The role of mesenchymal stem cell-derived exosomes in asthma (Review)

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Abstract. Asthma is a chronic respiratory disorder characterized by persistent inflammation, airway hyper-responsiveness and remodeling, leading to notable morbidity and decreased quality of life for patients. Mesenchymal stem cells (MSCs) have potential in regenerative medicine due to their potent immunomodulatory properties and anti-inflammatory effects. The therapeutic benefits of MSCs are largely mediated by secreted exosomes that facilitate intercellular communication by transferring bioactive molecules, including proteins, lipids and microRNAs. The present review explores the therapeutic potential of MSC-derived exosomes in asthma, highlighting their ability to modulate key pathological mechanisms underlying the disease.

Contents

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Abbreviations: ASMC, airway smooth muscle cell; BALF, bronchoalveolar lavage fluid; EV, extracellular vesicle; MSC, mesenchymal stem cell; MyD88, myeloid differentiation primary response 88; PI3K, phosphatidylinositol 3-kinase; TGF-β; transforming growth factor-β; TLR4, toll-like receptor 4; Treg, regulatory T cell; EMT, epithelial-mesenchymal transition; ILC2, group 2 innate lymphoid cell; Th2, T helper 2; TNF, tumor necrosis factor; LPS, lipopolysaccharide

Key words: asthma, mesenchymal stem cells, exosome, microRNA, therapy

1. Introduction

Asthma is a chronic respiratory disease characterized by recurrent episodes of airway inflammation, bronchoconstriction and hyperresponsiveness. It affects >300 million individuals globally and contributes to increasing morbidity and healthcare costs (1,2). The etiopathogenesis of asthma involves crosstalk between genetic predispositions and environmental factors, including allergens, infections and pollutants (3). Pathologically, asthma is marked by chronic inflammation of the airway, leading to structural changes and functional impairment (4). Patients with asthma present with intermittent and variable symptoms such as wheezing, shortness of breath, chest tightness and coughing, which result primarily from reversible airway obstruction and vary in intensity and frequency (5,6). Severity of symptoms ranges from mild to life-threatening exacerbations that may require emergency medical intervention (7). Factors such as respiratory infection, allergens and irritants can trigger these exacerbations, highlighting the need for effective long-term management strategies (8).

Current therapeutic strategies for asthma aim to relieve symptoms, improve lung function and decrease the frequency and severity of exacerbations (9). Primary therapeutic approaches include inhaled corticosteroids, long-acting β-agonists, leukotriene modifiers and monoclonal antibodies that target specific immune pathways (10,11). However, these treatments do not fully address the underlying mechanisms of airway remodeling and chronic inflammation, leading to persistent disease progression in patients with poor asthma control and frequent exacerbations (12,13). Therefore, novel therapeutic strategies are needed.

Mesenchymal stem cells (MSCs) are multipotent stromal cells that differentiate into various cell types, including osteocytes, chondrocytes and adipocytes (14). Extracellular vesicles (EVs) are a broad class of vesicles that are secreted by cells into the extracellular space. They can be classified into three subtypes, exosomes, microvesicles and apoptotic bodies, based on their size and mode of release. Exosomes are the smallest subtype of EV, typically 30-150 nm in diameter, and serve key roles in intercellular communication and disease mechanisms (15). MSC-derived exosomes mediate therapeutic effects of MSCs, and have a key role in cell-to-cell communication by transferring bioactive molecules to recipient cells,

affecting their behavior and function (16,17). In asthma, MSC-derived exosomes exert immunomodulatory effects that maintain immune homeostasis and suppress excessive immune responses (18,19). Additionally, they exhibit anti-inflammatory effects by inhibiting inflammation-associated signaling pathways and reducing the levels of pro-inflammatory cytokines, which are beneficial in treating asthma (20,21). Compared with drugs targeting IL-4 and IL-5, such as dupilumab and mepolizumab, MSC-derived exosomes offer a potential advantage by providing a more natural and less invasive approach to modulating immune responses (22). They exert long-term effects because of their ability to simultaneously influence multiple cellular pathways (8). While drugs are designed to target specific cytokines, MSC-derived exosomes serve as a multi-target therapy, potentially exerting more comprehensive effects on asthma (23).

