Current research progress on extracellular vesicles derived from mesenchymal stem cells in tuberculosis treatment (Review)

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Abstract. Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) have garnered research attention due to their unique biological functionalities and therapeutic potential. Compared with the parent MSCs from which they originate, MSC-EVs are typically free from systemic allergic reactions, hemolysis, pyrogenic reactions, abnormal hematological changes, and vascular and muscle irritation problems, and thus, exhibit therapeutic potential. The present review provides a comprehensive analysis of numerous isolation methodologies for MSC-EVs, with each method being evaluated based on key parameters, including principles, advantages, limitations and applications. Notably, the therapeutic potential of MSC-EVs in the treatment of tuberculosis (TB) has been emphasized. MSC-EVs have demonstrated unique capacities to modulate the T helper cell (Th)1/Th2/T regulatory cell balance, promote M2 macrophage polarization, alleviate inflammation through microRNA-mediated mechanisms and enhance host defense through antimicrobial peptide responses. The integration of MSC-EVs with anti-TB therapy can improve lung, kidney and bladder health by reducing TNF-α levels and increasing IL-10/TGF-β ratios. Notably, functional discrepancies between EVs derived from distinct MSC sources, such as umbilical cord vs. bone marrow cells, underscore the need for targeted optimization strategies. Adequate risk assessment is important before clinical trials, particularly concerning immunogenicity, potential pro-inflammatory effects and promotion of TB latency. The present review explores the potential clinical applications of MSC-EVs in TB and other infectious diseases, offering key insights into their therapeutic potential, with the aim of guiding future research.

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1. Introduction

Extracellular vesicles (EVs) are small vesicular structures released by cells, and contain a variety of bioactive molecules, including proteins, nucleic acids and lipids, which facilitate the transfer of information between cells. EVs play critical roles in a plethora of physiological processes and pathological mechanisms. These roles include transporting bioactive molecules, facilitating intercellular communication and modulating the functions of target cells via receptor interaction. Moreover, EVs have emerged as valuable tools in the fields of disease diagnosis and therapeutic intervention, particularly in the context of conditions like cardiovascular disorders and neurological ailments (1,2). Mesenchymal stem cells (MSCs) are pluripotent stem cells with self-renewal properties that serve a role in cell therapy due to their potent immunomodulatory and regenerative effects (2). Recent studies have highlighted the therapeutic potential of MSCs through their paracrine products. MSCs can regulate the immune response, promote angiogenesis and exhibit anti-inflammatory effects by secreting a series of bioactive factors and MSC-derived EVs (MSC-EVs), thus potentially offering therapeutic benefits for a variety of diseases (3-5). Isolation and purification techniques for MSC-EVs continue to be refined, emphasizing the importance of determining their identity. Although EVs have broad application prospects in the

medical field, there are still some challenges in their separation and purification techniques, such as improving the separation efficiency and avoiding contamination. A number of methods, including electron microscopy, nanotrack analysis, western blotting and flow cytometry, have been employed to identify MSC-EVs (2). Studies have shown that MSC-EVs exert similar biological effects as MSCs, including modulation of inflammatory responses, promotion of tissue repair and antioxidant properties (6-9). These features enable them to serve important roles in the regulation and treatment of numerous diseases. In the context of infectious diseases, such as renal tuberculosis (TB), urinary TB and TB, MSC-EVs have demonstrated marked efficacy in improving renal function and quality of life through mechanisms such as reduction of renal injury, stimulation of renal cell regeneration and repair, suppression of inflammatory responses, and antiviral/antibacterial pathways (10-13). Furthermore, comprehensive research and clinical trials are key in fully unlocking the therapeutic potential of MSC-EVs in disease treatment (10,14,15).

Based on the established understanding of *Mycobacterium tuberculosis* (Mtb) infection mechanisms and the unique properties of MSCs, therapeutic strategies utilizing MSCs for the treatment of TB and multidrug-resistant TB (MDR-TB) have garnered interest (11-13,15,16). Previous studies have further elucidated the therapeutic potential of MSCs (6-9,17,18). Yang *et al* (19) conducted a study in which human umbilical cord-derived MSCs (HUC-MSC-EVs) were co-cultured with Mtb-infected THP-1 macrophages. The findings indicated that MSCs were able to augment the immune response of macrophages to Mtb by activating immune receptors and inducing the production of inflammatory mediators. The present review provides an important platform for advancing TB diagnostics and therapeutic interventions, representing a notable step toward understanding and controlling Mtb pathogenesis in human hosts. Results from studies utilizing MSC-EVs have demonstrated the potential of MSC-EVs in therapeutic applications across diverse animal models, including cardiac, brain, kidney and lung injury animal models (Table I). Furthermore, MSC-EVs exhibit remarkable efficacy in mitigating the increased bacterial load associated with Mtb infection, while effectively suppressing pro-inflammatory cytokine production (10,14,20,21). However, research on the specific application of MSC-EVs in TB therapy remains relatively limited. This review aims to provide a comprehensive overview of various themes, encompassing an analysis of isolation methodologies for MSC-EVs and the therapeutic potential of MSC-EVs in a range of application areas, with a particular focus on their potential in the treatment of TB, current research trends and future directions in the field.

2. Biological effects of MSC-EVs

A core theory behind the enhanced biological effects of MSC-EVs is their ability to transfer bioactive molecules to target cells, thereby modulating numerous cellular processes. MSC-EVs can promote tissue repair, reduce inflammation and regulate immune responses, making them a promising therapeutic option for a range of diseases (6). The present research is primarily concerned with addressing challenges pertaining to the separation efficiency, stability and safety of MSC-EVs. Moving forward, additional enhancements in research methodologies and the accumulation of clinical trial data will be necessary to facilitate the progression of MSC-EVs therapy towards clinical implementation.

