The exosomes in tumor immunity

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Abbreviations: APC, antigen presenting cell; Breg, regulatory B cell; CTL, cytotoxic lymphocyte; DC, dendritic cell; DEX, dendritic cell-derived exosome; EGFR, epidermal growth factor receptor; EV, extracellular vesicle; HSP, heat shock protein; IFN, interferon; IL, interleukin; miRNA, microRNA; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NK cell, natural killer cell; NKG2D, natural killer group 2 member D; PRR, pattern recognition receptor; TEX, tumor-derived exosome; TGF-β1, transforming growth factor β 1; Th, helper T cell; TLR, toll-like receptor; Treg, regulatory T cell

Exosomes are a kind of nanometric membrane vesicles and can be released by almost all kinds of cells, including cancer cells. As the important mediators in intercellular communications, exosomes mediate exchange of protein and genetic material derived from parental cells. Emerging evidences show that exosomes secreted by either host cells or cancer cells are involved in tumor initiation, growth, invasion and metastasis. Moreover, communications between immune cells and cancer cells via exosomes play dual roles in modulating tumor immunity. In this review, we focus on exosome-mediated immunosuppression via inhibition of antitumor responses elicited by immune cells (DCs, NK cells, CD4+ and CD8+ T cells, etc.) and induction of immunosuppressive or regulatory cell populations (MDSCs, Tregs and Bregs). Transfer of cytokines, microRNAs (miRNAs) and functional mRNAs by tumor-derived exosomes (TEXs) is crucial in the immune escape. Furthermore, exosomes secreted from several kinds of immune cells (DCs, CD4+ and CD8+ Tregs) also participate in immunosuppression. On the other hand, we summarize the current application of DC-derived and modified tumor-derived exosomes as tumor vaccines. The potential challenges about exosome-based vaccines for clinical application are also discussed.

Introduction

Extracellular vesicle (EV)-mediated exchanges of proteins, RNAs and lipids are emerging as an important aspect in cell–cell communications.1 As the generic term for secreted membrane vesicles, EVs include different types of vesicles such as microvesicles (MVs) and exosomes.2 They are distinguished by intracellular site of origin, physical properties (size and morphology) and methods for collection. Accordingly, exosomes are often described as endosomal origin and 30 to 100 nm in diameter. However, previous studies had conflicting and ambiguous definitions of different EVs. In this review, we still use the term “exosomes” as the cited articles indicated. Exosomes can be released by different types of cell including cancer cells, fibroblast cells, immune cells and mesenchymal cells.3-5 When shuttled from a donor cell, they can transfer a broad array of biological contents including functional mRNAs, miRNAs, DNA fragments, lipids and proteins to recipient cells. Wrapped in bilayered membranes of exosomes, these contents are much stable even after being transferred to a distant site. Therefore, exosomes are an effective mode to affect surrounding or distant cells to induce systemic responses.6 Evidences have shown that this kind of intercellular communication by exosomes is involved in multiple physiological and pathological processes, especially cancers.7 Both cancer and non-cancer cells can produce large amounts of exosomes. They are widely distributed in plasma, ascites and pleural effusions from cancer patients and tumor-modeling animal.8-10 Through secreting exosomes, cancer cells communicate with host cells and exchange different cellular components, like a kind of “infection”. This subtle and sophisticated system can manipulate the local and distant environment to facilitate tumor progression, including tumor growth, invasion, metastasis and even tumorigenesis.11 In terms of immune system, exosomes can mediate immune activation or immunosuppression, thus dictating the outcomes of tumor progression. Numerous studies have indicated the roles of exosomes in tumor immunity.12 Yet, cross-talk between cancer cells and immune cells via exosomes remains not fully illustrated. The aim of this review is to gather the most recent data regarding the “yin and yang” of exosomes in the regulation of tumor immunity and immunotherapy, hoping to guide the current diagnostic and therapeutic regimens of cancers.

Overview of Exosomes in Cancer Progression

Exosomes have emerged as a new mode of intercellular communication during cancer via transferring of oncogenes and proteins between different cells.1 Recent studies have uncovered their roles in tumorigenesis. Melo et al. indicated that TEXs promoted tumorigenesis by modulating cell-independent miRNAs biogenesis.13 Exosomes from breast cancer cells contained miRNAs associated with the RNA-induced silencing complex (RISC), Dicer, TAR RNA-binding protein 2 (TRBP) and Argonaute-2 (AGO2). When transferred to recipient cells, the
Exosomes could efficiently silence mRNA expression and thereby instigate non-tumorigenic epithelial cells to form tumors in a Dicer-dependent manner.

