REVIEW

The effects of tumor-derived exosomes on T-cell function and efficacy of cancer immunotherapy

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Abstract
Tumor-derived exosomes (TEXs) are a class of extracellular vesicles which play an important role in the tumor microenvironment. These vesicles have multiple biological functions including promotion of cancer progression and reduction of anti-tumor immunity. Recently, interaction between TEXs and immune cells are of great interest in cell-based immunotherapy. Here, we review the effects of TEXs on the survival and functions of T cell subsets, as well as their clinical applications. Unraveling the immunoregulatory function of exosomes allows a better understanding of the molecular and cellular basis for cancer immunotherapy.

KEYWORDS
immunotherapy, T cells, tumor-derived exosomes, tumor microenvironment

1 | INTRODUCTION

Exosomes are a special group of extracellular vesicles (EVs) of 30–150 nm in diameter and released by almost all cells.1 In the early 1980s, Johnstone et al2 first discovered that some small vesicles loaded with transferrin receptors were released by the reticulocytes of sheep during their maturation. At one time exosomes were considered as “cell garbage collectors” to dispose of the cellular waste. Today, exosomes have been emerging as communication vehicles to transfer information between cells, and play a critical role in both health and disease.3–5

Tumor-derived exosomes (TEXs) have gained special research interests because of their unique functions, such as promoting tumorigenesis and metastasis, modulating anti-tumor immunity and neutralizing drugs to compromise therapeutic effects.5,7 Recently, immunotherapies, including immune checkpoint inhibitors (such as PD-1/PD-L1) and chimeric antigen receptor T (CAR-T) therapy, have revolutionized the field of cancer therapy and significantly improved the treatment responses and patients’ survival in both solid and blood cancers.6,8,9 However, there are still many patients resistant to immunotherapy, and the immunologic basis for differential treatment responses remain largely unknown. TEXs are a group of complex and highly...
heterogeneous carriers, containing various inhibitory lipids, proteins and nucleic acids, which have shown potential regulatory functions in immunotherapy. Since T lymphocytes are the major immune effector cells in anti-tumor immune responses, here we mainly focus on the effects of TEXs on T lymphocyte subsets, including CD4\(^+\), CD8\(^+\) and Treg cells, and review the complex mechanisms underlying the crosstalk between TEXs and T cells.

### 1.1 Three modes of interaction between TEXs and T cells

Generally, there are three pathways for TEXs to transfer information: (1) TEXs deliver intercellular signal through receptor-ligand binding; (2) TEXs fuse with the membrane of recipient cells and release their “cargo”; (3) Recipient cells can phagocytose and internalize TEXs.\(^{10}\)

In fact, how TEXs interact with T cells is still under debate. Muller et al.\(^{11,12}\) found that little PKH26-labeled TEXs are internalized by T cell subsets following 48–72 h co-incubation, suggesting that the receptor-ligand interaction alone is sufficient to affect T cell functions, while the internalization of TEXs is not required for signal delivery that causes changes in gene expression. In contrast, many authors argued that T cell functions can still be impaired by internalizing TEXs, although they are more difficult in internalizing TEXs than other immune cells. Vignard and colleagues\(^{13}\) found that resting or activated CD8\(^+\) T cells can internalize melanoma-derived exosomes as early as 5 h after exposure under electron microscopy or confocal microscopy, consistent with the previous studies.\(^{14}\) Moreover, the nucleic acids in the TEXs, especially mRNA and miRNAs, are also responsible for functional changes of T cells, which indicates that TEXs can reprogram the recipient T cells through internalization.\(^{15}\) For example, TEXs down-regulate the inhibitory genes in CD4\(^+\)T cells and result in a loss of CD69 expression on the surface of T cells.\(^{16}\) When transfected into normal T cells, the RNA purified from TEXs can change the T cell function.\(^{16}\) Together, TEXs can influence T cell functions through either receptor-ligand binding or internalization.

