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REVIEW

Role of T cell-derived exosomes in immunoregulation

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Abstract

Exosomes are small membrane vesicles of endocytic origin that are secreted by most cells. They are composed of a lipid bilayer containing transmembrane proteins and enclosing cytosolic proteins and RNA, mediating intercellular communication between different cell types in the body, and thus influencing various physiological and pathological functions of both recipient and parent cells. For their nanolevel structures with a stable nature and various biological functions, studies of exosomes have been the subject of increasing interest in the past few years. It is widely known that different T cell subsets play important roles in cellular and humoral immunity, and their exosomes were also reported to exert similar biological functions. While several groups reported the secretion of exosomes by various T cells, the systematic summary involved in these exosomes are deficient. In this review, we will summarize the structure and functions of exosomes derived from T cells in recent reports, discuss emerging therapeutic opportunities, and consider the associated challenges.

Keywords T cells · Exosomes · Immune regulation

Introduction

T cells play central roles in cell-mediated and humoral immunity. Several different subsets of T cells have been discovered, each with distinct functions. According to the phenotype, T cells can mainly be divided into $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells. $CD4^+$ T cells can be further divided into Th1, Th2, Th9, Th17, Th22, follicular helper T cells (Tfh), and regulatory T cells (Tregs), each of which produces specific effector cytokines under unique transcriptional regulation [1–7]. Intercellular communication is an essential hallmark of multicellular organisms and can be mediated through direct cell–cell contact or transfer of secreted molecules [8]. In 1983, exosomes were first found in the reticulocytes of sheep, and they were named "exosomes" by Johnstone in 1987 [9]. Increasing evidences have shown that the transfer of exosomes from one cell to another, as another novel mechanism of cell signal transduction, plays an increasingly important role in intercellular communication [10–12]. It has been well established that almost all living cells can secrete exosomes. These nanometer-sized particles can selectively carry proteins and RNA from their origin cells, thus exert their biological functions. Mostly, functions of these exosomes are similar to their sources, but they can also be diverse depending on the state of the origin cells [13]. These small vesicles can be taken up by target cells via different manners, such as direct membrane fusion, phagocytosis, endocytosis, and even pinocytosis [14]. The biological functions of exosomes can also behave in different ways. For instance, exosomes can regulate the expression of target protein by carrying mRNAs which can be translated into the corresponding protein, by carrying miRNAs that can degrade the intracellular mRNA of that protein, or by carrying siRNAs that can silence the gene corresponding to that protein [15–17]. With increasing numbers of studies on exosomes, functions of exosomes derived from T cells have largely been unearthed, such as effectively activating or suppressing the immune response, promoting the inflammatory response, and participating in autoimmune and infectious diseases [18, 19]. In this review, we will especially focus on the structural features and major surface markers of T

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cell-derived exosomes. We also further introduce their roles in mediating immune regulation and provide new ideas for the future treatment of autoimmune diseases and cancers.

The role of exosomes in immune system

In immune system, exosomes possess immunomodulatory properties, including antigen presentation, immune promotion, immune suppression, and immune tolerance. For their functions in antigen presentation, exosomes loaded with specific peptides or antigens are capable of promoting the activation of $CD4^+$ T cells and $CD8^+$ T cells, even in the absence of dendritic cells (DCs) [20]. In addition, exosomes derived from macrophages are able to transfer their surface antigens to DCs, thus enhancing the response of $CD4^+$ T cells [21]. What is more, after presenting antigens, DCs can also secrete exosomes to further activate $CD4^+$ T cells, $CD8^+$ T cells, and natural killer cells (NK cells) in an antigen-specific manner [22–24]. Recently, exosomes have been demonstrated to be involved in the proinflammatory response and the enhancement of immune function [25–28]. For instance, exosomes released by virus-infected macrophages can promote TNF-α secretion of macrophages and neutrophils. Moreover, pathogen-associated molecular patterns (PAMPs) on the surface of exosomes can also strengthen immune surveillance [29]. Clinical studies have also found that there are large amounts of exosomes in the bronchoalveolar lavage fluid of patients with sarcoidosis. These exosomes can significantly induce IFN-γ and interleukin (IL)-13 production in autologous PBMCs and stimulate epithelial cells to produce IL-8, which may contribute to the initiation of inflammation [30]. In addition, exosomes in the synovial fluid of patients with rheumatoid arthritis have also been reported to boost the immune inflammatory reaction and aggravate the disease process [31]. Recently, researches on the immunosuppressive functions of exosomes mainly concentrate on tumor cells and several immunosuppressive cells. Studies have already shown that exosomes derived from tumor cells can impair T cells, B cells, monocytes/macrophages, NK cells, and DC functions and even promote the proliferation of myeloid-derived suppressor cells (MDSCs) [32–37]. MDSCs are a heterogeneous immature myeloid cells that possess immunosuppression [38]. Interestingly, Wang and his colleagues found that MDSC-derived exosomes can attenuate dextran sodium sulfate-induced colitis by inhibiting the Th1 immune response [39]. Simultaneously, Treg-derived exosomes have received widespread attention for their ability to exert immunosuppressive effects, which can prolong survival in a kidney allograft rat model [40].