Biological function of EVs and MSC-EVs. EVs were first described in 1970 (22). Research has shown that EVs typically exhibit a spherical structure with a diameter ranging between 40 and 100 nm, and the density of the lipid membrane of the vesicle falls within the range of 1.13-1.19 g/ml (23). These vesicles carry a number of biomolecules, including proteins, lipids and nucleic acids. They are internalized by recipient cells through mechanisms such as endocytosis, phagocytosis or direct membrane fusion (24,25). While the composition of EVs may vary depending on their source, common proteins found in most EVs include integrin-associated proteins (such as annexin, G proteins and flotillin), heat shock proteins (Hsps; Hsp60, Hsp70 and Hsp90) and tetraspanins (CD81, CD63 and CD9). Lipids, including sphingomyelin and cholesterol, are also present (26). Increasing evidence has indicated that EVs serve a key role in certain biological processes, including intercellular vesicle transport, immune responses and development, as well as in neurobiology and microbiology (27-29). Additionally, these vesicles have been closely associated with numerous human diseases, including cancer, cardiovascular disease, neurodegenerative disorders and infectious diseases such as TB (30). Moreover, EVs exhibit marked biotechnological potential (15,21,31,32). More than 200 preclinical studies have investigated EV-based therapies in diverse animal models (24). These studies have demonstrated the therapeutic potential of cell-derived EVs in numerous contexts, including promoting wound healing in diabetic patients (33), improving cardiac function and inhibiting arrhythmia (34,35), serving as therapeutic targets for myocardial infarction (36), preventing endometrial injury (37), acting as diagnostic/prognostic biomarkers or treatments for Alzheimer's disease (38,39), improving renal function, reducing inflammatory responses and reducing apoptosis in acute kidney injury (40,41) and porcine kidney grafts (42), promoting liver repair (43), reducing inflammation in lung diseases (44-46), promoting immune response and microbial reconstruction in inflammatory bowel disease (47) and sepsis (48), and promoting the repair of the regeneration of vessels, nerves and hair follicles in skin wounds (49), as well as regulating inflammation and promoting cartilage matrix reconstruction in joint, osteoarthritis and bone regeneration applications (50-52). Furthermore, EVs play a crucial role in the immune response to bacterial infections (53-55). Previous representative preclinical studies on MSC-EVs, such as in myocardium diseases (56,57), brain diseases (58-60), lung diseases (61-64), knee disease (65), infectious diseases (66-68) and in kidney diseases (69,70), are summarized in Table I.

Immunomodulatory mechanisms of MSC-EVs. Exosomes have emerged as a promising alternative to MSCs, offering similar benefits without the risk of injection complications (71-73). Evidence has suggested that MSC-EVs, including HUC-MSC-EVs, are a safer therapeutic option, free from systemic allergic reactions, hemolysis, pyrogenic reactions, abnormal hematological changes, and vascular and muscle irritation problems (23). MSC-EVs contain a diverse range of biological molecules, including numerous types of RNA such

Table I. Representative studies on disease treatment using EVs.

Disease	Study model	Mechanism	(Refs.)
MI	Murine MI model	Mitochondria-rich EVs transfer their mitochondrial and non-mitochondrial cargos, contributing to improved intracellular energetics	(56)
Ischemic cardiomyopathy	Myocardial infarction rat model	iPSCM-derived EVs improve cardiac function by regulating numerous genes and pathways	(57)
Stroke	Stroke mouse model	Neural progenitor cell-derived EVs contribute to reverting peripheral post-stroke immunosuppression Intranasal	(58)
AD	AD mouse model	delivery of BACE1 siRNA and berberine via engineered stem cell exosomes	(59)
ICH	ICH rat model	Exosomes derived from human umbilical cord MSCs decrease neuroinflammation and facilitate the restoration of nerve function	(60)
Pneumonia	Murine cytomegalovirus-infected pneumonia model	MSC-EVs mediate their biological functions through the NF-κB/NLRP3 signaling pathway	(61)
Acute respiratory distress syndrome	LPS-induced acute lung injury mouse model	GMP-compliant EVs derived from umbilical cord MSCs reduce lung damage and inflammation; human adipose-derived MSCs were primed with IFN-γ and TNF-α to enhance the immunomodulatory properties of their secreted EVs	(62,63)
Lung injury	Bleomycin-induced pulmonary fibrosis mouse model	Human Wharton's jelly-derived EVs reduce inflammation and promote lung tissue repair	(64)
Knee OA	OA mouse model	HUC-MSC-EVs exert immunomodulatory effects by polarizing macrophages toward an anti-inflammatory M2b-like phenotype via STAT1 signaling modulation. Vesicles mitigate IL-1β-induced inflammatory responses in chondrocytes by the upregulation of COL2A1 expression and concomitant downregulation of IL-6 and MMP13 levels. Umbilical cord-derived MSC-sEV polarize macrophages to an anti-inflammatory M2b-like phenotype through STAT1 modulation	(65)
Pseudomonas aeruginosa burden and inflammation	Cystic fibrosis mouse model	Dual effects of MSC-EVs, mitigating inflammation and reducing bacterial burden	(66)
Sepsis	Septic mouse model	Combined treatment with dexamethasone and MSC-EVs significantly reduced the concentrations of pro-inflammatory cytokines IL-6 and TNF-α, elevated IL-10 and TGF-β in both BALF and serum; downregulated the expression of HMGB1, NLRP3, caspase-1, and caspase-3 in lung tissue; suppressed iNOS expression and upregulated Arg-1 expression in the spleen	(67,68)
CKD	CKD and renal anemia mice model; renal ischemic injury	Transferred erythropoietin mRNA into target cells; hypoxia significantly promotes the generation of MSC-EVs and enhances their therapeutic effects on renal IRI. The antioxidant stress effect induced by GSTO1 is identified as one of the most critical underlying mechanisms	(69,70)

MI, myocardial ischemia; AD, Alzheimer's disease; CKD, chronic kidney disease; ICH, intracerebral hemorrhage; OA, osteoarthritis; LPS, lipopolysaccharide; EV, extracellular vesicle; MSC, mesenchymal stem cell; siRNA, small interfering RNA; sEV, small EV; NLRP3, NLR family pyrin domain containing 3; BACE1, β-secretase 1; BALF, bronchoalveolar lavage fluid; iNOS,inducible nitric oxide synthase; Arg-1,arginase-1; GMP, good manufacturing practice; iPSCM, induced pluripotent stem cell-derived cardiomyocytes; CKD, chronic kidney disease; GSTO1, glutathione s-transferase omega 1.