### 2 TEXS DELIVER IMMUNOSTIMULATORY SIGNALS TO T CELLS

A variety of molecules on the surface of TEXs, such as major histocompatibility complex (MHC) I and II, tumor-associated antigens (TAA), HSP70 and CD40, are thought to enhance T cell-mediated immunity against tumor through dendritic cells (DCs).\(^{17-19}\) DCs that were stimulated by TEXs can simultaneously promote the proliferation of both CD4\(^+\) and CD8\(^+\) T cells and promote the differentiation of CD8\(^+\) T cells into CTLs, thereby enhancing the anti-tumor ability in vitro and in vivo.\(^{20,21}\) Thus, TEXs can serve as cancer vaccines for immunotherapy.\(^{22,23}\) Recently, an increasing number of studies focus on the modified TEXs, which can be efficiently uptaken by DCs to elicit a strong immunostimulatory response. Chen et al.\(^{17}\) demonstrated that exosomes secreted from heat-shocked (HS-Exo) lymphoma cells, with high expression of costimulatory molecules, can induce robust immune responses in vivo. Furthermore, HSP70 on the HS-Exo can also induce DCs to release IL-6 to block Treg cell differentiation, which is TGF-β-dependent, and promote Th17 cell differentiation.\(^{24}\) Interestingly, IL-12-anchored exosomes can directly induce T cell proliferation and enhance their cytotoxic effect by reversing the suppressed JAK2/STAT5 pathway.\(^{25,26}\)

### 3 TEXS DELIVER INHIBITORY SIGNALS TO DIFFERENT T CELL SUBSETS

#### 3.1 TEXs deliver inhibitory signals to CD8\(^+\) T cells

When binding to their cognate receptors, the inhibitory ligands on the TEXs, such as TGF-β, PD-L1, CD39 and CD73, can deliver negative signals to recipient T cells. The TEXs-induced immunoinhibitory responses vary among different T cells subsets (Figure 1). TEXs mainly inhibit CD8\(^+\) T cell activation and promote its apoptosis and exhaustion. Several mechanisms have been described to inhibit their activation. First, through TGF-β pathway TEXs suppress the response of CD8\(^+\)T cells to IL-2, a key cytokine essential for T-cell activation and proliferation.\(^{27,28}\) Second, the JAK/STAT pathway is crucial for the function of cytokines sharing the γ-chain of the IL-2 receptors, such as IL-2, IL-7 and IL-15; TEXs can reduce JAK3 expression and diminish cytokine productions, thereby inhibiting activation of CD8\(^+\) T cells.\(^{28-30}\) Third, TEXs are able to activate NF-κB signaling pathway of CD8\(^+\) T through Toll-like receptor 2/4 (TLR2/4), which leads to IL-6 upregulation and subsequent STAT3 activation.\(^{31-33}\) Fourth, TEXs containing PD-L1 can down-regulate CD69 expression on activated CD8\(^+\) T cells and decrease INF-γ production, which was partially blocked by anti-PD-1 monoclonal antibodies, suggesting that TEXs inhibited T cells activity through PD-1/PD-L1 interaction.\(^{32,34}\) Furthermore, Yang et al.\(^{35}\) found TEX-PD-L1 significantly inhibited CD3/CD28-induced ERK phosphorylation and NF-κB activation of T cells. Ricklefs et al.\(^{36}\) also suggested PD-L1 on TEXs blocked CD8+ T cells activation in response to TCR stimulation. Interestingly, CD80 is also a binding partner of PD-L1. Thus PD-L1 can inhibit the activation of T cells through PD-L1/CD80 signaling pathway.\(^{37}\) The signaling pathway after PD-1 binding to PD-L1 may involve SHP-1/2, TCR and their downstream signaling, such as ZAP70, PI3K, PKB/akt, mTOR, RAS, MAPK/MEK and ERK.\(^{37}\) Additionally, exosome PD-L1 was significantly increased in the responders during the early stages of immunotherapy, suggested that TEX-PD-L1 is a marker of adaptive immune activation.\(^{38}\)