The composition of exosomes

According to the current version of the exosomes database, Exocarta (http://www.exocarta.org), more than 9700 proteins have been found in exosomes, including cytoplasmic proteins, membrane proteins, Golgi-associated proteins, and endoplasmic reticulum-related proteins [41–43]. In addition, other metabolism-related enzymes, signal transduction proteins, carrier proteins, and some histocompatibility antigens are also widely found in exosomes [42].

Exosomes have a membrane structure that is rich in lipids. However, the lipid composition of exosomes differs from that of their source cells. There is much more sphingomyelin, phosphatidylserine, phosphatidylinositol, ceramide, and cholesterol in exosomes than in source cells, while source cells contain a higher proportion of phosphatidylcholine [44]. More interestingly, exosomes have the highest lipid packing density when compared to other extracellular vesicles, which shows that the structure of exosomes may be more stable [45].

Moreover, a major characteristic of exosomes that can distinguish them from other biological vesicles is that exosomes are rich in a large number of nucleotides, mainly including microRNAs and mRNAs [46]. In addition, exosomes also contain variety of other RNA species, including RNA transcripts overlapping with protein coding regions, repeat sequences, structural RNAs, tRNA fragments, vault RNA, Y RNA, circular RNA, and small-interfering RNAs [47–49].

The biological characteristics of exosomes

Studies have confirmed that surface markers of exosomes can be analyzed in vitro and their contents are quite stable [49, 50]. DC-derived exosomes can carry many effector molecules, such as MHC-I and MHC-II molecules, which could potentially stimulate $CD8^+$ and $CD4^+$T cells, respectively, as well as other costimulatory molecules [51–53], which means that exosomes are capable of sharing the faculties of their original cells. In addition, exosomes are able to reach a wide range of lymphoid organs through contact with corresponding cells, and exosomes are independent of chemokines [54, 55]. It was reported that high expression of fluorescence can be detected in the lung, liver, spleen, pancreas, GI tract, and kidneys in a dose-dependent manner 24 h after the intravenous injection of fluorescence-labeled exosomes [55]. These data demonstrated that the distribution of exosomes is rapid and extensive, which means that the biological effects of exosomes may also diverse in vivo. More importantly, exosomes prepared in vitro can be stored at − 80 °C for a long time and have no response to several associated immunosuppressive molecules [56]. Through the studies of biological characteristics of exosomes, it may provide the great directive significance to further clinical applications.

The surface molecules of T cell-derived exosomes

There are many function-related molecules in the membranes of T cells, which are involved in cells activation, proliferation, differentiation, antigen presentation, and effector functions. Interestingly, these molecules are also found to be expressed on T cell-derived exosomes.

The membrane of T cell-derived exosomes is a lipid bilayer that is commonly enriched in a set of proteins involved in the processes mentioned above. These small vesicles can express CD2, CD3/TCR, CD4, CD8, CD11c, CD25, CD69, LFA-1, CXCR4, FASL, GITR, etc. (Fig. 1).