More attention is paid to investigate the roles and the underlying mechanisms of exosomes in promoting tumor growth and aggressiveness. These exosomes contain large amount of tumor-promoting RNAs (mRNAs, miRNAs and other non-coding RNAs) and proteins (EGFR, HSps, KIT, etc.).

Exosome-mediated exchange of mRNAs and miRNAs (named as exosomal shuttle RNA, eRNA) is believed to be a novel way for genetic intervention between cells. Plenty of miRNAs had been detected in exosomes. A subset of highly expressed miRNAs (miR-584, miR-517c, miR-378, etc.) extracted from hepatocellular carcinoma (HCC)-derived exosomes had been identified. These miRNAs could target transforming growth factor (TGF-β) downregulation and then enhanced transformed cell growth in recipient cells. Zhang et al. reported that miR-150 could inhibit the invasion of prostate cancer cells via TGF-β receptor and Smad signaling pathways.

Clinical aggressive human gliomas often expressed the oncogenic protein EGFR variant 3, known as EGFRvIII, which could be transferred from EGFRvIII positive glioma cells to negative ones via exosomes. More attention is paid to investigate the roles and the underlying mechanisms of exosomes in promoting tumor growth and aggressiveness. These exosomes contain large amount of tumor-promoting RNAs (mRNAs, miRNAs and other non-coding RNAs) and proteins (EGFR, HSps, KIT, etc.).

Polarization of tumor-promoting macrophages
Macrophages display remarkable plasticity and change their physiology according to environmental cues, especially tumor microenvironment. It has been reported that macrophages could be activated by TEXs, but different in cytokine profiles from that by LPS and IL-4. After stimulated by exosomes, macrophages showed reduced levels of TIMP1, IFNγ, IL-16 and a marked increase in the levels of IL-8, CCL2, MIP2 and IL-1Ra, which were closely related with tumor invasion and metastasis. Direct communication between macrophages and cancer cells also plays crucial roles in the invasion of breast cancer. TEXs but not particle-free supernatants or exosomes from benign cells induced Wnt5a expression in macrophages. Wnt5a could be transferred from macrophages to cancer cells via exosomes, resulting in the activation of β-Catenin-independent Wnt signaling pathway. This interesting feedback loop provided a new mechanism for macrophage-induced tumor invasion.

Meanwhile, macrophages can recognize protein and RNA compounds in exosomes via PRRs to induce inflammatory responses and promote subsequent tumor progression. Recently, TEXs have been described as a ligand of TLR2. These exosomes stimulated TLR2 to activate NF-κB pathway in macrophages, resulting in the secretion of pro-inflammatory cytokines such as IL-6, TNF-α, and CCL2. Additionally, exosomes contain large clusters of immature myeloid cells with the ability to facilitate tumor progression. When added to the classical in vitro culture system of mouse DCs, TEXs inhibited the differentiation of BM myeloid precursors into DCs via induction of IL-6. In addition, exosomes from human cancers also induced CD14+ monocytes to differentiate into CD14+ HLA-DR−/low cells, which suppressed T cell proliferation and cytolytic functions. Detailed mechanisms of the inhibition have focused on protein contents in exosomes, such as TGF-β, IL-6, PGE2 and so on. Moreover, mice pretreated with TEXs also showed an accumulation of MDSCs in spleen, peripheral blood and lung. Interestingly, heat shock protein 72 (HSP72) expressed at the surface of TEXs could induce activation of Stat3 and production of IL-6 in a TLR2/MyD88-dependent manner, thus promoting suppressive functions of MDSCs.

Furthermore, TEXs could be uptaken by immature DCs and then block DC maturation. In a mouse model of delayed-type hypersensitivity (DTH), TEXs loaded with ovalbumin (OVA) failed to induce DTH responses by inhibiting DC maturation via TGF-β1. TEXs can also impair the antigen recognition of DCs via affecting their expression of pattern recognition receptors (PRRs). A typical study indicated that exosomes from pancreatic cancers regulated toll-like receptor 4 (TLR4) expression in DCs via miRNA-203, which was highly detected in exosomes derived from pancreatic cancer cells. When uptaken by DCs, these exosomes downregulated the expression of TLR4 and production of the related cytokines including TNF-α and IL-12 in DCs. As a result, exosomes inhibited DCs-mediated antitumor responses triggered by TLR4. In summary, TEXs mediate host immunosuppression by modulating the differentiation, maturation and function of DCs.