The present review discusses the pathogenesis of asthma and the basics of MSC-derived exosomes and emphasizes their potential therapeutic effect, as well as the prospects and challenges of translating MSC-derived exosome therapy from bench to bedside.

2. Pathological mechanisms of asthma

Asthma is characterized by chronic airway inflammation involving immune cells such as eosinophils, T lymphocytes, mast cells and dendritic cells. These cells release cytokines and chemokines, which perpetuate the inflammatory response and facilitate airway hyperresponsiveness and tissue damage (24,25). These immune cells serve a key role in airway inflammation during disease progression. For example, eosinophils secrete pro-inflammatory cytokines, chemokines, growth factors and lipid mediators that disrupt pulmonary homeostasis and induce inflammatory airway damage (26). They regulate immune responses by modulating T helper 2 (Th2) cell activation, M2 macrophage polarization and group 2 innate lymphoid cell (ILC2) differentiation, as well as upregulating the levels of IL-5 and IL-13, which primarily induce inflammatory tissue damage (27,28). Mast cells, in combination with IgE, are key for initiating inflammation in allergic asthma (29). They release histamine and other inflammatory mediators that contribute to bronchoconstriction and further inflammation (30). Neutrophils, particularly in severe asthma, release nuclear proteins and serine proteases that form neutrophil extracellular traps, which activate inflammasomes in monocytes or macrophages, leading to increased expression of inflammatory cytokines (31).

Chronic inflammation in asthma leads to structural airway alterations, collectively termed airway remodeling (1). This includes epithelial damage, mucous gland hyperplasia, subepithelial collagen deposition and increased proliferation of airway smooth muscle cells (ASMCs) (32-34). These changes cause persistent airflow limitation and airway hyperresponsiveness (35). Airway remodeling is driven by numerous factors, including transforming growth factor (TGF)-β, primarily secreted by bronchial epithelial cells and eosinophils (36). TGF-β promotes extracellular matrix deposition by stimulating fibroblasts and myofibroblasts to produce collagen and fibronectin, contributing to airway hyperresponsiveness (37). However, TGF-β exerts both pro-inflammatory and immunosuppressive effects in asthma during airway inflammation depending on cellular context. Elevated TGF-β1 expression in asthmatic airways aggravate eosinophilic inflammation by activating $CD8^+$ T cells while inhibiting Th1 and Th2 cell differentiation (38). It also modulates regulatory T cell (Treg) differentiation and limits the pathogenicity of $CD4^+$ T cells, thereby alleviating airway inflammation (39).

Numerous signaling pathways contribute to asthma pathogenesis. The NF-κB pathway regulates airway inflammation (40). Various stimuli, including pro-inflammatory factors, viruses, drugs and cigarette smoke, activate NF-κB (41). Once activated, NF-κB translocates to the nucleus and upregulates inflammatory gene expression (42). Another key signaling cascade in asthma is the toll-like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MyD88) pathway (43). Lipopolysaccharide (LPS) binding to TLR4 activates MyD88, leading to NF-κB nuclear translocation and amplification of the inflammatory response (44). Moreover, the phosphatidylinositol 3-kinase (PI3K)/Akt and Wnt/β-catenin signaling pathways are implicated in airway remodeling and hyperresponsiveness (45,46). These pathways contribute to ASMC proliferation and migration and epithelial-mesenchymal transition (EMT), enhancing airway remodeling (47,48).