as mRNA and microRNA (miRNA/miR), as well as proteins. These molecules serve a central role in promoting epithelial repair, tissue regeneration and the secretion of important cytokines, including TGF, keratinocyte growth factor, VEGF and hepatocyte growth factor, amongst others (74). Research has shown that MSC-EVs function by reducing the levels of TNF-α while increasing the levels of molecules such as TGF-β and IL-10 (75). In addition, MSC-EVs possess the ability to modulate the immune system by balancing the ratio of T helper cells (Th1/Th2, promoting the generation of regulatory T cells (Tregs) and inhibiting B cell activity (76). MSC-EVs not only boost the expression of indoleamine 2,3-dioxygenase and activate the CD39 and CD73 adenosine signaling pathways, but also help in converting inflammatory M1 macrophages into anti-inflammatory M2 macrophages. This transformation is important in regulating inflammation and decreasing the levels of TNF-α (14,15,77). MSC-EVs have been shown to stimulate angiogenesis and lymphangiogenesis in endothelial cells (ECs) within ischemic areas by transporting proteins and miRNA. This research is of great note, as it demonstrates the crucial role played by MSC-EVs, which may be regulated by integrin subunit α5 and neuropilin-1 proteins (78). MSC-EVs with elevated programmed death-ligand 1 (PD-L1) expression have demonstrated potential in the therapeutic management of autoimmune disorders. Through the employment of lentivirus-mediated gene transfection strategies, scientists have engineered MSC-small EVs (sEVs) that overexpress PD-L1 to modulate the immune response within targeted tissues. This innovative approach has demonstrated the capacity of MSC-sEVs-PD-L1 to orchestrate the conversion of multiple activated immune cells towards an immunosuppressive phenotype, thereby facilitating the restoration of the local immune microenvironment in autoimmune pathology (79). Pei *et al* (80) examined the immunomodulatory effects of MSC-EVs on sepsis-associated liver dysfunction in a mouse model induced by lipopolysaccharide (LPS). Their findings indicated that MSC-EVs could mitigate liver tissue damage and induce the transformation of M1 macrophages into M2 macrophages. *In vitro* experiments demonstrated that treatment with MSC-EVs markedly reduced the expression of glycolytic enzymes, diminished glycolytic activity and effectively suppressed the inflammatory response of macrophages by downregulating hypoxia-inducible factor 1α (HIF-1α) expression (80). MSC-EVs can regulate the immune system of the body, have antibacterial effects and promote tissue repair by containing a variety of bioactive substances, such as cytokines, growth factors and nucleic acids. These bioactive substances can regulate the physiological processes within the body through various signaling pathways, thereby playing a role in treating diseases, such as drug-resistant infections, sepsis and viral pneumonia (14,80-83) (Fig. 1) (14,15,20,74,76-78,84-87).

Novel discoveries regarding the therapeutic potential of MSC-EVs. MSC-EVs, noted for their enhanced functionality, have attracted considerable research attention. Previous studies (21,32,73) have made notable advancements in uncovering their therapeutic potential. Research utilizing bone marrow-derived MSC-EVs (BM-MSC-EVs) has demonstrated their effects on ECs within ischemic tissue, both *in vitro* and *in vivo*. MSC-EVs have been demonstrated to promote angiogenesis and lymphangiogenesis in ECs located within ischemic regions. This effect is mediated by the transfer of proteins and microRNAs by MSC-EVs, demonstrating their pivotal role in facilitating these physiological processes (78). In a mouse model of severe hind limb ischemia, MSC-EVs were found to enhance the recovery of blood flow in ischemic muscle tissue, leading to an increase in blood vessel density *in vivo*. This pro-angiogenic effect was accompanied by an increase in nitric oxide production in ischemic muscle (78). The findings have indicated that fibroblasts-EVs showed the worst effect on chondrogenesis, while juvenile chondrocyte-EVs and adult chondrocyte-EVs showed a comparable effect on chondrogenic differentiation as BM-MSC-EVs, and BM-MSC-EVs showed the best effect on cell proliferation and migration. In the rat model, a small intestinal submucosal acellular extracellular matrix hydrogel carrying BM-MSC-EVs was successfully utilized to treat articular cartilage defects, resulting in a marked improvement in cartilage regeneration (88). An additional investigation of miRNA-26b-5p-enriched MSC-EVs in spinal cord injury (SCI) revealed that MSC-EVs could ameliorate motor dysfunction, inflammation and oxidative stress in SCI rats. The delivery of miR-26b-5p by MSC-EVs to PC12 cells led to reduced inflammatory responses and reactive oxygen species (ROS) production induced by LPS, along with enhanced cell viability. In addition, miR-26b-5p suppresses the activity of KDM6A, which reduces H3K27me3 levels at the NOX4 promoter and thereby promotes NOX4 expression. However, overexpression of either KDM6A or NOX4 abrogates the protective effects conferred by MSC-EVs (89). Previous research has also demonstrated that HUC-MSC-EVs could effectively and safely improve chronic kidney disease. Following treatment with HUC-MSC-EVs, notable improvements were observed in the estimated glomerular filtration rate, serum creatinine levels, blood urea levels and the urine albumin-creatinine ratio (90). In addition, Ma *et al* (84) reported that in a mouse model of renal ischemia-reperfusion injury, administration of human placental MSC-EVs led to marked improvements in renal function, a decrease in the severity of acute kidney injury and a reduction in chronic interstitial fibrosis. MSC-EVs mainly achieved renoprotection by regulating Bax/Bcl-2-dependent apoptosis during acute kidney injury and mostly reduced tubular atrophy and kidney interstitial fibrosis by regulating Ras-pERK-Ets1-p53 pathway-dependent cell senescence (84). Researchers have also explored the potential enhancement of EVs derived from induced MSCs for treating acute kidney injury through stimulation by stimulating them with pan-peroxisome proliferator-activating receptor agonists (81). Shi *et al* (85) investigated potential therapeutic interventions for renal fibrosis and found that HUC-MSC-EVs could retard the progression of renal fibrosis by suppressing ADAM17. Notably, miR-13474 was highly enriched in HUC-MSC-EVs and efficiently targeted ADAM17 mRNA for inhibition, thereby reducing Notch1 activation, blocking TGF-β signaling pathway engagement and decreasing collagen deposition, all of which contribute to mitigating fibrotic development (85). Preclinical studies have also shown promising results in the treatment of acute and chronic renal failure and bladder reconstruction, For instance, preclinical studies have been applied in the treatment of acute and chronic renal failure, as well as in bladder reconstruction (91,92). In addition, it has been reported that