Exosome-Mediated Immunosuppression in Tumor-Bearing Host

Impairment of dendritic cell differentiation and maturation
Dendritic cells (DCs) are professional antigen-presenting cells (APCs) with unique ability of antigen presentation and initiation of primary T cell responses, including antitumor responses. Although DC-based tumor vaccines are now one of the most prominent strategies for cancer therapy, DCs without artificial intervention are usually dysfunctional and unable to trigger effective T cell responses. Under tumor conditions, exosomes released from tumor cells can inhibit both differentiation and maturation of DCs.

Myeloid precursors in the BM give rise to DCs, which is greatly obstructed by TEXs. In turn, the myeloid precursors will differentiate into myeloid-derived suppressor cells (MDSCs), as a cluster of immature myeloid cells with the ability to facilitate tumor progression. When added to the classical in vitro culture system of mouse DCs, TEXs inhibited the differentiation of BM myeloid precursors into DCs via induction of IL-6. In addition, exosomes from human cancers also induced CD14+ monocytes to differentiate into CD14+ HLA-DR−/low cells, which suppressed T cell proliferation and cytolytic functions. Detailed mechanisms of the inhibition have focused on protein contents in exosomes, such as TGF-β, IL-6, PGE2 and so on. Moreover, mice pretreated with TEXs also showed an accumulation of MDSCs in spleen, peripheral blood and lung. Interestingly, heat shock protein 72 (HSP72) expressed at the surface of TEXs could induce activation of Stat3 and production of IL-6 in a TLR2/MyD88-dependent manner, thus promoting suppressive functions of MDSCs.

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amounts of small non-coding RNAs, especially miRNAs, which can function as agonists of RNA-binding TLRs. TLR7 and TLR8 were found to recognize exosome-derived miRNAs and stimulate downstream NF-κB pathway and inflammatory cytokine secretion in macrophage. Therefore, induction of tumor-associated chronic inflammation by TEXs promotes tumor growth, invasion and metastasis. Besides TLRs, a recent study mentioned above showed that exosomes from stromal cells contained 5′-Triphosphate RNAs, which could activate RIG-I in breast cancer cells and promote resistance to radiation therapy.

Decrease of NK cell cytotoxicity

Natural killer (NK) cells are a typical cytotoxic lymphocyte in innate immunity and take a variety of strategies to kill cancer cells directly. It has been reported that exosomes derived from anticancer drug-treated human HCC cells were rich in heat shock proteins, which could act as endogenous danger signals to stimulate NK cell-elicited antitumor responses in vitro. However, more studies indicated that the cytotoxicity of NK cells was greatly impaired in tumor conditions.

Activating receptors such as NKG2D, NKP30, NKP46 and NKG2C play an important role in NK cell cytotoxicity. However, TEXs restrained the expression of these receptors, among which NKG2D was the most profound one. Clinical researches showed reduced surface expression of NKG2D on circulating NK cells in cancer patients compared to healthy individuals. Human prostate cancer cells-derived exosomes were found to express ligands for NKG2D, resulting in downregulation of NKG2D on NK cells and impaired NK cell cytotoxic function, which might be due to TGF-β1 presented by TEX. Neutralizing TGF-β1 antibody strongly abrogated NKG2D reduction on NK cells, suggesting TGF-β1 may be an effective mediator. This was consistent with the report that TGF-β1 derived from exosomes in AML patients’ sera could induce Smad phosphorylation in NK cells and reduce NKG2D expression.