The mechanisms underlying the induction of CD8\(^+\) T cell apoptosis by TEXs have been extensively studied.\(^{39,40}\) TEXs express FasL (Fas Ligand), a transmembrane type II protein belonging to the TNF protein superfamily, which plays a pivotal role in Fas receptor-mediated apoptosis of CD8\(^+\) T cells.\(^{41-43}\) Priyanka et al.\(^{32}\) found that apoptosis of CD8\(^+\) T cells is TEXs dose-dependent, and can be neutralized by anti-Fas (ZB4) mAbs. Moreover, the FasL on the TEXs downregulates the TCR/CD3ζ expression in T cells, which is correlated with a poor
prognosis in several tumors. TEXs can also reduce the expression of JAK3 and up-regulate the proapoptotic Bax levels of CD8+ T cells to induce apoptosis. Alternatively, TEXs promote p38MAPK phosphorylation that induces endoplasmic reticulum stress, which activates the PERK-eIF2α-ATF4-CHOP signaling axis, eventually leading to CD8+ T cell apoptosis. Of note, TEXs expression PD-L1 also promote CD8+ T cells apoptosis through PD-1/PD-1 interaction. Interestingly, even in models resistant to anti-PD-1 mAb, the removal of exosomal PD-L1 can still inhibit tumor growth and enhance systemic memory immune activity, which has become a new strategy for immunotherapy. Of note, PD-L1 can transfer to both tumor cells and immune cells, such as macrophages and DCs, through TEX-PD-L1, which play an important role in the regulation of immunity in TME. Particularly, it was reported that CLL cell-derived exosomes also express PD-L1 and induce CD19-directed chimeric antigen receptor T (CAR-T) cell exhaustion. TGF-β is another inhibitory receptor. Chatterjee et al. found that the level of PD-L1 expressed on TEXs was highly correlated with the level of TGF-β in tumors. In other words, TGF-β may induce the expression of PD-L1 in TEXs, thereby synergistically impair CD8+ T-cell function.
these SP phenotypes of CD8+ T cells lack CD27/CD28 expression, and suppress the function of normal T cells.16,56,57 The inhibitory NKG2D ligand, MIC A/B, binds to NKG2D, down-regulates NKG2D expression and inhibits CD8+ T cells-mediated cytolysis.58 In hepatocellular carcinoma, TEXs induce CD8+ T cell exhaustion by delivering 14-3-3ε, an immunosuppressive molecule that promotes the proliferation of cancer cells and induces epithelial-mesenchymal transition (EMT).59 The miRNA within TEXs play an important role in T cell exhaustion. For example, Hsa-miR-498 can inhibit cytokine synthesis such as TNF-α and CD8+ T cells-mediated cytotoxicity in vivo and in vitro.60,61

Recently, accumulating evidence suggest that TEXs can reprogram the cell metabolism to facilitate cancer progression, angiogenesis, metastasis, drug resistance and immunosuppression.10,61 Similarly, TEXs also can modulate CD8+ T cell function through alteration of cellular metabolism.62,63

### 3.2 TEXs deliver inhibitory signals to CD4+ T cells

TEXs inhibit proliferation of CD4+ T cells by impairing its response to IL-2 through TGF-β pathway and promote cell apoptosis.64 Huang et al.65 found that silencing TGF-β in TEXs promotes CD4+ T-cell proliferation and Th1 cytokines production. The immuno-inhibitory molecules, CD39 and CD73, are expressed on the surface of TEXs, and can convert ATP into adenosine, which significantly suppresses CD4+ T cell proliferation.12,66

Besides inhibiting cell proliferation, TEXs also induce CD4+ T cell apoptosis. Zhou et al.67 found that TEXs activate the mitochondria caspase pathway in vivo and in vitro. Among the key players in the apoptosis of CD4+ T cell subsets, galectin-9, a ligand for the membrane receptor Tim-3, tiggers apoptosis in Th1 lymphocytes;68,69 Fas, Fasl and TRAIL induce Th2 cells apoptosis through caspase 8 activation.70 Additionally, Ali et al.70 found that neuroblastoma cell-derived exosomes also impair tumor cytotoxicity of CD4+ CD171+ specific CAR T cells.

