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MINIREVIEWS

Regulatory roles of extracellular vesicles in immune responses against *Mycobacterium tuberculosis* infection

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Abstract

Extracellular vesicles (EVs) are cystic vesicles naturally released by most mammalian cells and bacteria. EV contents include proteins, lipids, and nucleic acids. EVs can act as messengers to transmit a variety of molecules to recipient cells and thus play important regulatory roles in intercellular signal transduction. EVs, released by either a host cell or a pathogen, can carry pathogen-associated antigens and thus act as modulators of immune responses. EVs derived from *Mycobacterium tuberculosis* (*Mtb*)-infected cells can regulate the innate immune response through various pathways, such as regulating the release of inflammatory cytokines. In addition, EVs can mediate antigen presentation and regulate the adaptive immune response by transmitting immunoregulatory molecules to T helper cells. In this review, we summarize the regulatory roles of EVs in the immune response against *Mtb*.

Key Words: Extracellular vesicles; Exosomes; *Mycobacterium tuberculosis*; Infection; Antigen; Immune regulation

Core Tip: Extracellular vesicles (EVs) are nanoscale membrane-bound structures released by mammalian cells and bacteria and play essential regulatory roles in intercellular signal transduction and the immune response. In this review, we discuss

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the regulatory role of EVs released by *Mycobacterium tuberculosis* (*Mtb*)-infected cells in the anti-*Mtb* immune response. Specifically, we focus on providing the most cutting-edge information on EVs released by *Mtb*-infected cells regulating the body's immune response, including the regulatory roles in innate and acquired immune responses. In addition, we describe the basis for EV-mediated regulation of the immune response in detail, *i.e.*, the EVs released by *Mtb*-infected host cells contain *Mtb*-associated antigens.

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INTRODUCTION

Tuberculosis (TB) is one of the major lethal infectious diseases caused by *Mycobacterium tuberculosis* (*Mtb*). According to the World Health Organization's global TB report of 2020, approximately 10 million people were infected with *Mtb* in 2019, causing approximately 1.4 million deaths[1]. Although several public health measures have been taken to prevent the spread of *Mtb*, the situation is concerning[2]. Drug-resistant *Mtb*, especially rifampicin-resistant *Mtb*, has become one of the deadliest pathogens in the world[1,2]. Therefore, the development of novel anti-*Mtb* reagents or vaccines is urgent and essential. Investigating the molecular mechanism of the immune response against *Mtb* is of great value because this information is the basis for preventive and therapeutic approach developments.

Extracellular vesicles (EVs) are nanoscale membrane-bound structures released by mammalian cells and bacteria. They contain proteins, lipids, and nucleic acids. EVs can be categorized into four types according to their biological origin, release pathway, size, and content: Exosomes, microparticles, microvesicles, and apoptotic bodies. Exosomes are mainly formed through the fusion of multivesicular bodies with the plasma membrane and the extracellular release of intracavitary vesicles, with a diameter of 30–100 nm and a buoyancy density of 1.13-1.19 g/mL. Exosomes are cup-shaped under a transmission electron microscope and characterized by the expression of CD63 and CD61[3]. The term "exosome" was first proposed by Trams *et al*[4] in 1981. Johnstone and Harding first isolated exosomes while studying the transferrin cycle[5,6]. Exosomes can be secreted by various eukaryotic cells, including macrophages, dendritic cells (DCs), neutrophils, lymphocytes, epithelial cells, mast cells, mesenchymal stem cells, and cancer cells[7,8]. Microparticles are 100-500 nm in diameter and share many characteristics with exosomes. They express member markers such as TyA, C1a, and CD35. Microvesicles are larger than exosomes and 100-1000 nm in diameter. They originate from the outer bud of the cytoplasmic membrane and carry selectins and integrins on the surface. The diameter of apoptotic bodies is 1-5 μm, and these EVs are the result of the disintegration of apoptotic cells[9]. Accumulated studies have indicated that EVs can be taken up by recipient cells and subsequently release their content to regulate gene expression in the recipient cells[9,10]. Therefore, EVs are critical regulators of various biological processes, such as embryonic development, angiogenesis, and the immune response. This review aims to summarize the research progress on the regulatory role of EVs in the immune responses against *Mtb*.