Impairment of CTL response and induction of regulatory T cells

Effective CD4+ and CD8+ T cell responses are critical for antitumor immunity. However, TEXs can affect proliferation, activation and apoptosis of these T cells. In human nasopharyngeal carcinoma (NPC), miRNAs from TEXs inhibited T cell proliferation and differentiation into Th1 and Th17 cells, while promoting regulatory T cell (Treg) generation. Five over-expressed miRNAs were identified in the exosomes from patient sera and NPC cell lines: hsa-miR-24-3p, hsa-miR-891a, hsa-miR-106a-5p, hsa-miR-20a-5p and hsa-miR-1908. These miRNA clusters could downregulate the MARK1 signaling pathway through decreasing phosphorylation of ERK, STAT1 and STAT3. In a mouse model of glioblastoma, transfection of exosomes derived from glioblastoma cell line GL26 reduced the percentages of CD8+ T cells and inhibited the activation of CD8+ T cells, including decreased expression of IFNy and granzyme B. CD3-ζ chain, as an integral component of T-cell receptor (TCR) complex, is important for competent signaling after TCR–MHC–peptide interactions and T cell activation. Exosomal TNF-α from cancer cells affected TCR–CD3 complex by a reactive oxygen species way. As a result, signals to activate CD4+ and CD8+ T cells were disrupted. TEXs also induce apoptosis of T cells. Fas ligand (Fasl)-positive membranous exosomes isolated from sera of oral cancer patients could induce apoptosis of activated T lymphocytes. TEXs could also mediate Fas/Fasl-associated apoptosis of CD8+ T cells and downregulate expression of CD3ζ and Janus kinase 3 (JAK3) in activated T cells.

Apart from TEXs, our works revealed that exosomes from gene-modified DCs inhibited Th1 and Th17 activation but maintained the regulatory capacity of T cells via TGF-β1. Interestingly, these exosomes expressing membrane-associated TGF-β1 (mTGF-β1) demonstrated more potent immunosuppressive activity. We also found that Fasl-expressed exosomes derived from activated CD8+ T cells could promote the invasion of murine melanoma cell line B16 and Lewis lung cancer cell line 3LL. However, they had little effect on apoptosis induction and proliferation of these two indicated cancer cell lines.

Tregs use a variety of strategies to help cancer cells escape from immune attack by secreting immunosuppressive cytokines (IL-10, TGF-β1, etc.). In addition to impairment of cytotoxic lymphocyte (CTL) responses, TEXs could promote the generation and function of Tregs. When co-incubated with exosomes purified from supernatants of tumor cells, CD4+ CD25− T cells were converted into Tregs. These Tregs displayed elevated expression of IL-10, TGF-β1 and CTLA4. Once secreted, tumor-derived miRNA-214 was transferred into T cells through exosomes, and then downregulated phosphatase and tensin homolog (PTEN) in T cells so as to promote Treg expansion. Another study revealed that exosomes from lung cancer were rich in the EGFR. These exosomes induced tolerogenic DCs, which further facilitated Treg generation.

Tregs can also act as immune suppressors via exosomes. Okoye et al. found that Tregs could suppress effector T cells by delivering miRNAs via exosomes. Treg-derived exosomes contained mature and mature miRNAs, particularly with pro-apoptotic or anti-proliferative functions. These miRNAs could inhibit Ptg2s, thus limiting Th1 cell-associated responses. In a mouse model of B16 melanoma, exosomes secreted by natural CD8+ CD25+ Tregs were capable of suppressing CTL responses. Both in vitro and in vivo experiments indicated that exosomes derived from CD8+ Tregs inhibited DC-activated CD8+ T cell responses. Therefore, exosomes derivied from Treg cells may be a potential target for the design of cancer immunotherapy.

Induction of regulatory B cells

Synthesis and release of exosomes from activated B cells can stimulate effective T cell responses against cancer cells and elicit antitumor immune responses. However, a few studies focused on the roles of TEXs in the induction of regulatory B cells. Yang et al. found that exosomes from mycoplasma-infected tumor cells carried mycoplasma components, and these components could promote the generation of regulatory B cells and then inhibit T cell activity. This interesting finding provides a new mechanism
for mycoplasmas-infected tumor cells to modulate B cells with inhibitory property by exosomal pathway.61

### Exosome-Mediated Activation of Immune Response Against Tumors

**Dendritic cell-derived exosomes (DEXs) as tumor vaccine**

Through intercellular communication, exosomes may trigger the immune system to elicit antitumor responses, in which APCs take the central place.62 At early time in 1996, B lymphocytes were found to secrete extracellular antigen-presenting vesicles.60 This kind of exosomes released by B cells carried Major Histo-compatibility Complex (MHC) class II, co-stimulatory and adhesion molecules. As a result, B cell-derived exosomes could directly stimulate effective CD4+ T cell responses against cancer cells. Two years later, the groups of Dr Zitvogel, Dr Raposo and Dr Amigorena described that DCs produced antigen-presenting exosomes, which contained functional MHC class I and class II, and co-stimulatory molecules.63 Accordingly, DEXs primed specific CTL response and promoted antitumor responses in a T cell-dependent manner. Since then, DEXs as cell-free tumor vaccines have aroused widespread concerns.