Unlike CD8+ T cells, CD4+ T cells can differentiate into Treg cells that are CD25+ and Foxp3+, and suppress immune response.71 TEXs can induce Treg cell differentiation through PD-L1/PD-1 signaling pathway, and block differentiation towards CD4+ IFN-γ+ Th1 cells.72 Also, TGF-β is essential for FOXP3 expression, which not only inhibits T cell proliferation but also promotes Treg cell phenotype differentiation.55,73 Conversely, when TGF-β is neutralized with mAb or silenced by shRNA, the immunosuppressive effect of TEXs on other immune cells will be alleviated.74 TEXs also promote the expansion of Treg cells and confers the resistance to apoptosis via TGF-β and IL-10.75,76 Moreover, TEXs can recruit Treg cells to the tumor through CCL20, thereby inhibiting the proliferation of other T cell subsets.75,76 TEXs also enhance the immune inhibitory function of Treg cells, which is mainly mediated by the CD73 and CD39 on the surface of TEXs.12,77 What’s more, MHC class II molecules, as ligands of LAG3, may enhance Treg cells function through TEXs.78 Additionally, the inhibitory molecules, such as galectin-9 (TIM3 ligand), CD160 (BTLA ligand), can also exert immunosuppressive effects through TEXs.30

### 3.3 Indirect T cell inhibition by TEXs

Besides direct signal transfer to T cells, TEXs can regulate T cell functions through other immune cells, such as DCs, macrophages, myeloid-derived suppressor and NK cells (Figure 2).

As effective antigen present cells, DCs have dual regulatory functions in TME. DCs can extract and process TAAs from TEXs, and then present the antigens to T cells to elicit anti-tumor immune response.7 Therefore, TEX-loaded DCs may be used as cancer vaccines to improve therapeutic response. Marton et al.79 found that TEXs from melanoma activate DCs, which in turn promote CD4+ T cell proliferation. As for CD8+ T cells, on the one hand, TEX-loaded DCs strengthen CD8+ T cell cytotoxicity;80 TEXs attenuate DCs function through CD73/CD39 signaling pathway driven by prostaglandin E2 (PGE2), leading to decreased TNFα and IL-12 and increased immunosuppressive adenosine, and thus inhibit the cytotoxicity of CD8+ T cells.81 Therefore, TEX-loaded DCs have dual effects on the immune system, with immunosuppression predominates in vivo.7 To induce remarkable anti-tumor response, new strategies have been explored to retain strong immunogenicity and reduce immunosuppression simultaneously. For example, the use of TGF-β1 antibodies or TGF-β1 downregulation improves the anti-tumor capability;65 the addition of cytokines like IL-2 or GM-CSF enhances the cytotoxicity of TEXs-stimulated CD8+ T cells.82 Alternatively, exosome-based modification has been shown to improve the vaccine efficacies. For example, heat-stressed tumor cells-derived exosomes contain high level of HSP70, which stimulates DCs to secrete IL-6 for converting Treg into Th17 cells, and induce strong antitumor immune responses.21 Anchoring IL-12 to TEXs can improve the anti-tumor capacity of T lymphocytes because IL-12 abrogates the inhibitory effect conferred by TEXs alone.25,26 Besides, Rab27a plays a major role in the secretory pathway of exosomes,83 and TEXs derived from Rab27a-overexpressing cancer cells stimulate DCs maturation and promote CD4+ T cell proliferation.21