SUMMARY OF THE IMMUNE RESPONSE AGAINST *MTB*

After being inhaled into the respiratory tract, *Mtb* is first recognized by antigen-presenting cells (APCs) resident in the lungs, including alveolar macrophages, pulmonary macrophages, and DCs[11]. The pattern-recognition receptors expressed on the APC surface sense pathogen-associated molecular patterns and endocytose *Mtb* to form a phagolysosome. Simultaneously, the innate immune response is initiated,

and several inflammatory cytokines are released to promote the clearance of *Mtb* in APCs. Subsequently, the APCs migrate to the lymph nodes and initiate an adaptive immune response through antigen presentation and cytokine secretion[12-14].

However, *Mtb* has a variety of immune evasion strategies[15]. For example, it can inhibit the acidification and maturation of phagolysosomes *via* multiple virulence factors, such as protein tyrosine kinase[16], protein tyrosine phosphatase[17], and lipoarabinomannan (LAM)[18]. *Mtb* can also affect the adaptive immune response by regulating antigen presentation. For example, *Mtb* lipoarabinomannan mannose can bind to CD209 on DCs and inhibit DC maturation[19], promote the release of interleukin (IL)-10, reduce the synthesis of IL-12, and ultimately inhibit the release of interferon-γ (IFN-γ) by T helper (Th) cells[20]. The immune evasion mechanisms of *Mtb* are beyond the scope of this review; for more details, please refer to the review by Lerner *et al*[11].

EVS RELEASED BY HOST CELLS CONTAIN *MTB*-ASSOCIATED ANTIGENS

Some *in vitro* experiments have indicated that *Mtb* infection can increase the exosome yield and alter the protein composition of EVs released by host cells. For example, the exosome yield of mouse macrophages increases approximately two-fold after *Mtb* infection[21]. However, not all types of cells produce increased amounts of exosomes after *Mtb* infection. For example, Diaz *et al*[22] found that the exosome yields of THP-1-derived macrophages infected with *Mtb* or left uninfected were comparable.

Mtb infection can alter the protein profile of exosomes released by a host cell. A study applying liquid chromatography-tandem mass spectrometry revealed that there were 355 host proteins in the exosomes released by *Mtb*-infected macrophages. Most of the proteins were membrane proteins, and 41 of the proteins, including Hsp90, vimentin, Coronin 1 C, and moesin, were increased after *Mtb* infection[22]. In addition, *Mtb* itself can also release vesicles, which are termed bacterial vesicles (BVs)[23,24]. BVs are rich in *Mtb* antigens, such as SodB, EsxN, and Ag85b[23,24]. The protein composition of BVs is different from that of *Mtb* itself[23]. Furthermore, there is great overlap between the protein profile of vesicles released by *Mtb*-infected cells and BVs in aseptic culture[22,23,25-27]. Several studies have confirmed that exosomes released by *Mtb*- or *Mycobacterium bovis* (*M. bovis*) BCG-infected cells contain *Mtb*-related antigens and thus are potentially immunogenic. For example, THP-1 cells infected with *M. bovis* BCG can release exosomes containing *Mtb* 19-kDa lipoprotein and LAM, two *Mtb* antigens[25]. J774 cells stimulated with *M. bovis* BCG also release exosomes containing the Ag85 complex[26], the most common secretory protein in *Mtb* culture medium [28]. In addition, *Mtb* DNA was also observed in exosomes released by *Mtb*-infected RAW246.7 cells[29]. Notably, a study revealed that there are two subtypes of EVs (mostly exosomes) released by *Mtb*-infected mouse macrophages. One subtype expressed CD69 and CD9 but did not contain *Mtb* antigens, while the other expressed *Mtb* antigens, such as lipomannan (LM) and LAM[27]. These two subtypes of exosomes could be separated by sucrose density gradient centrifugation. These findings were validated by a subsequent study[24].

Notably, no *Mtb* antigens have been observed in exosomes released by mouse macrophages infected with heat-inactivated or γ-ray-inactivated *Mtb*[27,30], while the exosomes produced by J774 cells treated with *Mtb* culture filtrate protein 10 were shown to contain *Mtb* antigens[30]. In addition, heat-inactivated *Mtb* cannot release BVs when cultured alone[31]. Taken together, these findings imply that the *Mtb* antigens in *Mtb*-infected cell-released exosomes are induced by live *Mtb* or *Mtb* secreted proteins rather than mycobacterial lysis within the infected cell.