3. Basics of MSC-derived exosomes

MSCs were first identified by Friedenstein *et al* (49) in the 1960s when they isolated fibroblast colony-forming units from bone marrow. MSCs are present in virtually all postnatal organs and tissues, including the bone marrow, adipose tissue, umbilical cord and placenta (50,51). MSCs express specific surface markers such as CD73, CD90 and CD105 but lack hematopoietic markers such as CD34 and CD45 (52). MSCs can differentiate into osteoblasts, adipocytes and chondroblasts, making them promising candidates for therapeutic application due to their plasticity (53,54).

Exosomes are small EVs ranging from 30 to 150 nm in diameter, released by various cell types into the extracellular environment (55). They originate within the endosomal compartment of the cell and are secreted when multivesicular bodies fuse with the plasma membrane (56) (Fig. 1). Exosomes carry proteins, lipids and nucleic acids, reflecting the content and physiological state of the originating cells (57). This cargo includes mRNA, microRNAs (miRNAs or miRs) and other non-coding RNAs (58-60). The biological properties of exosomes make them key mediators of intercellular communication (61). They influence target cells by transferring their cargo, thereby modulating cellular processes, such as proliferation, differentiation and immune responses (62).

Numerous methods have been developed for exosome isolation and characterization, which are key for studying their biological functions and clinical application. Ultracentrifugation is the most commonly used technique, and is considered the gold standard for exosome isolation. It involves sequential centrifugation steps to remove cells, apoptotic bodies and other EVs, followed by high-speed ultracentrifugation to pellet exosomes (63). By using sucrose or iodixanol gradients to separate exosomes based on density, density gradient centrifugation refines ultracentrifugation and improves purity by separating exosomes from

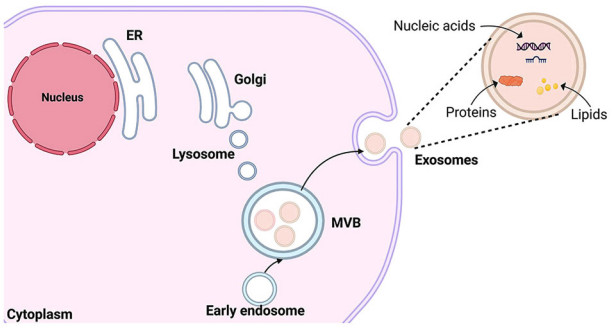

Figure 1. Biogenesis and delivery of exosomes. Early endosomes are produced when the parent cell undergoes endocytosis. It then experiences the second invagination of the plasma membrane, leading to the formation of ILVs. The endosomes that contain ILVs are referred to as MVBs. MVBs fuse with the plasma membrane, releasing the ILVs as exosomes, which are packed with various molecules, including nucleic acids, proteins and lipids. ER, endoplasmic reticulum; ILV, intraluminal vesicle; MVB, multivesicular body.

contaminants (64). Size-exclusion chromatography separates vesicles based on size using porous columns, allowing exosomes to be eluted while smaller proteins and particles are retained, which maintains exosome integrity and biological activity (65). Additionally, polymer-based precipitation uses polymers such as polyethylene glycol to precipitate exosomes from biofluids, followed by low-speed centrifugation to collect the pellet, which is suitable for processing large sample volumes (66). For small sample volumes, microfluidic platforms use nanoscale filtration, immunoaffinity capture or acoustic forces to isolate exosomes with high precision (67). Serving as a highly specific isolation method for exosome subpopulations, immunoaffinity-based isolation uses antibodies targeting exosome surface markers conjugated to magnetic beads or chromatography matrices (68). Standard characterization techniques of exosomes include morphological analysis, size determination, marker profiling and functional validation. Nanoparticle tracking analysis measures the size distribution and concentration of exosomes in a liquid suspension based on Brownian motion (69). Transmission electron microscopy provides high-resolution images of exosomes, allowing visualization of their characteristic cup-shaped morphology (70). By analyzing scattered light fluctuations, dynamic light scattering determines the hydrodynamic diameter of exosomes (71). In addition, western blotting detects exosome-specific protein markers, whereas flow cytometry allows high-throughput analysis using fluorescently labeled antibodies (72). Thus, the combination of multiple techniques can ensure accurate identification and functional validation. Future research should focus on developing standardized protocols and scalable isolation techniques to enhance reproducibility and facilitate clinical translation.