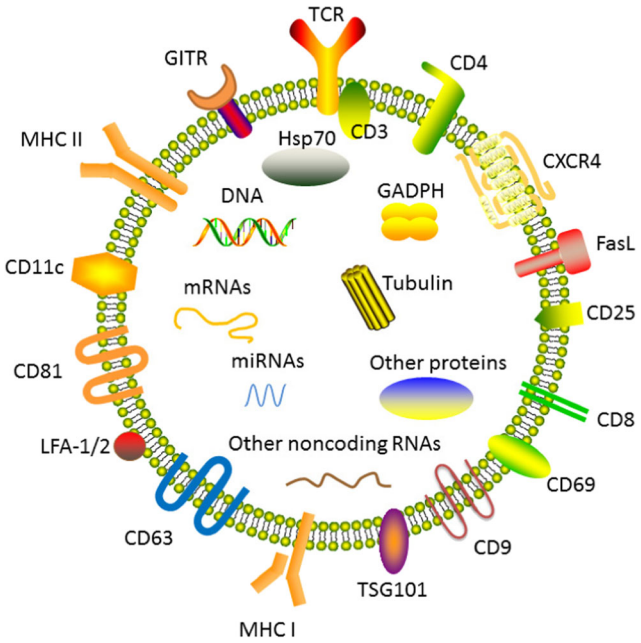

Fig. 1 Typical surface molecular of T cell-derived exosomes. Important membrane molecules found in a typical exosomes produced by T cells. GITR glucocorticoid-induced tumor necrosis factor receptor, MHC I/II major histocompatibility complex I/II, LFA-1/2 lymphocyte function-associated antigen 1/2, TSG101 tumor susceptibility gene 101; FasL Fas ligand or CD95L, CXCR4 C-X-C chemokine receptor type 4 or CD184, TCR T-cell receptor. For more information about exosome composition, please see http://www.exocarta.org or http://www.microvesicles.org

The functions of T cell-derived exosomes

In vitro studies have shown that T cells that were co-stimulated with TCR and CD28 can secrete more exosomes in vitro [57]. Moreover, T cells are able to regulate the release of distinct exosomes subpopulations depending on their activation status [58]. However, other activators such as PMA and ionomycin fail to promote the secretion of exosomes, which indicates that exosomes secretion may be related to a kind of physiological response occurring [59]. In the following discussion, we will further summarize different functions of T cell-derived exosomes (Fig. 2).

The immunosuppressive effects of T cell-derived exosomes

Tregs are a subset of T cells with immunosuppressive functions [60]; more and more studies have focused on Treg-derived exosomes due to their considerable immunosuppressive effects, which can also be useful when considering possible therapeutic tools in autoimmune diseases and transplantation [61]. Interestingly, it is reported that Tregs can secrete more exosomes than other T cells, and the surfaces of those exosomes mainly express CD25, CTLA-4, and CD73. Specifically, CD73-expressing exosomes perform immunosuppressive functions through the production of adenosine, which plays an important role in the anti-inflammatory response [62–64]. They can also carry let-7b, let-7d, and microRNA-155, which can inhibit the Th1 immune response and mediate immune suppression [18]. With in-depth studies on the biogenesis of exosomes, multivesicular body (MVB)-dependent secretion may be one of the most important pathways in exosome secretion. Proteins of the Ras-related proteins in brain (RAB) family, such as RAB11, RAB35, RAB7, RAB27A, and RAB27B, have been shown to be involved in exosome secretion in tumor cell lines of various origins [65–69]. Interestingly, It was shown that Rab27-DKO Tregs failed to release exosomes and thus failed to suppress Th1 cells [18], which mean that the proteins of RAB family also play a significant role in exosomes secretion in T cells. However, although the immunosuppressive functions of Treg-derived exosomes are quite strong, the specific mechanism is still unknown. Besides adenosine converted by CD73 and some miRNAs mentioned above, IL-10 and TGF-β may be two additional important negative regulatory factors [70, 71]. Nevertheless, it is unknown whether these cytokines are contained in Treg-derived exosomes. However, we believe that this assumption was established based on the fact that several cytokines were found in exosomes, and DC-derived exosomes were reported to contain IL-10 and TGF-β [72, 73]. In conclusion, Treg-derived exosomes show great potential for regulating the body's immunity and can further be applied to inhibit the graft rejection. In fact, Yu and colleagues have already observed that the adoptive transfer of autologous Treg-derived exosomes from rats can strengthen kidney function and prolong the survival of kidney allografts post-transplantation [40].

