting the secretion of exosomes, blocking the transport process and resisting tumor cells are all different mechanisms induced by exosomes to increase the strength of resistance from tumor cells.

Conclusion

In conclusion, exosomes play an important role in tumorigenesis, development, invasion, metastasis, the tumor microenvironment and drug resistance. Exosome biogenesis opens a wider field

of study where therapeutic targets could be found that may increase the effectiveness of cancer treatment. TDEs may progressively apply to the early prediction, clinical evaluation of staging, diagnosis and treatment of malignant tumors. With the gradual deepening of the understanding of tumor-origin exosomes, their application in the clinical setting will show a good prospect of development. New strategies for targeted therapies using TDEs may bring new hope to cancer patients and a new therapeutic option. However, the current understanding of exosomes is still relatively limited, and its mechanisms in immunomodulation and the promotion of tumor cell resistance have not yet been elucidated. Additionally, the influence of exosomes on secretory cells should be studied in depth [36]; therefore, further studies are needed in the future.

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Conflict of interests

The authors declare no conflict of interests.

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