MSC-derived exosomes are key for mediating the therapeutic effects of MSCs. They promote tissue repair and regeneration by transferring growth factors and miRNAs that enhance cell proliferation and differentiation (73). In addition, they modulate immune responses by altering the phenotype and function of immune cells such as T and B cells and macrophages (74). MSC-derived exosomes suppress pro-inflammatory cytokine production and induce anti-inflammatory cytokine release (75). By inhibiting inflammation-associated signaling pathways such as NF-κB, they decrease pro-inflammatory cytokines levels and exert potent anti-inflammatory effects (76). These properties make MSC-derived exosomes promising therapeutic tools for inflammatory and degenerative disease. Their ability to mimic MSC functions while avoiding the risks associated with direct cell transplantation makes them attractive candidates for clinical application.

4. Effects of MSC-derived exosomes on asthma

Immunomodulation. MSC-derived exosomes exhibit immunomodulatory effects, which are key in the context of asthma, a disease characterized by immune dysregulation (77). These exosomes modulate the activity of immune cells, such as T cells and macrophages, suppressing asthma exacerbation. For example, in mice with severe refractory asthma and neutrophil-mediated allergic airway inflammation, systemic administration of exosomes from human bone marrow-derived MSCs ameliorates airway hyperreactivity and pulmonary inflammation by reducing Th2 and Th17 phenotypes (78). Suppressing Th2 and Th17 cell proliferation is important to prevent immune system overactivation during disease progression (79,80). Mechanistically, exosomal miR-146a-5p inhibits Th2 cell differentiation by downregulating expression of plasminogen activator inhibitor-2 (81). Th17 cells serve a key role in the pathogenesis of steroid-resistant asthma, characterized by neutrophilic airway inflammation (82). As an inactivator of Th17 cells, exosomes derived from human MSCs decrease IL-17A levels in bronchoalveolar lavage fluid (BALF) and Th17 cell numbers in lung tissue by suppressing the Janus kinase 2/signal transduction and activator of transcription 3 (STAT3) signaling pathway. This further decreases the infiltration of inflammatory cells, particularly neutrophils (83). Similarly, the increased Treg population can produce anti-inflammatory cytokines such as IL-10 and TGF-β, leading to the maintenance of immune homeostasis in asthma (39,84). Du *et al* (85) demonstrated that MSC-derived exosomes elevate the proliferation and immunosuppressive capacity of Tregs in patients with asthma by upregulating the expression of IL-10 and TGF-β1 in peripheral blood mononuclear cells. miR-1470 within MSC-derived exosomes facilitates the differentiation of $CD4^+CD25^+FOXP3^+$ Tregs in patients with asthma by upregulating $p27^{kip1}$, a cyclin-dependent kinase regulator that controls cell differentiation (86,87). Therefore, exosomes from MSCs modulate T cell activation and proliferation, decrease overactivated immune responses and further mitigate asthma severity. MSC-derived exosomes also mediate the polarization of macrophages towards the M2 phenotype, which is associated with anti-inflammatory and tissue repair function (88). Exosomes from MSCs from human umbilical cord inhibit M1 macrophage polarization and induce M2 polarization by targeting tumor necrosis factor receptor-associated factor 1 (89). They suppresses NF-κB and PI3K/Akt signaling, and reduce airway hyperresponsiveness and damage, highlighting the therapeutic function of MSC-derived exosomes in moderating immune responses through macrophage polarization (89).