Macrophages, a group of essential innate immune cells, are able to differentiate into either M1 subtype which is mainly involved in the inflammatory response and produce considerable amount of pro-inflammatory cytokines, or M2 subtype which secrete anti-inflammatory cytokines (such as TGF-β and IL-10) and interfere with anti-tumor T cell response. Tumor-associated macrophages (TAMs) refer to the macrophages accumulated in cancer microenvironment.48 TEXs from gastric cancer could induce TAMs to differentiate into M2 subtype with PD-1 expression, leading to severely impaired CD8+ T-cell functions.84 TAMs usually display M2 phenotype that is pro-tumorigenic. Like Treg cells, TAMs produce inhibitory cytokines, such as IL-10 and TGF-β, to suppress T cell function. In glioblastoma patients, serum TEXs can drive transformation of macrophages into M2 phenotype, indicating a bias toward T-helper cell type 2 environment.85
TEXs induces the activation of NF-κB signaling pathway through MYD88 or Toll-like receptor 2 (TLR2) in macrophages, as a result, a number of pro-inflammatory cytokines such as G-CSF, CCL2, IL-6 are markedly increased to promote the immunosuppressive function of TAMs.86

Myeloid-derived suppressor cells (MDSCs), consist of a group of immune cells including monocytes, granulocytes, and precursors of DC, and typically express myeloid markers CD11b and CD33.87 MDSCs are considered to be immunosuppressive within tumor microenvironment. TEXs regulate MDSC functions through various signaling pathways, thereby inhibiting T cell activation and promoting T cell depletion. Ling et al.88 demonstrate that hypoxic TEXs enhanced the suppressive effect of MDSCs on T cells through a miR-21/PTEN/PD-L1. Additionally, TEXs-associated HSP72 restrains tumor immune surveillance by promoting MDSC suppressive functions through STAT3/TLR2/MYD88 signal pathway.89

Other immune cells, such as NK cells and stromal cells, are also influenced by TEXs, although it is not clear if these cells could induce T cell exhaustion. Usually, the NK cells and T cells are activated through the binding of NKG2D receptors to MICA/MICB. However, the NK cell cytotoxicity is suppressed when cells are exposed to MICA *008, a human NKG2D ligand releasing from TEXs.90 Also, TEXs can attenuate the response of NK cells to IL-2, a crucial cytokine that stimulate NK cell expansion and the release of perforin.91 TEXs from CLL can be internalized by stromal cells, and the microRNA and proteins are delivered to transform stromal cells into inflammatory phenotypes, which secrete inhibitory cytokines and promote CLL cell survival.92

4 TEXS FUNCTION AS CANCER BIOMARKERS AND TARGETS FOR CANCER IMMUNOTHERAPY

4.1 TEXs are valuable markers for the diagnosis, prognosis, and therapeutic choices in cancer patients

In the precedent years, TEXs have attracted increasing interest in the field of liquid biopsy. As previously described, they can be isolated from almost all human biological fluids, such as blood, urine, amniotic fluid and saliva. The proteins, nucleic acids and other molecules in TEXs contain a large amount of information about tumor antigens, genetic material, and immune stimulating molecules. Therefore, TEXs are helpful in the diagnosis of disease, especially for patients with difficulty in obtaining tissue biopsy.53 In addition, TEXs have important clinical prognostic value as biomarkers. Elevated levels of TEXs in liquid biopsies of cancer patients are usually associated with a higher tumor burden, and immunosuppressive molecules of TEXs, such as PD-L1, CTLA-4, TIM3 in the TEXs are also correlated with poor prognosis or disease progression.53,94 Also, genetic materials such as microRNA, lncRNA, circRNA and DNA are associated with cancer progression and prognosis.95–97 Exosome DNA usually contains a variety of clinically relevant tumor-specific mutations such as EGFR, BRAF, RAS, IDH, and HER2, which making it a promising therapy recommendations for “liquid biopsy.”98 Nowadays, TEXs are undergoing extensive clinical trials as a biomarker for disease diagnosis, prognosis and immunotherapy in different cancer patients, which will give us more insights in the future (Table 1)
### TABLE 1 Clinical trials involving exosomes