The immunological synapse between T cells and antigen presenting cells (APCs) was reported to promote the efficiency of exosomes transfer [19]. Exosomes can be taken up by DCs via peptide/major histocompatibility complex (pMHC)-II/TCR and CD54/LFA-1 interactions. The surface molecule FasL can bind its receptor Fas on DCs, which leads to the

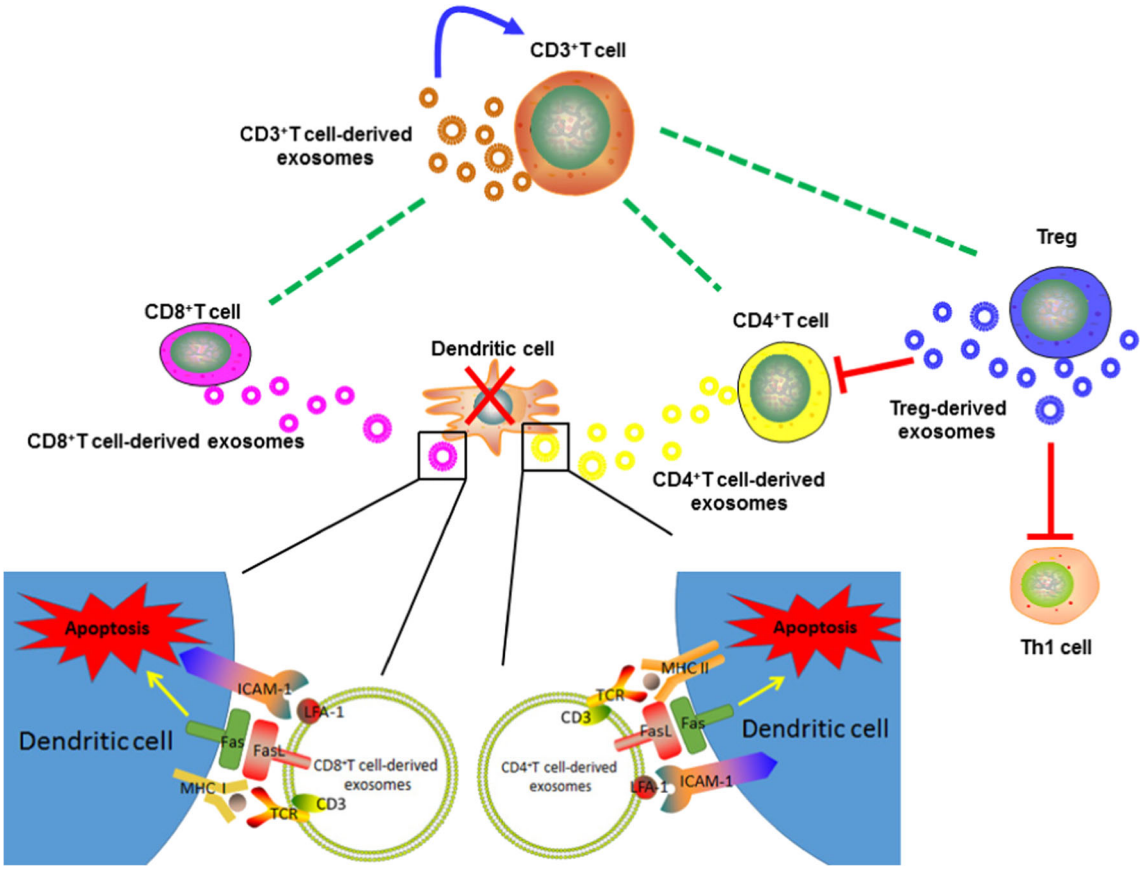

Fig. 2 The immunoregulation of T cell-derived exosomes. Different subtypes of T cells can secret their own exosomes. $CD3^+$ T cells can take up their own exosomes to promote the proliferation by an autocrine manner. Exosomes derived from $CD4^+$ T cells and $CD8^+$ T cells can bind to dendritic cells though peptide/major histocompatibility complex MHC/TCR and ICAM-1/LFA-1 interactions, which lead to the apoptosis of dendritic cells (DCs) by Fas/FasL and thus mediate the DC-mediated T cell silence in antigen-specific way. For regulatory T cells, they can secret exosomes which contain Let-7b, Let-7d, and microRNA-155 to inhibit Th1 immune response and mediate immune suppression. In addition, CD73-expressing Treg-derived exosomes are able to produce adenosine which may further inhibit the activation and proliferation of $CD4^+$ T cells