A previous study revealed that the *Rab27a* gene is essential for the synthesis of mammalian exosomes[32]. *In vitro* experiments indicated that *Rab27a* knockout could decrease the exosome yield and the content of *Mtb* proteins in exosomes[21]. Furthermore, compared with wild-type mice, *Rab27a* knockout mice had decreased serum exosome levels after *Mtb* infection[21]. The bacterial load was also shown to be increased in *Rab27a* knockout mice, suggesting that exosomes participate in the immune response against *Mtb*[21]. In another study, Bhatnagar *et al*[25] infected mice with *M. bovis* BCG and found that the exosomes in the bronchial lavage fluid contained both human components (Hsp70) and *Mtb* proteins, such as LAM and 19 kDa lipoproteins.

Mtb antigens have also been found in the serum exosomes of TB patients. Kruh-Garcia *et al*[33] used the multiple reaction monitoring technique to analyze the protein profiles of serum exosomes from patients with active TB. They found that there were 76 peptides (33 proteins) in the serum of TB patients, and 20 of them were increased when compared to the levels in TB-negative patients. These proteins were derived from *Mtb* and are critical to the survival of *Mtb*.

In conclusion, *in vitro*, animal, and clinical studies have revealed that *Mtb* can induce the release of exosomes that contain *Mtb* proteins. These exosomes may play crucial roles in the anti-*Mtb* immune response.

REGULATORY ROLE OF EVS IN THE INNATE IMMUNE RESPONSE AGAINST *MTB*

As mentioned above, EVs released by cells infected with *Mtb* or *M. bovis* BCG carry *Mtb* proteins, such as LAM[24,25,27], the Ag85 complex[26,30], lipoproteins (LpqH and LprG)[21,27], and 19 kDa lipoproteins[25,30]. Therefore, these EVs can trigger an inflammatory response after being taken up by APCs. In addition, these EVs have been confirmed to promote the migration of macrophages, neutrophils, and lymphocytes to the lungs both *in vivo* and *in vitro*[34].

Exosomes released from *Mtb*- or *M. bovis* BCG-infected J774 cells, THP-1 cells, and RAW264.7 cells can trigger mouse macrophages to release inflammatory cytokines, such as IL-1β, IL-6, IL-12p70, tumor necrosis factor-α (TNF-α), and regulated upon activation normal T cell expressed and secreted factor, and upregulate the expression of iNOS[25,30,31,34]. Exosomes from the serum of mice infected with *M. bovis* BCG can also promote the expression of inflammatory factors in mouse macrophages[34]. The induction of IL-1β and IL-6 is mediated by Toll-like receptor (TLR) 2, while the release of IL-10 and CCL3 is independent of TLR2[31]. The induction of TNF-α is also MyD88 and TLR4 dependent[25]. In addition, exosomes can promote the phosphorylation of p38 and IκB in mouse bone marrow-derived macrophages[25], suggesting that p38 and IκB are also involved in the production of inflammatory cytokines.

IFN-γ can enhance the clearance of *Mtb* in three ways: (1) Promoting the clearance of intracellular pathogens by supporting macrophages to enhance the response to reactive oxygen species or reactive nitrogen[35]; (2) Promoting the adaptive immune response by enhancing the expression of major histocompatibility complex II (MHC II)[36]; and (3) Promoting an autophagic response against pathogens[37]. The exosomes released by *Mtb*-infected RAW264.3 cells can inhibit the upregulation of MHC II and CD64 induced by IFN-γ in uninfected mouse macrophages through TLR2 and MyD88[24,38]. This inhibitory effect of exosomes is associated with the cargo *Mtb* lipoprotein, as exosomes produced by RAW264.7 cells infected with *lspA* knockout (unable to synthesize lipoprotein) *Mtb* fail to inhibit CD64 expression induced by IFN-γ[38].

The expression of miR-18a is increased in *Mtb*-infected RAW264.3 cells[39], while the expression of miR-20b-5p is decreased[40]. These two microRNAs can regulate the survival, apoptosis, and proliferation of macrophages[39,40]. Both of these microRNAs were also found to be elevated in exosomes released by *Mtb*-infected RAW 264.3 cells, but it remains unknown whether these exosomes can be taken up by uninfected macrophages. Two studies compared the microRNA profiles of exosomes released by cells infected with *Mtb* or *M. bovis* BCG or left uninfected and verified many differentially expressed microRNAs[29,41]. Bioinformatic analysis showed that these differentially expressed microRNAs are involved in the regulation of multiple signaling pathways, including central carbon, fatty acid, and sugar metabolism[42], but whether these microRNAs can regulate the immune response remains unclear.