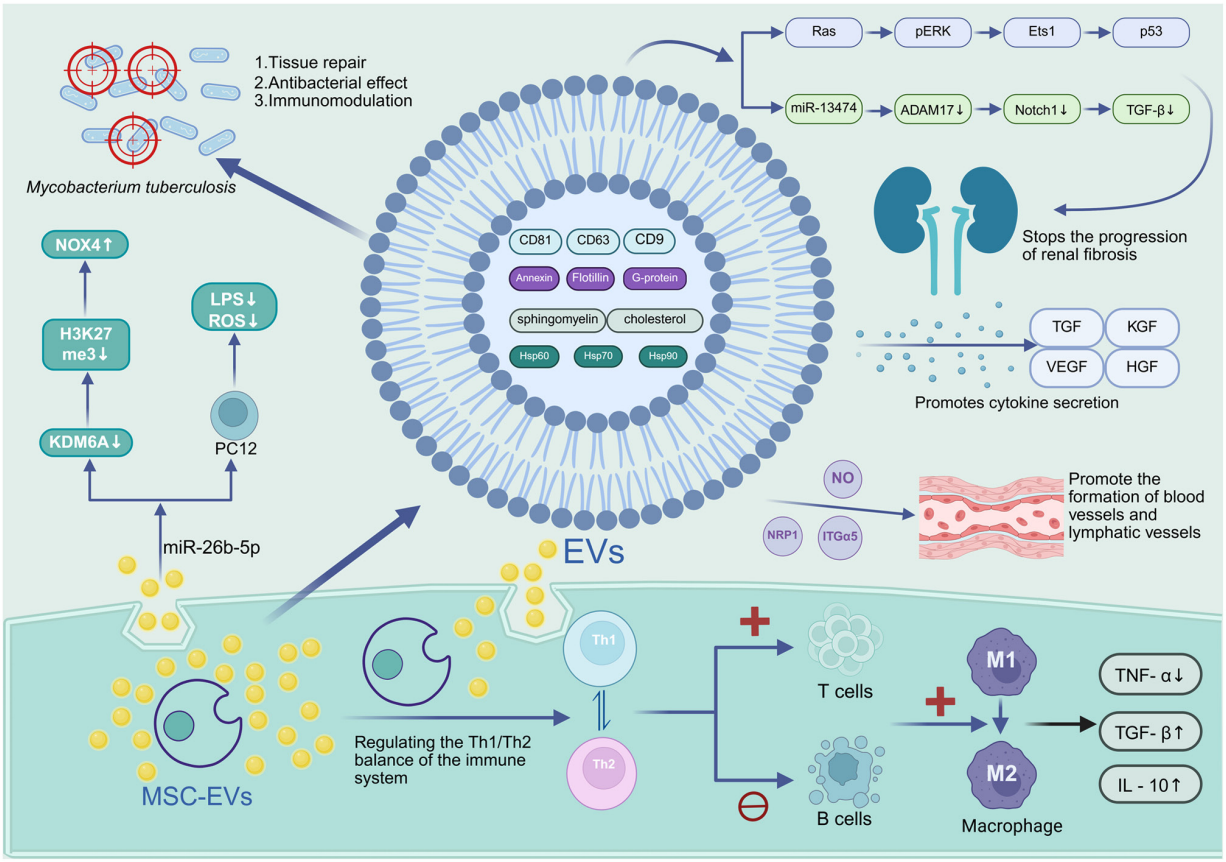

Figure 1. Structure and biological function of MSC-EVs. MSC-EVs are small membrane-bound vesicles released from MSCs, which carry various bioactive molecules. The structure of MSC-EVs includes a lipid bilayer membrane that encapsulates these bioactive molecules. This unique structure allows MSC-EVs to serve a key role in intercellular communication and tissue regeneration. Biological functions of MSC-EVs include tissue repair, antibacterial effects, immunomodulation, anti-inflammatory effects, anti-fibrotic effects and pro-angiogenic effects. For example, MSC-EVs can regulate the Th1/Th2 balance, promote macrophage polarization toward the M2 phenotype, inhibit oxidative stress, delay the progression of renal fibrosis, and enhance cytokine secretion, as well as the formation of blood and lymphatic vessels MSC, mesenchymal stem cell; EV, extracellular vesicle; NOX4, NADPH oxidase 4; H3K27em3, trimethylation of histone H3 at lysine 27; pERK, phosphorylated extracellular signal-regulated kinase; KDM6A, lysine demethylase 6A; LPS, lipopolysaccharide; ROS, reactive oxygen species; miR/miRNA, microRNA; Th, T helper cell; Hsp, heat shock protein; ITGα5, integrin subunit α5; NRP1, neuropilin-1; ADAM17, ADAM metallopeptidase domain 17; Ets1, ETS proto-oncogene 1; HGF, hepatocyte growth factor; KGF, keratinocyte growth factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; Ras, rat sarcoma virus oncogene; ETS1, E26 transformation-specific proto-oncogene 1; p53, tumor protein p53; NO, nitric oxide.

Mtb can successfully evade the effects of drugs and inflammatory cytokines within MSCs during the treatment of infectious diseases. MSCs offer a protective environment for Mtb, aiding in its resistance to anti-TB medications. Despite possessing phagosome maturation capabilities, MSCs readily engulf Mtb and facilitate its proliferation. In contrast to the behavior of Mtb within macrophages, which is known to be susceptible to anti-TB drugs, Mtb residing within MSCs demonstrates a pronounced resistance or tolerance to the same drugs, primarily attributed to the presence of ATP binding cassette subfamily C member 1, ATP binding cassette subfamily G member 2 and vacuolar H^+-ATPase (93).

In the case of TB infection, MSC-EV treatment can lead to the following benefits: i) Immune balance reconstruction by inhibiting the excessive activation of macrophages and reducing inflammatory damage in the vicinity of granulomas to combat intracellular Mtb; ii) enhancing host defense through the delivery of miRNA, where MSC-EVs activate macrophage autophagy, aiding in the clearance of Mtb and preventing immune evasion by Mtb; and iii) tissue repair, where MSC-EVs contribute to the reduction of tissue fibrosis by inhibiting fibroblast transformation and downregulating the TGF-β/Smad pathway (10,20,94). MSCs are a natural reservoir for latent Mtb infection, whereas macrophages promote an environment conducive for Mtb replication. Mtb can enter a dormant state within MSCs, prompting Mtb to enter a quiescent state. This process leads to the synthesis of lipid droplets by MSCs, which helps Mtb evade the immune response of the host. Successful treatment of TB necessitates eradication of both actively replicating and dormant bacteria. Dormant bacteria typically do not respond to conventional antibiotics; however, they can be targeted by autophagy induction. Thus, the combination of antibiotics and autophagy inducers is a promising approach for the effective treatment of TB (95). Studies have shown that MSC-EVs from different sources (such as the bone marrow, umbilical cord and adipose tissue) may have different therapeutic effects. Specifically, BM-MSC-EVs have demonstrated promising results in stimulating angiogenesis. On the other hand, HUC-MSC-EVs exhibit superior capabilities in modulating anti-inflammatory responses and regulating the immune system (23,96). In addition, adipose-derived MSC-EVs exhibit marked effects in the

treatment of fat metabolism-related diseases such as diabetic nephropathy, but their antibacterial activity may not be as good as that of other MSC-EVs (97). Therefore, for the treatment of TB, the selection of MSC-EVs from different sources and the role of MSC-EVs require further in-depth research.