How DEXs can stimulate effective antitumor responses has been investigated intensively. These exosomes are enriched in membrane proteins involved in antigen presentation, including MHC Class I and II molecules, MHC Class I-like molecule (CD1), co-stimulatory molecules (CD80 and CD86), adhesion molecule (ICAM-1, MFG-E8).64-67 Proteomic analysis of DEXs also identified new exosomal proteins, which were mainly cytoskeleton-related molecules (cofilin and profilin I) and membrane transport and signaling factors (annexins, rab 7 and 11, rap1B, and syntenin), suggesting a role of exosomes in transmembrane transport.64 Furthermore, HSP73 was another exosomal content presented in endocytic compartments of DCs, which could elicit antitumor responses through T cell-dependent or -independent way.68

As indicated above, DEXs present peptide-loaded MHC Class I and II complexes to stimulate both CD8+ CTL and CD4+ T cell responses, collaborating with co-stimulatory and adhesion molecules.69 In addition, MHC class I-restricted, peptide-specific CTL priming is critical for effective antitumor responses.70 Interestingly, CTL responses mediated by DEXs were not only dependent on CD4+ T cells but also on B cells. Mice deficient in B cells showed lower responses to protein-loaded DEXs because of impaired complement activation and antigen shuttling by B cells.71 However, DEXs are less efficient in stimulating naïve CD4+ T cells than stimulating activated and memory T cells. DEXs also needed DCs to efficiently stimulate specific T cells.66,72,73 In coculture system with T cells in vitro, DEXs could not induce antigen-dependent T cell activation unless DEXs were incubated with mature DCs in the cultures. Accordingly, exosomes mediated exchange of functional peptide-MHC complexes with bystander DCs, thus amplifying adaptive immune responses by increasing the number of DCs bearing antigen peptides.66

Besides T cells, DEXs can promote NK cell proliferation and activation, resulting in NK cell-dependent tumor rejection.74-76 A series of membrane stimulators were found in DEXs. They expressed functional IL-15R and promoted proliferation and IFNγ secretion by NK cells.75 DEXs also harbored multiple TNF superfamily ligands (TNFSF1s) on their surface and activated NK cells through interaction of DEX-expressing TNF with TNF receptors on NK cells.75 Activating receptors expressed on NK cells are critical for direct cytotoxicity against tumor cells. Exosomal expression of Nkp30 ligand BAT3 (HLA-B-associated transcription 3) and NKG2D ligand had been implicated in direct activation of NK cells.75,76

On the basis of these clues, DEXs have been used as a cell-free vaccine to trigger host antitumor immune response to suppress tumor growth. Vaccination of patients with DEXs from metastatic melanoma and advanced non-small cell lung cancer resulted in activation of immune responses and prolonged stability of diseases, as demonstrated in phase I clinical trials.77,78 However, how to break down the obstacles of host immunosuppression and rescue insufficient T cell responses when using DEXs as tumor vaccines calls for further studies.

**Modified tumor cell-derived exosomes (TEXs)**

TEXs carry tumor antigens and can also trigger efficient antigen presentation of APCs. Because of easy and non-traumatic acquisition, these exosomes are taken as ideal resources of antigens for DC education.12 Early reports showed that antigens in TEXs could be transferred to DCs and induce specific CTL activation.10 Whole native tumor antigens were found in exosomes, e.g. HSP70-80, Her2/Neu, Mart1, TRP and gp100 in melanoma, P1A (intracisstitial A particle protein) and HSP70 in plasmacytoma cells.79,81 However, these antitumor immune responses induced by TEXs are relatively weak and prone to induce tolerance. Therefore, these strategies are limited to in vitro observations and mouse model studies.