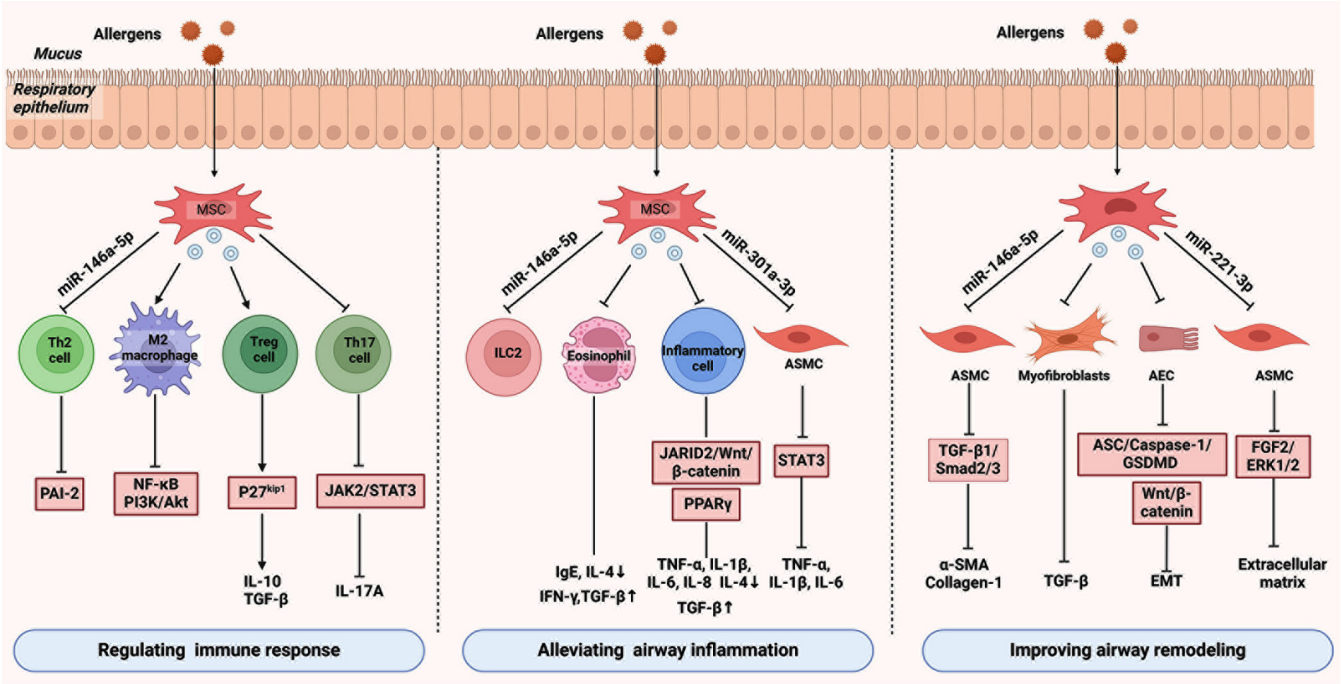

Figure 2. Role of MSC-derived exosomes in asthma. MSC-derived exosomes regulate the immune response, alleviate airway inflammation and improve airway remodeling by acting on key cells, such as T lymphocytes, macrophages, AECs and ASMCs. They regulate the secretion of inflammatory cytokines by influencing signaling pathways, such as JAK2/STAT3, JARID2/Wnt/β-catenin and TGF-β1/Smad2/3. AEC, airway epithelial cell; ASMC, airway smooth muscle cell; α-SMA, α-smooth muscle actin; EMT, epithelial-mesenchymal transition; FGF2, fibroblast growth factor 2; GSDMD, gasdermin D; ILC2, group 2 innate lymphoid cell; IL, interleukin; JARID2, Jumonji, AT-rich interaction domain containing 2; MSC, mesenchymal stem cell; miR, microRNA; STAT3, signal transduction and activator of transcription 3; TGF-β, transforming growth factor-β; Th, T helper; Treg, regulatory T cell; PPAR, peroxisome proliferator-activated receptor γ; PAI-2, plasminogen activator inhibitor-2.