| Source of Exosomes | Role in cancer therapy | Trial |
|--------------------|------------------------|-------|
| NSCLC              | immunotherapy          | NCT03236675 |
| NSCLC              | diagnosis               | NCT04529915 |
| NSCLC              | diagnosis               | NCT03228277 |
| NSCLC              | diagnosis, prognosis, monitor | NCT04499794 |
| NSCLC              | immunotherapy monitor   | NCT04427475 |
| NSCLC              | immunotherapy           | NCT02890849 |
| NSCLC              | immunotherapy           | NCT02869685 |
| Lung Cancer        | diagnosis               | NCT03830619 |
| Lung Cancer        | diagnosis, prognosis, monitor | NCT04629079 |
| Lung Cancer        | diagnosis               | NCT04315753 |
| Lung Cancer        | diagnosis               | NCT04323579 |
| Lung Cancer        | diagnosis               | NCT03317080 |
| Lung Cancer        | diagnosis, prognosis    | NCT04182893 |
| Lung Cancer        | diagnosis               | NCT03542253 |
| Breast Cancer      | diagnosis, prognosis    | NCT01344109 |
| Breast Cancer      | diagnosis               | NCT03974204 |
| Breast Cancer      | immunotherapy           | NCT04288141 |
| Breast Cancer      | monitor, Metastatic     | NCT04258735 |
| Breast Cancer      | diagnosis               | NCT04781062 |
| Triple Negative Breast Cancer | diagnosis, prognosis | NCT04530890 |
| Prostate Cancer    | diagnosis, prognosis    | NCT02702856 |
| Prostate Cancer    | diagnosis               | NCT03032913 |
| Prostate Cancer    | immunotherapy           | NCT03236688 |
| Prostate Cancer    | diagnosis               | NCT04556916 |
| Prostate Cancer    | diagnosis               | NCT03694483 |
| Prostate Cancer    | diagnosis               | NCT04661176 |
| Prostate Cancer    | diagnosis, monitor      | NCT03911999 |
| Pancreatic Cancer  | diagnosis, prognosis    | NCT03821909 |
| Pancreatic Cancer  | prognosis               | NCT02393703 |
| Pancreatic Cancer  | diagnosis               | NCT03711890 |
| Pancreatic Cancer  | diagnosis               | NCT03791073 |
| Pancreatic Cancer  | diagnosis               | NCT04636788 |
| Colorectal Cancer  | diagnosis               | NCT04394572 |
| Colorectal Cancer  | diagnosis, prognosis    | NCT04523389 |
| Rectal Cancer      | monitor                 | NCT03874559 |
| Rectal Cancer      | prognosis               | NCT04852653 |
| Gastric Cancer     | diagnosis               | NCT01779583 |
| Oropharyngeal Squamous Cell Carcinoma | diagnosis | NCT02147418 |

(Continues)

### TABLE 1 (Continued)

| Source of Exosomes | Role in cancer therapy | Trial |
|--------------------|------------------------|-------|
| Thyroid Cancer     | prognosis              | NCT02862470 |
| Thyroid Cancer     | prognosis, monitor, Therapy | NCT03488134 |
| Malignant Glioma   | immunotherapy          | NCT01550523 |
| Malignant Glioma   | immunotherapy          | NCT02507583 |
| DLBCL              | immunotherapy          | NCT03985696 |
| Lymphoma, T-Cell, Peripheral | prognosis, monitor | NCT02535247 |
| Gallbladder carcinoma | prognosis             | NCT03581435 |
| Cholangiocarcinoma | prognosis              | NCT03102268 |
| Ovarian Cancer     | diagnosis, prognosis   | NCT03738319 |
| Ovarian Cancer     | prognosis              | NCT02063464 |
| Bladder cancer     | diagnosis              | NCT04155359 |
| Melanoma           | Treatment, drug resistance | NCT02310451 |
| Sarcoma            | monitor, prognosis     | NCT03800121 |
| Osteosarcoma       | biomarker for lung metastases | NCT03108677 |
| Bone Metastases    | diagnosis              | NCT03895216 |
| Malignant solid tumor | diagnosis            | NCT02662621 |