3. Comparison of isolation methods and purification techniques for MSC-EVs

The isolation of EVs is crucial for scientific research (98) and forms the basis for maintaining their purity, yield and accuracy in subsequent functional studies. The source of MSCs used in EV research varies, with the majority being isolated from the bone marrow (51%), followed by umbilical cord/placental tissue (23%) and adipose tissue (13%). In addition, MSCs derived from embryonic or induced pluripotent stem cells account for 8% of MSCs, while other sources account for 5% of the total (26). Currently, a number of methods are commonly used for EV separation, including differential centrifugation, size exclusion chromatography, immunoaffinity capture, ultracentrifugation and ultrafiltration, each with its own unique attributes (99).

Differential centrifugation. A primary technique for EV separation is differential centrifugation, which separates EVs based on their differing settling velocities in a liquid medium. By adjusting factors such as the centrifugal force, time and rotor type, different particle sizes can be effectively separated. For example, extending the centrifugation time can enhance the yields of RNA and proteins in EVs (100). While this method is easy to use and cost-effective, it is heavily reliant on specific equipment and can introduce impurities, such as cell debris, thereby impacting the purity of the final product (100-102).

Size-exclusion chromatography. By size exclusion chromatography, exosomes can be separated based on their particle size, resulting in high purity and enhanced functionality. This method is characterized by its simplicity, excellent repeatability, scalability, affordability and the fact that it does not require specialized equipment or expert knowledge (103). However, relying solely on size-exclusion chromatography can result in residual impurities. Therefore, the combination of size-exclusion chromatography and ultracentrifugation has garnered interest, as it effectively enhances the quality and purity of exosomes in serum (104).

Immunoaffinity capture method. This technique involves the use of antibody-coated magnetic beads to selectively isolate exosomes that express specific surface markers with high specificity. Particularly beneficial for processing low concentration samples, this method has a higher cost and is limited by the specificity and efficacy of the antibodies used (99,105). Brambilla *et al* (106) introduced an innovative capture and release approach utilizing DNA-directed fixation of anti-CD63 antibodies. By employing deoxyribonuclease I, the authors effectively isolated all EVs and conducted a comprehensive analysis using advanced imaging technologies, including nanoparticle tracking analysis, transmission electron microscopy and single-particle interferometric reflectance imaging sensing (101,106).

Ultrafiltration. A main principle of this technique is to separate vesicles based on their size and to concentrate them from biological fluids using centrifugal enrichment equipment. Although this method is fast, its ability to separate small vesicles is limited (99). Membranes with low protein-binding properties are ideal for this process because they reduce the adherence of EV proteins and enhance their recovery (101,102). Typically, ultrafiltration is combined with other methods (such as use of differential ultracentrifugation, filtration, concentration and high-resolution density-gradient fractionation) to enhance the purity and separation efficiency (102,107).

Ultra-centrifugation. This approach utilizes centrifugal force for vesicle separation. The benefits of ultra-centrifugation encompass superior purity, consistency and functional efficacy of isolated EVs, ultimately leading to a potential increase of >22% in the activity of hypoxic cells. However, drawbacks include the risk of vesicle rupture, difficulty in handling small sample volumes, high cost and the specialized nature of ultracentrifuges (108). In EV research, the importance of separation efficiency and sample purity is indisputable. A previous study conducted a comparative analysis of two EV purification techniques, namely ultrafiltration combined with liquid chromatography and ultracentrifugation itself. The findings revealed that the combination of ultrafiltration and liquid chromatography resulted in a notable enhancement of EV production compared with ultracentrifugation, while maintaining the protein composition of EVs. Notably, experimental data demonstrated that EVs purified using ultrafiltration and liquid chromatography retained their inherent biophysical characteristics (107). In another experiment, a combination of analytical techniques, including dynamic light scattering, scanning electron microscopy and flow cytometry, were utilized to isolate and characterize EVs. The findings of this investigation demonstrate that the efficient loading of ovalbumin (OVA) onto SMC-EVs had been successfully optimized. Specifically, it was ascertained that the most advantageous outcome was achieved when the initial concentration of OVA was 500 μg/ml and the incubation duration was set at 6 h (105). However, there are variations in the secretion and function of MSC-derived EVs from different sources. Data have revealed that MSCs for exosome-enriched fractions studies have been isolated from a variety of tissues (26). Based on the diverse advantages and disadvantages of different EV isolation technologies (as summarized in Table II), researchers should carefully select an isolation method that aligns with their objectives.

4. MSCs and their derived EVs in the treatment of TB

Although research on MSC-EVs in the treatment of intrapulmonary or extrapulmonary TB is still limited, preliminary findings have shown promising results (10,20). This necessitates further investigation and summarization of the current research in this area.

According to statistics from the World Health Organization, the global TB incidence reached 10.8 million in 2023, which was a 0.9% increase from 10.7 million in 2022 (109). Among extrapulmonary TB cases, genitourinary TB, particularly renal TB, is the most prevalent form (110). Previous studies have increasingly suggested that MSCs hold therapeutic promise for

Table II. Comparison of EV separation methods.

Method	Principle	Advantages	Limitations	Applications	(Refs.)
Differential centrifugation	Separation based on particle sedimentation velocity under varying centrifugal forces, durations and rotor types	Simple operation and low cost; prolonged centrifugation enhances RNA/protein yield in exosomes	High equipment dependency; potential contamination by cellular debris (low purity)	Routine EV isolation; requires complementary methods for improved purity	(100-102)
Size exclusion chromatography	Separation based on particle size through porous stationary phase	High purity and functional integrity; excellent reproducibility, scalability and cost-effectiveness	Residual impurities when used alone; requires ultra-centrifugation for enhanced purity	High-purity EVs from complex samples (such as serum); large-scale studies	(103-104)
Immunoaffinity capture	Antibody-coated magnetic beads selectively bind EVs with specific surface markers	High specificity; effective for low-concentration samples; DNAse I enables intact EV release	High cost; antibody-dependent efficiency; nonspecific binding interference	Isolation of EV subtypes (such as biomarker studies)	(105,106)
Ultrafiltration	Size-based enrichment using centrifugal concentrators with molecular weight cut-off membranes	Rapid processing; low protein-binding membranes minimize exosomal protein loss	Limited efficiency for small EVs; often requires combination with other methods	Rapid concentration of large-volume samples; coupled with techniques such as UF-LC	(99,101, 102,107)
Ultracentrifugation	High-speed centrifugation (100,000-200,000 x g) to pellet EVs	High purity, homogeneity and bioactivity; EVs enhance cell viability (for example, +22% in hypoxia models)	Risk of vesicle damage; expensive equipment; unsuitable for small sample volumes	High-purity EVs for functional studies	(108)
UF-LC	Combined ultrafiltration and liquid chromatography for optimized EV isolation	Superior EV yield; preserves biophysical properties and protein composition	Multi-step workflow; technical complexity	High-yield EV production (for example, for therapeutic carrier development)	(105,107,108)