In summary, MSC-derived exosomes exert immunomodulatory effects on asthma by modulating immune cell populations, including Th17 cells, Tregs and macrophages, through distinct signaling pathways and miRNA-mediated mechanisms. Their therapeutic potential in asthma management offers a novel approach for treating severe and refractory forms of the disease. Future studies should focus on elucidating the precise mechanisms of action to validate these findings in preclinical settings

Airway inflammation. Anti-inflammatory properties of MSC-derived exosomes are attributed to their ability to decrease the infiltration of inflammatory cells and generation of pro-inflammatory cytokines in the airway (85,90). For example, MSC-derived EVs decrease inflammatory cell counts within the lung tissue and alleviate cellularity and eosinophilia in BALF, which is associated with lower levels of eotaxin-2 in a murine model of allergic airway inflammation (91). Ovalbumin-loaded MSC-derived exosome formulation decreases levels of inflammatory cells and eosinophilia in the lung tissues. This effect is accompanied by reduced IgE and IL-4 levels but elevated interferon (IFN)-γ and TGF-β production (90). Moreover, exosomes carry anti-inflammatory molecules, such as miRNAs, that modulate the infiltration of inflammatory cells and expression of cytokines (88,92). MSC-derived exosomal miR-146a-5p hinders the function of ILC2s and decreases inflammatory cell infiltration, pulmonary mucus production and Th2 cytokine secretion, thus alleviating airway hyperresponsiveness in a mouse model of ILC2-dominant asthma (83). By inhibiting the Jumonji AT Rich interacting domain 2/Wnt/β-catenin axis, miR-188 from MSC-derived exosomes decreases inflammation infiltration, mucus production and collagen deposition in lung tissue of asthmatic mice (93). Additionally, in LPS-stimulated alveolar macrophages, MSC-derived conditioned medium can modulate the release of TNF-α, IL-6, and TGF-β1. This indicates the therapeutic potential of MSC-derived exosomes in lung inflammatory disorder (94). Similarly, exosomes from MSCs have been shown to downregulate the transcription and protein expression of pro-inflammatory cytokines such as IL-1β, IL-8 and IL-6 by upregulating the expression of peroxisome proliferator-activated receptor γ, which serves as a transcription factor controlling anti-inflammatory and antioxidant mechanisms via NF-κB and heme oxygenase-1, thereby attenuating inflammation and oxidative stress in asthma (95). By preventing the activation of STAT3, exosomal miR-301a-3p from adipose-derived MSCs decreases the generation of inflammatory factors, including TNF-α, IL-1β and IL-6, in ASMCs treated with platelet-derived growth factor. This is accompanied by suppressed proliferation and migration of ASMCs, thus alleviating airway inflammation and remodeling in an ovalbumin-induced asthma mouse model (96). The aforementioned studies highlight the potential of MSC-derived exosomes in modulating airway inflammation in asthma.

Altogether, MSC-derived exosomes impede inflammatory cell infiltration and pro-inflammatory cytokine production by

Table I. Exosomal miRs derived from MSCs that inhibit asthma progression.