4.2 | **TEX-targeted cancer immunotherapy**

TEXs play an important role in tumor progression, drug resistance and metastasis. Previously, we found that TEXs stimulated T cells via DC cells in vitro, while in vivo it was beneficial for tumorigenesis. There are two ways to treat cancer patients. One is to inhibit the immuno-suppressive molecules on the surface of TEXs or/and enhance the immunostimulatory molecules on the surface of TEXs, thereby bias the balance in the direction of the immune stimulation. Immune checkpoint inhibitors are the most promising approach to neutralize the immuno-suppressive effect of TEXs. Poggio et al found that gene blockade of exosomal PD-L1 can significantly extend the survival period of mice, thereby exosomal PD-L1 represents a new therapeutic target to improve the therapeutic effect. Gao et al revealed that increased level of plasma exosomal Tim-3/Galectin-9 in NSCLC patients, was correlated with an aggressive phenotype, and Tim3/Galectin-9 may represent another novel therapeutic target. In order to enhance immunostimulatory molecules, exosomes derived from heat-shocked mouse B lymphoma cells contain more HSP90, HSP60, CD40 and CD86, which are benefit for anti-tumor effects.17,24 Another approach is to look for TEXs release inhibitors to enhance the antitumor effect of chemotherapy. Nowadays, a number of compounds have the ability to block or at least limit the formation and release of exosomes, such as Y27632, GW4869, bisyndoylmaleimide I and dimethyl amiloride.99 Kosgodage et al reported that chloramidine/Bisindolylmaleimide, a kind of microvesicles release inhibitors, is effective to enhance...
cancer chemotherapy efficacy. In addition, the reduction of TEXs may also improve the TME, thus enhance the function of immune cells, especially T cells.

4.3 TEX-based cancer vaccines

TEXs have potential application in the development of cancer vaccines due to its ability to stimulate specific antitumor immune responses via TAA and costimulatory molecules within. The uptake of TEXs by DCs can induce antigen-specific CTL responses, increase the number of CD8+ T cells, and activate CD4+ T cells, thus enhancing antitumor immunity. In previous studies, TEX-carrying DC immunotherapy has been shown to improve survival. In addition, TEXs show stronger antitumor immunity compared with tumor lysates. In order to further improve the anti-tumor immune response, some studies aim to manipulate TEXs or insert specific microRNAs into dendritic cells to enhance immunogenicity. Recently, Shi et al identified a novel exosome vaccine (IFN-γ-modified prostate cancer cell-derived exosome vaccine) that increased the number of M1 macrophages, CD4+ T cells and CD8+ T cells, thus prolonging survival in mice with prostate cancer. Huang et al also found that exosomes from TGF-β1-silenced leukemia cells (L1210) could improve the efficacy of DC-based vaccine. However, in some types of tumors, stimulation of exosomes may lead to immune tolerance of DCs, therefore, another possibility to consider is to use exosomes of DCs that were previously stimulated by tumor cells.

5 CONCLUSIONS

Although having immunostimulatory effects on T cells, TEXs induce immunosuppressive effects predominantly in TME through both direct and indirect mechanisms. TEXs impair the function of CD8+ T cells by directly inhibiting the activation, proliferation and cytotoxicity, as well as promoting apoptosis. Other immune cells, such as DCs, macrophages, myeloid-derived suppressor cells and NK cells contribute to indirect immune suppression by TEXs. Of note, exosomes from CAR-T cells represent a novel strategy of cancer immunotherapy and merits further investigations.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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