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Review article

The effects of mesenchymal stem cells on asthma

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Abstract

Asthma is an inflammatory disease of the respiratory system characterized by cough, shortness of breath, wheezing, sputum, obstruction and bronchial hyperactivity. Asthma leads to disruption of epithelial structure, subepithelial fibrosis, inflammation, and ultimately airway reorganization. MSCs migrate into inflammatory tissue and settle there. Once in the tissue, the MSCs suppress inflammation and improve the internal structure of the tissue. These effects are achieved by transforming into tissue cells, producing anti-inflammatory and growth factors, and releasing microRNAs and extracellular vesicles. The effect of MSCs on asthma is based mostly on *in vivo* experimental animal models and *in vitro* studies of airway cells. While ovalbumin, cockroach extract and house dust mite are mostly used for *in vivo* experimental animal models, airway smooth muscle cells are mostly used for *in vivo* studies. This study aims to objectively present the information obtained from reliable articles about whether MSCs can be used in the treatment of asthma, a chronic inflammatory lung disease.

Keywords: *Asthma models; identification of MSCs; inflammatory disease; mesenchymal stem cells*

1. Introduction

Asthma affects more than 300 million people worldwide (Di Cicco et al., 2023). Airway remodeling and inflammation occur in patients with asthma. In addition, asthma-induced structural changes include disruption of epithelial structure, goblet cell hyperplasia, subepithelial fibrosis and increased smooth muscle hypertrophy. These changes lead to airway obstruction, cough, sputum production, hyperreactivity and impaired lung function (Lambrecht et al., 2017; Banno et al., 2020). Therefore, while the most common treatments for asthma are mainly anti-inflammatory agents and bronchodilators (Xie et al., 2018), new treatments and therapeutic targets are needed to better control symptoms and exacerbations in patients with severe asthma and to protect them from the side effects of medications (Cevhertas et al., 2020).

Mesenchymal stem cells (MSCs) have been shown to localize mostly in the lungs after intravenous injection (Brychtova et al., 2019). MSCs provide therapeutic effects for asthma, an inflammatory lung disease, by controlling cellular activity or releasing bioactive factors (Bonfield et al., 2010). Airway hyperresponsiveness (AHR) and bronchoalveolar lavage fluid counts in mice sensitized with ovalbumin (OVA) were considerably reduced by both single and double human mesenchymal stem cell (hMSC) treatments. Furthermore, a single hMSC treatment significantly reduced allergic airway inflammation. However, inflammatory cell infiltration and TH2 cytokine levels were further elevated by repeated treatment with hMSCs during OVA sensitization and challenge (Hur et al., 2020). Both *in vitro* and *in vivo* (by inhalation), MSC-EV treatment encouraged macrophage polarization toward an M2 phenotype. The activity of MSC-EVs against acute lung injury (ALI) was linked to immunological and redox mediators, such as TLR4, ARG1, and HO-1, according to RNA sequencing (Zhao et al., 2022). Administration of normoxic human umbilical cord MSC-EVs (Nor-EVs) or hypoxic MSC-derived EVs (Hypo-EVs) to animals with OVA-induced asthma significantly improved pro-inflammatory mediators (IL-4 and IL-13), eosinophils, and bronchoalveolar lavage fluid (BALF) total cells (Liyang Dong et al., 2021). In conclusion, asthma,

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which has not yet been fully treated, is an inflammatory disease and MSCs have anti-inflammatory and immunomodulatory effects. Therefore, this study aims to evaluate the effect of MSCs on asthma, a respiratory system disease, and to provide information to researchers and physicians about whether MSCs can be an alternative treatment for asthma.