First author, year	Exosomal miRs	Downstream target	Outcome	Experimental model	(Refs.)
Zhou *et al*, 2021	miR-146a-5p	SERPINB2	Inhibits the differentiation of Th2 cells and allergic inflammation	Patients with allergic rhinitis	(81)
Fang *et al*, 2020	miR-146a-5p	Unknown	Decreases ILC2 levels, inflammatory cell infiltration and mucus production in the lung, as well as Th2 cytokines and airway hyperresponsiveness	IL-33-stimulated ILC2, IL-33-treated mice	(83)
Zhuansun *et al*, 2019	miR-1470	c-Jun/$p27^{kip1}$	Upregulates the proportion of $CD4^+CD25^+FOXP3^+$ Tregs and inhibits asthma progression	IL-2-stimulated $CD4^+$ T cells	(86)
Shan *et al*, 2022	miR-188	JARID2/Wnt/β-catenin	Attenuates the proliferation and migration of ASMCs, as well as decreasing inflammatory cell infiltration, mucus production and collagen deposition in lung tissue	TGF-β1-stimulated ASMCs, OVA-sensitized mice	(93)
Feng *et al*, 2022	miR-301a-3p	STAT3	Suppresses the proliferation and migration of ASMCs, as well as decreasing the secretion of inflammatory factors and lung injury	PDGF-treated ASMCs, OVA-sensitized mice	(96)
Liu *et al*, 2022	miR-221-3p	FGF2/ERK1/2	Attenuates the proliferation, migration and ECM deposition in ASMCs and alleviates airway hyperresponsiveness and asthma progression	TGF-β1-treated ASMCs, OVA-sensitized mice	(103)
Dong *et al*, 2021	miR-146a-5p	TGF-β1/Smad2/3	Decreases levels of IL-4, IL-13 and eosinophils, as well expression of α-SMA and collagen-1	TGF-β1-stimulated fibroblasts, OVA-sensitized mice	(104)
Li and Yang, 2023	miR-223-3p	NLRP3/ASC/caspase-1/GSDMD	Mitigates airway inflammation and remodeling	OVA-sensitized mice	(105)

ASMC, airway smooth muscle cell; α-SMA, α-smooth muscle actin; FGF2, fibroblast growth factor 2; GSDMD, gasdermin D; ILC2, group 2 innate lymphoid cell; JARID2, Jumonji, AT-rich interaction domain containing 2; MSC, mesenchymal stem cell; miR, microRNA; NLRP3, NOD-like receptor family pyrin domain-containing 3; SERPINB2, serpin family B member 2; TGF, transforming growth factor; Th, T helper; Treg, regulatory T cell; OVA, ovalbumin; PDGF, platelet-derived growth factor; ASC, apoptosis-associated speck-like protein.

modulating key inflammatory signaling pathways, providing new avenues for developing effective and targeted therapies for asthma. Further research is needed to identify the precise molecular mechanisms by which MSC-derived exosomes exert anti-inflammatory effects in asthma.

Airway remodeling. As a hallmark of chronic asthma, airway remodeling is characterized by structural changes, such as subepithelial fibrosis, increased smooth muscle mass and mucus gland hyperplasia, which can be mitigated by MSC-derived exosomes (97,98). For example, exosomes from MSCs inhibit the deposition of collagen fibers in the airway and lung parenchyma and reduce eosinophil counts in lung tissue and BALF, thereby decreasing subepithelial fibrosis. This effect is mediated by the downregulation of fibrogenic factors, such as TGF-β, and the inhibition of myofibroblast differentiation (99). Furthermore, MSC-derived exosomes decrease the number of immune cells in BALF, proliferation of goblet cells and deposition of collagens by inactivating the Wnt/β-catenin signaling pathway, which ameliorates EMT and airway remodeling in asthmatic rats (100). Furthermore, MSC-derived exosomal miRNAs decrease allergic airway inflammation and further alleviate airway remodeling by modulating signaling pathways involved in ASMC proliferation and migration (101,102). This helps prevent thickening of the airway wall and maintain airway patency (97). Exosomal miR-221-3p derived from human bone marrow MSCs can restrict ASMC proliferation, migration and extracellular matrix deposition by targeting fibroblast growth factor 2, thus inhibiting the ERK1/2 signaling pathway, which lessens airway hyperresponsiveness and histopathological damage in an ovalbumin-induced asthmatic mouse model (103). Similarly, exosomal miR-146a-5p derived from human umbilical cord MSCs cultured under hypoxic conditions is capable of decreasing the expression of profibrogenic markers such as α-smooth muscle actin and collagen-1. It is associated with the suppression of TGF-β1/Smad2/3 signaling pathway, thus ameliorating airway remodeling in mice with chronic asthma (104). Li and Yang (105) revealed that miR-223-3p, which is highly expressed in bone marrow MSC-derived exosomes, alleviates airway inflammation and remodeling by targeting the nucleotide-binding domain, leucine-rich–containing family, pyrin domain-containing-3-induced apoptosis-associated speck-like protein/caspase-1/gasdermin D signaling pathway (105), which accelerates the restoration of the epithelial barrier function and decreases mucus hypersecretion. The aforementioned findings suggest therapeutic potential of MSC-derived exosomes in addressing airway remodeling in asthma.