EV, extracellular vesicle; UF-LC, ultrafiltration-liquid chromatography; DNAse I, deoxyribonuclease I.

inflammatory and sclerotic diseases, including renal TB (11,12). Supporting this potential, one study has evaluated BM-MSCs as a combination therapy for experimental renal TB model in rabbits. Researchers induced renal TB by injecting TB H37Rv into the renal cortex under ultrasound guidance. All animals developed renal failure within 2.5 months. Anti-TB drugs reduced the levels of albumin, copper protein and elastase, improved the balance of mediators/inhibitors, and enhanced the inflammatory response, while BM-MSC transplantation exhibited different benefits. At 1 month post-transplant, inflammatory protein levels decreased, kidney-specific destructive inflammation subsided and mature connective tissue was formed, indicating activated repair mechanisms (86). Researchers compared the cellular reactions of MSCs to the virulent H37Rv strain and the attenuated H37Ra strain. The results showed that early infection (≤24 h) with H37Rv led to a marked increase in the phosphorylation of toll-like receptor (TLR)-2, protein kinase AMP-activated catalytic subunit-α (PRKAA)-1 and PRKAA2 in MSCs compared with attenuated H37Ra infection. Activation of the TLR2-AMPK pathway enhanced autophagic induction in H37Rv-infected MSCs, as demonstrated by elevated Atg9b expression and an increased LC3-II/LC3-I ratio. In addition, metabolic analysis revealed that, compared with H37Ra infection, H37Rv infection led to increased expression of SLC2A3, PFKFB3, HK1 and ABCA1 in MSCs. Despite the differences in autophagy induction, the bacterial loads between the two strains remained similar, indicating a potential role of apoptosis and immune inflammation in the control of mycobacterial growth (111).

EVs exhibit therapeutic relevance in TB. Host- or pathogen-derived EVs carry pathogenic antigens, regulating immune responses, metabolism and cell death (112). Specifically, EVs from Mtb-infected cells control inflammatory cytokines through antigen presentation, transmit immunoregulatory molecules to T helper cells and promote adaptive immune responses (113,114). Studies have shown that infection with Mtb promotes the release of MSC-EVs without affecting MSC proliferation; these vesicles can be internalized by macrophages and induce time-dependent pro-inflammatory responses through upregulation of TNF-α, RANTES and iNOS. This process is primarily mediated via the TLR2/4-MyD88 signaling pathway, and *in vivo* experiments further demonstrate that EVs derived from Mtb-infected MSCs (Mtb-MSC-EVs) can trigger pro-inflammatory responses in mice even during anti-TB treatment (87). A rabbit model of renal TB was established by injecting Mtb H37Rv into the renal cortical parenchyma, followed by intravenous administration of MSC-EVs in combination with standard anti-TB therapy (ATT). Compared with ATT alone, the combination treatment significantly increased serum anti-inflammatory cytokine levels while reducing pro-inflammatory cytokines and improving alkaline phosphatase, adenosine deaminase and body weight. Further analyses indicated that MSC-EVs are enriched with antimicrobial peptides such as lactotransferrin, lysozyme and cystatin B, as well as proteins with anti-inflammatory and immunomodulatory properties, suggesting a potential role in alleviating renal injury (15).

Beyond therapy, Mtb-derived membrane vesicles show potential as next-generation vaccines, eliciting stronger adjuvant-free immunity compared with the traditional Bacillus Calmette-Guérin (BCG) (115). EV-associated genes may also serve as biomarkers or therapeutic targets (114). Given their efficacy in preclinical models of acute/chronic kidney inflammation and functional impairment, MSC-EVs represent a promising strategy for renal TB treatment (10,91,116).

The lungs are particularly susceptible to Mtb infection (117). A clinical trial has investigated the systemic transplantation of autologous MSCs in patients with MDR-TB or extensively drug-resistant TB refractory to conventional therapy. A group of patients who did not respond well to standard TB treatment showed positive outcomes after receiving stem cell therapy with MSCs. At 36 months postoperatively, all 27 patients exhibited clinical improvement. Within 3-4 months after surgery, 20 patients cleared bacteria from their lungs and 11 had reduced lung tissue cavities. A total of 16 patients received stem cell therapy along with standard treatment, 9 patients experienced sustained remission of TB for up to 2 years, and 6 patients showed marked improvements in both bacterial load and structural changes in their lungs. The study suggested that combining autologous MSCs with conventional TB therapy may improve outcomes in patients with drug-resistant TB (118).

In a Cornell model of Mtb persistence in mice (119), it was observed that the highly virulent green fluorescent protein-labeled Mtb strain H37Rv persisted in $CD271^+$ BM-MSCs 90 days after treatment with isoniazid and pyrazinamide. Infected BM-MSCs were identified using pyronidazole, an *in vivo* marker of hypoxia. Notably, the treatment regimen successfully eradicated Mtb infection in the lungs of the mice. Subsequent experiments involved the isolation of $CD271^+$ BM-MSCs from post-treatment mice, which were then transplanted into healthy mice. Notably, the recipients developed active TB infections in their lungs, determining the presence of viable Mtb within BM-MSCs. In addition, this study revealed that Mtb infection induced a notable increase in the hypoxic phenotype of $CD271^+$ BM-MSCs. In a parallel investigation involving individuals previously treated for TB, Mtb-containing $CD271^+$ BM-MSCs exhibited heightened expression of HIF-1α and reduced levels of CD146, a cell surface marker typically downregulated in hypoxic human BM-MSCs. These findings suggested that the Mtb harbored by $CD271^+$ BM-MSCs may be situated within an anoxic microenvironment, which serves a key role in promoting the quiescent state of Mtb (119). Chenari *et al* (120) conducted a study in which MSCs were isolated from mouse adipose tissue, and their phenotype and differentiation properties were evaluated. Cell-conditioned medium (CM) collected from these MSCs was administered intranasally to mice. This study showed that CM helped achieve an improved balance in the inflammatory response to BCG infection, thereby reducing lung tissue damage. Previous studies have identified two types of scavenger receptors (macrophage receptor with collagenous structure and scavenger receptor class B member 1) that are involved in the ability of MSCs to phagocytize Mtb (121,122). Blocking the receptor with antibodies or inhibiting its expression through siRNA technology has been proven to reduce the uptake of Mtb. Additionally, research has indicated that infusion of autologous MSCs into patients with TB is safe and can enhance lung immunity (121). Furthermore, a study explored the potential of MSC-EVs in combatting Mtb