Accordingly, researches have made some effects to develop modified exosome-based tumor vaccines artificially. One of the common strategies is to make genetic modification of original cells to improve immunogenicity of exosomes. For example, we extracted exosomes from tumor cells genetically modified with cytokine genes (IL-2 and IL-18).82,83 These exosomes were found to induce DC maturation and CTL responses efficiently. Exosomes from Rab27a-overexpressing lung cancer cells and OVA-expressing EG7 elicited efficient antitumor immune responses.81,84 Other successful examples based on this strategy included CD40L-modified lung cancer cells, CIITA-transfected CT26 cells and TNF-engineered J558 tumor cell.85-87

Apart from genetic modification, external stimulus is added to drive tumor cell release of exosomes. We have extracted exosomes from a series of stress-induced tumor cells such as lymphoma cells, CEA-positive tumor cells, Lewis lung carcinoma and melanoma cells. These exosomes contained more immunogenic substances (MHC-I, CD40, CD86, RANTES, CEA, HSP70, etc) as well as chemokines.88-90 Resistant anticancer drugs were found to enhance release of exosomes coated with heat shock proteins (HSP60, HSP70, and HSP90) from human hepatocellular
carcinoma cells. The HSP-bearing exosomes efficiently stimulated NK cell cytotoxicity against tumors.39

Other strategy involves direct fusion of TEXs with antigens and combined therapies. As GM-CSF and IL-12 anchoring tumor cells induced tumor-specific T cell responses, we modified TEXs via surface anchorage of superantigen SEA, resulting in enhanced antitumor immune responses.91 Exosomes in combination with cyclophosphamide (CTX) and polyinosinic-polycytidylic acid (poly I:C) were shown to promote the cytotoxic effect of T cells and suppress tumor growth.92,93

Taking together, application of TEXs as tumor vaccines is dependent on types of cancers and immunogenicity of their antigens. Modification of TEXs is developed to improve their immunogenicity, aiming to make full use of TEXs as tumor vaccines.

Conclusions and perspectives

Exosomes are well-known as mediators of intercellular communication and participate in multitude biological processes. In the past decade, numerous studies have indicated roles of exosomes in multiple aspects of tumor processes as well as in interactions with the immune system. Now, much more researches reveal that TEXs suppress host immune responses and induce immune tolerance via their contents including miRNAs, cytokines, etc (Fig. 1). However, exosomes can be recognized by APCs to induce antitumor responses as sources of natural tumor antigens, and accordingly, exosome-based vaccines have been developed for cancer therapeutics (Fig. 2). Therefore, several fundamental issues must be fully addressed before their applications in clinic. First, the mechanism for exosome release from original cells has not been fully understood. Cancer cells may secrete abundant exosomes under stress, such as surgery, radiotherapy and chemotherapy. Controlling the release of immunosuppressive exosomes may benefit these treatments. Secondly, the different effects mediated by exosomes are dependent on their proteins and genetic contents. So composition analysis of these contents is important for substantial application. RNA composition between original cells and exosomes was found different, making this issue to be more interesting and challenging. Lastly but not least, how can we adjust the

Figure 1. Exosome-mediated immunosuppression of tumor immunity. Exosomes derived from cancer cells have been shown to be involved in the modulation of tumor immunity in various ways: (A) Inhibition of proliferation and differentiation of CD4+ T cells into Th1 and Th17, inhibition of cytotoxicity of CTLs, NK cells and macrophages, inhibition of differentiation and maturation of DCs. (B) Promotion of CD4+, CD8+ Tregs and Bregs generation, induction of myeloid precursor differentiation into MDSCs, alternative activation of macrophages.
researches may finally make the diagnostic and therapeutic tumor immunity is attracting increasing attention. Further while bypass the disadvantages of exosomes in modulating tumor immunity. How to make best use of the advantages investigation. In sum, exosomes have paramount functions in effects of exosomes, the key point which needs further inves-

tion, the balance between tumor-promoting effects and antitumor effects of exosomes, the key point which needs further investigation. In sum, exosomes have paramount functions in tumor immunity. How to make best use of the advantages while bypass the disadvantages of exosomes in modulating tumor immunity is attracting increasing attention. Further researches may finally make the diagnostic and therapeutic potential of exosomes to be a reality in the clinics.

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Figure 2. Strategies for exosome-based tumor immunotherapy. This figure presents two main strategies for application of exosomes in tumor therapeu-
tics. Exosomes secreted from antigen-loaded DCs carry functional peptide-MHC complexes, co-stimulatory and adhesion molecules and induce activa-
tion of CD4+ T cells, CD8+ T cells and NK cells, thus mediating cytotoxicity to tumor cells and inhibition of tumor growth. These molecules can also be exchanged between DCs to induce antitumor immune response indirectly. Additionally, tumor-derived exosomes (TEXs) carry tumor antigens and can trigger efficient antigen presentation of APCs, thus being used as resources of tumor antigens to prepare tumor vaccines. Moreover, modification of TEXs is developed to improve their immunogenicity, such as genetic engineering stress and protein loading.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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