MSC-derived exosomes ameliorate airway remodeling through various mechanisms, including the inhibition of key signaling pathways associated with ASMC proliferation and migration, modulation of immune cell function and suppression of pro-inflammatory cytokines. Future research should focus on the precise molecular mechanisms underlying the severity of asthma. MSC-derived exosomes may represent a promising frontier in the development of innovative therapy for asthma.

In conclusion, MSC-derived exosomes alleviate asthma progression by modulating immune responses and mitigating airway inflammation and remodeling (Fig. 2). They modulate multiple molecular pathways, including NF-κB, TGF-β/Smad and JAK/STAT, which are central to inflammation and tissue remodeling in asthma. Therefore, MSC-derived exosomes have a potential as treatments for asthma. Future investigations should focus on identifying the mechanisms by which these exosomes suppress pathological processes and alleviate disease severity. Exosomes from MSCs transfer proteins such as ovalbumin that are decorated with a dendritic cell-specific aptamer, which have been shown to improve the efficacy of specific immunotherapy in asthma model (106). Furthermore, MSC-derived exosomal miRNAs inhibit disease progression (81,83,93,96,103-105) (Table I). Targeting exosomal miRNAs presents a novel therapeutic approach for asthma treatment. Strategies to control exosomal miRNA activity include the use of miRNA mimics to restore the function of downregulated miRNAs and miRNA inhibitors to block the activity of upregulated miRNAs (107,108).

5. Future directions

MSC-derived exosomes offer a novel therapeutic approach for asthma with the potential to modulate immune responses, decrease inflammation and repair airway damage (83,86). Their ability to deliver bioactive molecules such as proteins, lipids and nucleic acids to target cells makes them a versatile tool for therapeutic intervention. The immunomodulatory and anti-inflammatory properties of MSC-derived exosomes have been demonstrated in various preclinical models (103-105), demonstrating promise for decreasing asthma symptoms and improving lung function.

Despite their therapeutic potential, several challenges must be addressed before MSC-derived exosomes can be translated into clinical application. First, standardizing exosome isolation and characterization methods is essential to ensure reproducibility and consistency. Different techniques used to isolate exosomes, such as ultracentrifugation, size exclusion chromatography and immunoaffinity capture, yield exosomes with varying purity and characteristics, potentially affecting their therapeutic efficacy. Secondly, understanding the pharmacokinetics and biodistribution of MSC-derived exosomes is key for optimizing their therapeutic use. The mechanisms underlying their uptake, distribution and clearance *in vivo* need to be investigated to improve targeted delivery to the lungs and minimize off-target effects. Additionally, the potential immunogenicity and long-term safety of MSC-derived exosomes require evaluation in both preclinical and clinical studies.

Further research is essential to elucidate the therapeutic potential of MSC-derived exosomes. Future studies should focus on defining their mechanisms of action, determining optimal dosing regimens and exploring combination therapies to enhance their efficacy. Advances in exosome engineering may enable the customization of exosome content and surface modification to improve their targeting and therapeutic effects. Moreover, the development of advanced delivery systems to enhance targeted lung delivery is key for maximizing the therapeutic potential of MSC-derived exosomes.

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Authors' contributions

KL, JG and LY wrote and revised the manuscript. XY edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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