apoptosis of DCs and mediates the silencing of the T cell response in antigen-specific ways [74]. Interestingly, recent studies have also shown that $CD8^+$ T cell-derived exosomes can regulate the functions of target cells, and these exosomes can be endocytosed by APCs and B cells via pMHC-I/TCR interactions and inhibit antigen-specific DCs mediated $CD8^+$ CTL responses. In addition, these exosomes can also inhibit anti-tumor immunity and diabetes in antigen-dependent way [75]. Furthermore, macrophages cultured with $CD8^+$ T cell-derived exosomes lost contact sensitivity (CS), which may be related to the induction of Tregs and inhibition of effector T cells proliferation [76]. Moreover, by carrying miRNA-150 and transferring it to effector T cells, antigen-specific $CD8^+$ T cell-derived exosomes can mediate immunosuppressive function and inhibit experimental allergic contact dermatitis induced in mice by high doses of reactive hapten. When miRNA-150 was knocked down, this phenomenon disappeared, which suggested that microRNA-containing exosomes may also play a significant role in intercellular communication of lymphocytes [77]. However, determining the function of these exosomes merely by focusing on single or several molecules on their surface is unreasonable and ambiguous, especially on lymphocytes, exosomes induce diverse immune responses dependent on the different cells they are targeting. Moreover, several other factors can play a role in the final immunological effect of an exosome, including other molecules on the exosomes surface, other types of RNA in the exosomes, and even some kinases in exosomes that can directly activate target cells [78]. As a result, further studies are needed to figure out what exact functions exosomes have.

T cell-derived exosomes in promoting immune responses

We have mentioned that T cells can secrete more exosomes when co-stimulated with TCR and CD28. Valadi and his colleagues documented that $CD3^+$ T cell-derived exosomes were involved in the stimulation and proliferation of resting $CD3^+$ T cells. When together with IL-2, the $CD3^+$ T cell-derived exosomes can induce a relative increase of $CD8^+$ T cells,

which is similar to what would be seen with IL-2 combined with anti-CD3 and anti-CD28 mAbs. Moreover, the authors also showed that these exosomes may contain CCL5 (RANTES), which has major effects on HIV inhibition [79]. $CD8^+$ T cells were first confirmed to secrete secretory lysosomes, which can carry granzyme, perforin, and other effector molecules and which play an important role in the specific delivery of cytolytic molecules to target cells [80]. Coincidentally, exosomes derived from $CD8^+$ T cells were proved to suppress the CCR5-tropic (R5) and CXCR4-tropic (X4) replication of HIV-1 in vitro [81]. This evidence indicated that there is an intracellular signaling mechanism involved in the exosomes-mediated suppression of HIV-1 transcription, which could be of potential interest for anti-viral treatment. Overall, the studies on the immunological enhancement of T cells are insufficient. The contradiction is that most T cell subtype-derived exosomes show more immunosuppressive properties, which are inconsistent with their source cells' function. This phenomenon may be related to the different target cells they interact with. When $CD4^+$ T cells interact with DCs through (pMHC)-II/TCR and CD54/LFA-1, FasL can be the main effector molecule, thus leading to the apoptosis of DCs and silencing of the T cell response. However, as a traditional group of helper T cells, $CD4^+$ T cells also highly express CD40L and ICOS after activation [82, 83]. The consequences may be different when their exosomes are taken up by B cells. Whether $CD4^+$ T cell-derived exosomes can carry related effector molecules to activate B cells and promote humoral immunity remains to be further studied.

T cell-derived exosomes in tumor

Studies have also shown that T cell-derived exosomes may be involved in the progression of tumor formation or tumor invasion. Exosomes from activated $CD8^+$ T cells were shown to activate ERK and NF-κB in melanoma cells, leading to increased MMP9 expression and promoting cancer cell invasion in vitro, suggesting a role for T cell-derived exosomes in tumor progression [84]. Using a Jurkat T cell line to study natural T cells, Roberts and his colleagues discovered that T cell-derived exosomes can alter endothelial gene expression and physiological processes, such as regulating endothelial cell proliferation and vascular endothelial growth factor (VEGF) signaling in a CD47-dependent manner [85], which means that CD47-positive exosomes may also modulate tumor angiogenesis. In addition, Sun reported that exosomes derived from irradiated esophageal carcinoma-infiltrating T cells could promote the metastasis of esophageal cancer cells by inducing epithelial mesenchymal transition [86]. These studies all documented that T cell-derived exosomes may play an important role in tumor formation and invasion. However, although Jurkat cells are characterized as immortalized T cells, the biological characteristics of Jurkat cells and human natural T cells are not entirely consistent. For example, experiments have proven that only 40% of proteins are shared between these two exosomes according to proteomic analysis [87]. As a result, many more studies are needed to confirm the precise biological functions of T cell-derived exosomes.