REGULATORY ROLE OF EVS IN THE ADAPTIVE IMMUNE RESPONSE AGAINST *MTB*

As mentioned earlier, Rab27a is a key regulator of the fusion of exosomes and the plasma membrane[32]. Smith *et al*[21] found that *Mtb*-infected *Rab27a* gene-deficient mice released decreased amounts of exosomes and consequently had an increased bacterial load and a significantly reduced activated $CD4^+$ T cell population in the spleen, indicating that exosomes promote the adaptive immune response against *Mtb in vivo*. Furthermore, exosomes promote the T cell response during *Mtb* mouse infection. Since IFN-γ is mainly produced by Th1 cells during *Mtb* infection[43], these

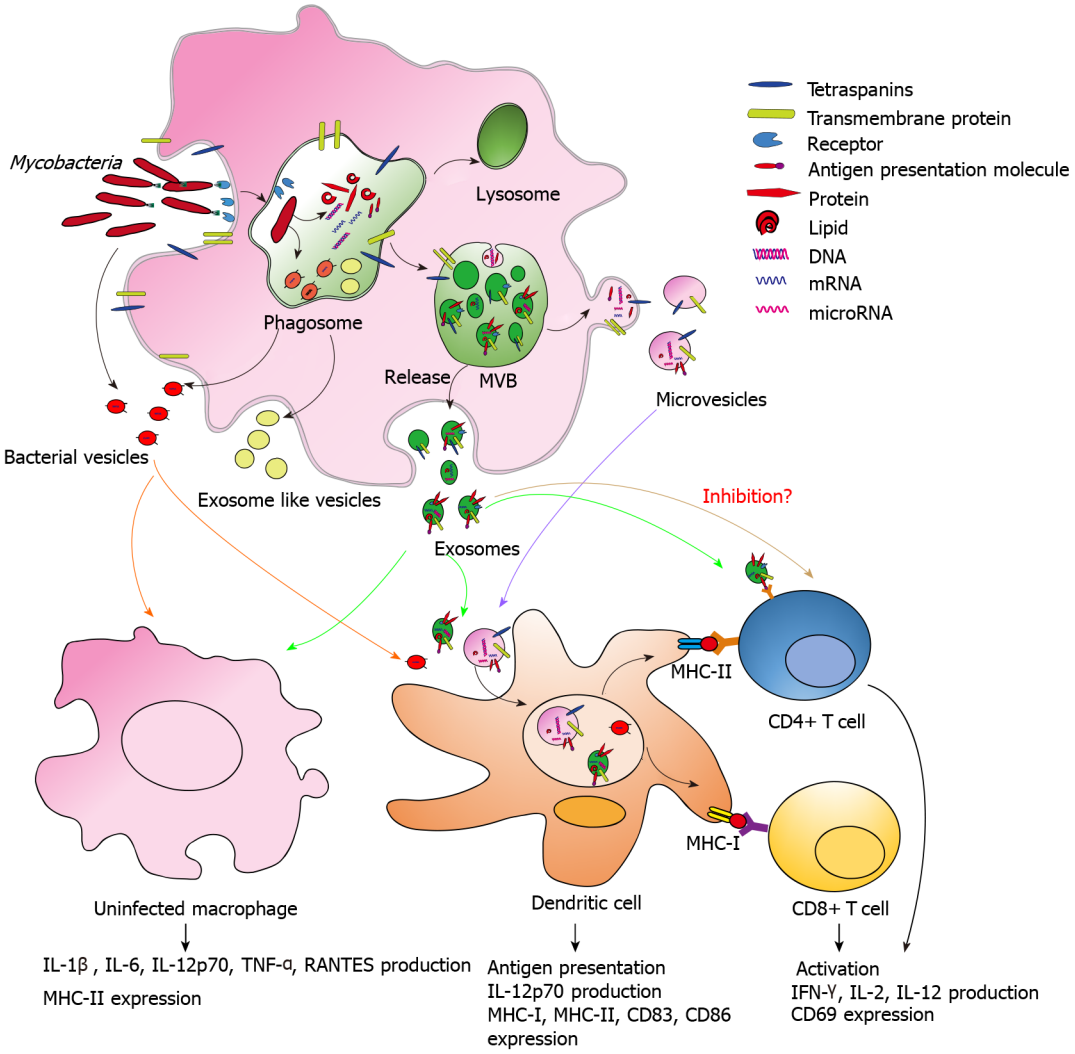

Figure 1 Regulatory roles of extracellular vesicles in the immune response against *Mycobacterium tuberculosis*.