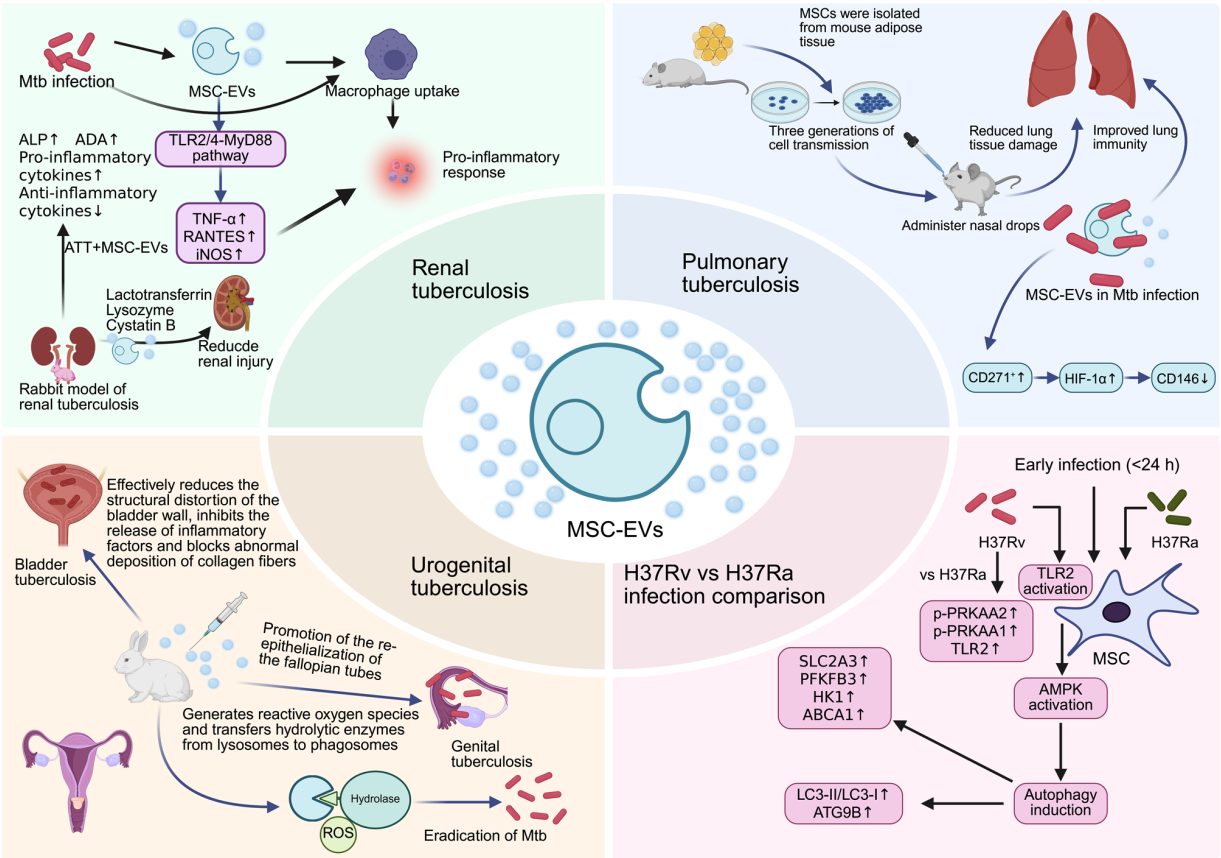

Figure 2. Research progress of MSC-EVs in the treatment of tuberculosis. MSC-EVs have shown potential immunomodulatory, antimicrobial and tissue repair effects in the treatment of tuberculosis. Novel advances have been made in the treatment of tuberculosis of the kidney, lung and the genitourinary system. MSC, mesenchymal stem cell; EV, extracellular vesicle; ROS, reactive oxygen species; AMPK, AMP-activated protein kinase; HIF-1α, hypoxia-inducible factor 1-α; MyD88, myeloid differentiation primary response 88; RANTES, regulated on activation, normal T-cell expressed and secreted; TLR2, toll-like receptor 2; TLR4, toll-like receptor 4; CD271, cluster of differentiation 271; CD146, cluster of differentiation 146; TNF-α, tumor necrosis factor-α; iNOS, inducible nitric oxide synthase; p-PRKAA1, phosphorylated protein kinase AMP-activated catalytic subunit α1; p-PRKAA2, phosphorylated protein kinase AMP-activated catalytic subunit α2; SLC2A3, solute carrier family 2 member 3; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; ABCA1, ATP binding cassette subfamily a member 1; ATG9B, autophagy related 9B; HK1, hexokinase 1; Mtb, *Mycobacterium tuberculosis*; ALP, alkaline phosphatase; ADA, adenosine deaminase.

infection in alveolar epithelial type II cells. Treatment with MSC-EVs markedly inhibited the increase in bacterial load induced by Mtb infection and prevented the production of pro-inflammatory cytokines (20).

Genitourinary TB commonly results in bladder contracture and diminished bladder capacity, and in severe cases, a notably reduced bladder size until the bladder becomes completely atretic (59). Conservative treatment of stage IV bladder TB is typically ineffective, warranting consideration of surgical intervention. Although numerous surgical strategies have proven to be effective, there is a substantial risk of complications (110). Electrolyte imbalances, metabolic abnormalities, excessive mucus production, stone formation, recurrent urinary infections and altered drug metabolism should be considered when addressing potential serious complications and surgical techniques in the context of the urinary system (123). In a study utilizing a New Zealand rabbit model of bladder TB, the efficacy of interstitial injection of MSCs combined with standard anti-TB treatment in restoring bladder function was determined. To track the localization of MSCs in tissues, cells were tagged with superparamagnetic iron oxide nanoparticles. The findings indicated that the nanoparticles were readily absorbed by the cells without compromising their proliferation ability. A single administration of MSCs directly into the bladder mucosa proved to be effective in reducing bladder wall deformation and inflammation (54). In a treatment trial involving 20 female 'Totoro' rabbits with experimental genital TB, the administration of MSCs markedly enhanced the repair process of the body and effectively promoted re-epithelialization of the fallopian tubes 2 months after inoculation. MSCs also exhibit a bactericidal mechanism similar to that of macrophages, involving the production of ROS and the transfer of hydrolases from lysosomes to phagosomes. In addition, MSCs exhibit the potential to enhance the bactericidal capacity of macrophages by regulating their phenotypes. These findings serve as an important theoretical foundation for the development of novel approaches for TB treatment using EVs (55). A number of studies regarding the use of MSC-EVs for TB treatment are ongoing and summarized in Fig. 2 (15,54,55,87,111,119,120,123). In addition, a summary of research on EVs specifically targeting TB is provided in Table III. This includes studies involving EVs derived from Mtb-infected cells and patients, EVs administered to mice for immunization purposes, EVs isolated from serum samples of TB patients, EVs investigated in TB animal models and EVs discovered in pleural fluid samples (10,20,124-133).