Reflections on T cell-derived exosomes

A large amount of studies have showed that exosomes can also be used as biological markers for clinical diagnosis. They can be detected in patient biofluids including serum, urine, semen, saliva, and bronchoalveolar lavage [88–92]. For example, in the early stages of tumor formation, cancer cell-derived exosomes, which play an important role in tumor immune escape, angiogenesis, and invasiveness [93, 94], can be detected in the peripheral blood, suggesting that tumor exosomes can act as a biomarker for early tumor screening [95]. T cell-derived exosomes can also be used as early markers of disease development, for example, high concentrations of $CD4^+$ T cell-derived and $CD8^+$ T cell-derived exosomes were detected in serum from the peripheral blood of chronic hepatitis B patients, while patients with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis had high levels of invariant natural killer T (iNKT) cell-derived and macrophage/monocyte-derived exosomes [96].

The latest studies on exosomes showed that donor exosomes, rather than passenger leukocytes, could initiate alloreactive T cell response after transplantation, which showed the rapid and efficient function of exosomes in immunoregulation [97]. For T cell-derived exosomes, Treg-derived exosomes have been shown to mediate immunosuppressive effects and to be effective in inhibiting the development of murine arthritis, and their clinical value has been extensively discussed [61]. In addition, $CD4^+$ T cell-derived exosomes can specifically inhibit $CD4^+$ T cell proliferation and $CD8^+$ CTL responses, which provide the potential possibility of $CD4^+$ T cell-derived exosomes being used for the treatment of autoimmune diseases and as preventers of immune rejection. Currently, chimeric antigen receptor gene-modified T (CAR-T) cells have been widely recognized as a novel form of viable tumor treatment by the medical community for their exciting efficacy in blood cancer therapies. Although the treatment showed unprecedented efficacy in hematologic malignancies, some problems still exist in CAR-T cell treatments. These problems include CAR-T cell-induced cytokine release syndrome (CRS), which can lead to hypotension, nausea, tachycardia, headache, rash, and shortness of breath caused by the release of cytokines from immune cells after the treatment. CAR-T cell therapies can even lead to high fever, hypotension, organ failure, and death [98]. As a consequence, some scholars propose the application of CAR-T cell-derived exosomes in cancer therapy. First, modified CAR-T cell-

derived exosomes may kill target cells by granzymes and lysosomal enzymes. It is known that the biological effect of granzymes is dependent on perforin which polymerizes in the cell membrane to form a nonspecific ion pore [99]. However, exosomes can directly transfer these granzymes by membrane fusion with target cells or be endocytosed [80]. In addition, for its nonliving property, CAR-T cell-induced toxicity can be more easily controlled by using CAR-T cell-derived exosomes than traditional treatment. Second, exosomes, as a kind of small nanometer-sized particles, can easily cross biological barriers such as the blood–brain barrier (BBB) and blood–tumor barrier(BTB) [100]. Moreover, CAR-T cell-derived exosomes show greater potential in penetrating the extracellular matrix (ECM) of a solid tumor than CAR-T cells, which means that these small nanometer-sized particles may be more helpful in treating solid tumor and brain tumor. Third, since exosomes resemble liposomes consisting of a bi-lipid membrane and an aqueous core, anti-cancer agents can be directly loaded into CAR-T cell-derived exosomes which can be used to kill target cells [101].

As discussed, although numerous researches have focused on exosomes, the structure, formation, secretion, and their function are still unclear. Especially for T cells and other original lymphocytes derived exosomes, because of the difficulty of obtaining a mass of high-purity cells, diverse responses to different stimulations, and a great diversity of cell subsets, the researches about T cell-derived exosomes are limited. In general, there are still insufficient findings on exosomes derived from T cells, and much more remains to be confirmed by extensive experimental studies.

At present, many studies have focused on the regulation of T and B cells by other nonlymphoid cells, such as DC-derived exosomes, mesenchymal stem cell (MSC)-derived exosomes, and tumor cell-derived exosomes. However, the communication between lymphocytes via exosomes must also exist, and the effects of these exosomes may be more specific and more powerful. For B cell-derived exosomes, it was shown that they are involved in antigen presentation, leading to the activation of primed $CD4^+$ T cells and antigen-specific T cells [102, 103]. Additionally, a strong cytotoxic effect on several kinds of tumor cells and immune cells has been observed with NK cell-derived exosomes [104]. Therefore, through the study of T cell or other lymphocyte-derived exosomes, it may have a directive and practical importance to utilize artificially modified exosomes to treat autoimmune diseases and cancers.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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