studies suggest that exosomes are involved in the adaptive immune response against *Mtb* and can promote an antigen-specific T cell response[21].

The exosomes secreted by *M. bovis BCG*-infected J774 macrophages can enhance the expression of CD83, CD86, IL-12p40, and MHC II in mouse bone marrow-derived dendritic cells (BMDCs) and thus promote BMDCs mutation[26]. The release of IL-12p40 by DCs can promote the Th1 response[44,45]. Therefore, exosomes containing *Mtb* antigens can promote a subsequent Th1 response *via* DCs. In addition, *Mtb* itself can also release EVs (termed BVs) in culture, and these vesicles can upregulate the expression of CD86, MHC I, and MHC II in mouse BMDCs, which thereby enhances the release of IL-2 by Ag85-specific T cells[24]. Ramachandra *et al*[46] found that macrophages infected with *Mtb* could release EVs containing MHC II, including microvesicles and exosomes, in which ATP greatly enhanced the release of vesicles. Microvesicles and exosomes have the ability to present *Mtb* peptide–MHC II complexes to T cells[46]. These results suggest that innate immune cells can deliver *Mtb* antigens to T cells outside the infected site by releasing microvesicles and exosomes.

The exosomes released from *M. bovis* BCG-infected J774 cells can promote the proliferation of T cells and upregulate the expression of CD69[26], which is a marker of T cell activation[47]. In addition, these exosomes can directly enhance IFN-γ release from $CD4^+$ and $CD8^+$ T cells in *M. bovis* BCG-immunized mice[26]. These biological functions can be further enhanced in the presence of DCs[26]. *In vivo* studies have indicated that treating mice with exosomes can increase the proportion of spleen effector T cells (CD62L-low, CD44-high)[26]. These findings were further validated by subsequent studies. Exosomes from *Mtb* antigen-treated cells (*Mtb* CFP-treated J744 cells[30] or *Mtb* CFP-treated RAW264.7 cells[48]) can also activate T cells from *Mtb* antigen-immunized mice and enhance T cell production of IFN-γ[26,30] and IL-12[48]

in vitro. Interestingly, adjuvants have little effect on the production of IFN-γ and IL-12 [26,30], indicating that these exosomes may contain some types of substances similar to adjuvants. Furthermore, these exosomes can induce the production of memory T cells in mice[26,30] and reduce the susceptibility of mice to *Mtb*[48].

Athman *et al*[49] found that EVs released by macrophages from mice infected with *Mtb* and *Mtb* BVs could directly inhibit the anti-CD3 and anti-CD28 antibody-induced activation of naive T cells and effector T cells. This inhibitory effect was mainly attributed to *Mtb* antigens in the EVs, including LAM, LM, PIM1/2, and PIM6. Previous studies have shown that these *Mtb* antigens can inhibit the activation of T cells, which represents one of the immune evasion mechanisms of *Mtb*[50]. EVs can transmit *Mtb* antigens to T cells and promote the expression of GRAIL[49], a negative regulator of T cell activation[51,52]. Therefore, EVs can regulate the adaptive immune response against *Mtb* in at least two ways: Modulating the antigen presentation process and directly regulating T cells.

CONCLUSION

In recent years, several studies have been performed to explore the characteristics and potential biological functions of EVs in the immune response against *Mtb*. However, our understanding of the immunomodulatory role of EVs in *Mtb* infection is still in its early stages. The regulatory roles of EVs in the immune response against *Mtb* are summarized in Figure 1. The EVs released by *Mtb*-infected host cells contain *Mtb*-related proteins and nucleic acids, which establishes the foundation for a regulatory role in the immune response against *Mtb*. EVs regulate both the innate and adaptive immune responses against *Mtb* through various pathways. Therefore, EVs may represent a key factor in the development of an *Mtb* vaccine.

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