Table III. Studies on EVs targeted to TB.

Cell/animal/patient model	Mechanism	(Refs.)
Mtb-infected cells	EVs carrying a CA composed of three Mtb antigens were developed as a candidate TB vaccine using endogenous antigen loading	(124)
Clinical patients	Urine-derived EVs from patients with Mtb infection may reflect raft-dependent biological processes associated with TB pathogenesi	(125)
Mice immunized by EVs	Immunization with EVs released from Mtb-infected macrophages induced robust cytokine responses, and EV-associated antigens (Ag85B, ESAT-6, and Rv0580c) showed effective immunogenicity	(126)
Serum of patients with TB	Small EVs are rich in proteins, nucleic acids and lipids, act as messengers, and may exhibit altered composition in disease conditions	(127)
Serum of drug-resistant patients with TB	EVs in serum containing host-derived miR-let-7e-5p and Mtb-derived RNA were proposed as dual biomarkers for monitoring TB treatment response	(128)
Mouse myeloid dendritic cells	Mtb-EVs can upregulate intracellular ROS levels in dendritic cells and induce the release of IL-1β and IL-6	(129,130)
TB mouse model	EVs released from J774A.1 macrophages infected with Mtb H37Rv showed distinct biological effects; S-EVs reduced mycobacterial burden and cytokine production *in vitro* and decreased lung bacterial load *in vivo*	(130)
Renal TB rabbit model	Therapy with MSC-EVs increased anti-inflammatory cytokines, decreased pro-inflammatory cytokines, and alleviated renal inflammation and kidney injury	(10)
AECII-like MLE-15 and A549 cells	In AECII treatment, MSC-EVs prevent the increase in the bacterial load and prevent the production of pro-inflammatory cytokines	(20)
Mtb-infected macrophages	EVs produced by neutrophils stimulated with Mtb activate macrophages and promote the clearance of intracellular Mtb through early superoxide anion production and autophagy induction	(131)
Mtb-infected macrophages or mice	EVs released from Mtb-infected macrophages stimulated recipient cells to produce type I interferons and promoted the maturation of Mtb-containing phagosomes.	(132)
Pleural fluid	Pleural fluid-derived EVs contain concentrated Mtb antigens and may serve as targets for antigen detection assays in pleural TB diagnosis	(133)

EVs, extracellular vesicles; TB, tuberculosis; Mtb, *Mycobacterium tuberculosis*; CA, chimeric antigen TB vaccine; AECII, alveolar epithelial type II cells; pEV, pleural fluid-derived EV; miR, microRNA; pTB, pleural TB; MSC, mesenchymal stem cell; ROS, reactive oxygen species; Ag85, antigen 85; ESAT-6, early secreted antigenic target 6 kDa; Rv0580c, an *M. tuberculosis* antigen; S-EV, surface extracellular vesicle.

5. Summary

MSC-EVs show marked promise in TB treatment, offering potent immunomodulation, direct antibacterial effects and tissue repair capabilities. MSC-EVs improve pathological outcomes, reduce inflammation and combat Mtb through numerous mechanisms. Furthermore, MSC-EVs improve kidney function, promote weight gain and restore serum adenosine deaminase activity. Targeted elimination of HIF-1α-high/CD146-low MSCs within hypoxic niches could potentially eradicate latent TB infections. MSCs can eliminate Mtb through delivery of ROS and lysosomal enzymes as aforementioned. Technologically, methods such as ultrafiltration combined with liquid chromatography enhance the purity and functional capacity of MSC-EVs. Notably, their therapeutic efficacy is dependent on the tissue source of the parent MSCs. Key challenges requiring resolution include establishing standardized protocols for mass production and determining long-term safety (134-137). In summary, the primary focus of current research encompasses enhancing the preparation techniques of MSC-EVs, elucidating the mechanisms underlying the biological action of MSC-EVs and utilizing MSC-EVs for the treatment of infectious diseases such as TB.

Future research directions include engineering EVs (such as MSC-EVs with high PD-L1 expression, conducting multi-omics studies and accelerating clinical translation. From a technological standpoint, there is a need to continue optimizing existing technologies and to investigate novel isolation strategies in order to improve the purity, yield and efficiency of MSC-EVs. This will provide strong support for the utilization of MSC-EVs in disease diagnosis, treatment and biomarker research, thereby advancing the field of EV-related research towards clinical applications. A key aspect in MSC-EVs clinical translation involves understanding how these conditions, such as temperature, storage duration and freeze-drying affect key properties such as morphology, functionality and therapeutic payload. Research has shown that MSC-EVs maintain their core biological activities, including anti-inflammatory effects and enhanced angiogenesis promotion, for up to 4-6 weeks when stored at temperatures of -20˚C and -80˚C. In addition, freeze-drying successfully preserved these functional properties (138). A combination of *in vitro* experiments and *in vivo* wound healing models has demonstrated that optimal storage conditions not only preserve stability but also ensure the functionality of miRNA and long non-coding RNA cargos within EVs (138). While there is currently a dearth of research specifically investigating the effects of MSC-EVs on Mtb infection utilizing integrated omics methodologies, findings from related studies offer encouraging prospects for utilizing MSC-EVs as therapeutic agents for TB. For example, a recent study took a comprehensive approach by integrating proteomics, metabolomics and transcriptomics analyses to elucidate the inhibitory mechanism of MSC-EVs on the HepG2 cell line of hepatocellular carcinoma, thereby contributing to advancements in this field (139). Despite their potential, current production platforms for MSC-EVs face a number of limitations during clinical application, including variability arising from donor sources, scalability challenges and inconsistent therapeutic outcomes. To effectively address these shortcomings, it is imperative to establish a scalable, standardized production platform that integrates high-quality MSC-EVs manufacturing with artificial intelligence-integrated, fully automated, Good Manufacturing Practice of Medical Products-compliant manufacturing of therapeutic EVs suitable for clinical translation (140). Collectively, MSC-EVs represent a promising novel therapeutic strategy with the potential to address drug-resistant TB and other challenging infections (125,141-143). However, prior to clinical translation, it is important to perform a thorough risk assessment, including analysis of factors such as immunogenicity, potential pro-inflammatory effects and the possibility of promoting TB dormancy.

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YY and LY conceived the review idea and obtained the funding. DF was responsible for organizing the manuscript, designing the narrative to enhance coherence and completing the writing of the manuscript. YY and LY edited the manuscript and provided supervision. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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