2. The effect of mesenchymal stem cells on asthma

2.1. In vivo studies

2.1.1. Ovalbumin-induced asthma model

OVA makes up more than half of egg white. OVA contains 386 amino acid residues with acetylated glycine at the N-terminal end and proline at the C-terminal end. Thirty percent of OVA's amino acid residues are acidic, and fifty percent are hydrophobic. In addition, OVA contains four free sulfhydryl groups, one disulfide connection, and six cysteine residues. Moreover, OVA may exhibit antioxidant properties thanks to its ability to bind metal ions and may cause allergies (Rostamabadi et al., 2023). OVA is used to create an experimental animal asthma model. For this purpose, OVA can be administered intravenously, intraperitoneally, intratracheally and intranasally (Leite-Santos et al., 2023).

Studies on the direct use of MSCs: MSCs are thought to be effective in the treatment of asthma, an inflammatory disease, due to their immunomodulatory properties. Airway inflammation and remodeling were found to be evident in asthmatic mice. In addition, low levels of IL-12, fewer CD4+CD25+ regulatory T cells, and high levels of IL-4, IL-13, OVA-specific IgE, IgG2a, and IgG1 were detected in the asthmatic group. The use of BM-MSCs for transplantation notably reduced airway remodeling and inflammation, the level of OVA-specific IgE, OVA-specific IgG1, and IL-4, but increased the number of CD4+CD25+ regulatory T cells and the level of IL-12 in asthmatics. BM-MSCs did not support lung regeneration and IFN-γ, IL-13, and IL-10 levels were not significantly affected by BM-MSCs (Ge et al., 2013). In a study comparing the effects of BM-MSCs and AD-MSCs, hBM-MSC treatment significantly reduced airway hyperresponsiveness, but hAD-MSC treatment did not. Although both MSCs decreased airway inflammation, the effects of hBM-MSCs were typically more significant. Treatment with hBM-MSCs decreased Th2-cytokine levels, but not with hAD-MSCs. Serum resistin-like molecule-β level was found to be lower in asthma patients than in controls, but increased in both treatment groups (Choi et al., 2022). Intravenous Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) administration decreased mucus production, inflammation and airway resistance in a mouse model of asthma. hUC-MSCs not only attenuated Th17 cells and Th2 cells, but also enhanced regulatory T cells (Tregs). In addition, hUC-MSCs successfully inhibited ILC2s by down-regulating key regulators of ILC2s, such as *Tcf7 and Gata3* (Innate to lymphoid cells). As a result, hUC-MSCs decreased the total quantity of macrophages, particularly the percentage of the population composed of macrophages produced from monocytes. Upon closer inspection of monocyte-derived macrophages, hUC-MSCs were found to lower M2c and M2a populations (Ahmadi et al., 2017; Kang et al., 2017; Mo et al., 2022) (Table 1). Methacholine-bronchial hyperresponsiveness and eosinophil count in bronchoalveolar lavage fluid cells significantly decreased upon administration of huMSCs. In a similar way, following huMSC injection, lung and spleen tissues produced significantly fewer Th2 cytokines (IL-5, IL-13, and IL-4) and IgG1 and IgE levels, and additionally, the proportion of regulatory T cells increased (Kang et al., 2017). It was noted that rBM-MSCs restored the synthesis of INF-γ, IL-12, IL-5, VCAM-1, and ICAM-1 to normal levels and significantly reduced pathological injuries in lung samples of asthmatic rats (Rahbarghazi et al., 2019) . When gum-derived mesenchymal stem cells were used in another study, they found that MSCs greatly reduced eosinophil infiltration by blocking the growth of CD11b+CD11c+ proinflammatory dendritic cells (DCs) and the differentiation of Th2 cells. It was also revealed that gingival-derived mesenchymal stem cells' production of hepatocyte growth factor effectively reduced airway inflammation (Fang et al., 2024). In lung tissue, MSC injection was observed to significantly inhibit macrophage M2 polarization. Additionally, in a chronic allergy mouse model caused by OVA, MSC treatment decreased oxidative stress, ER stress, and nuclear translocation of NF-κB p65. MSC treatment stopped OVA-induced chronic airway remodeling through these processes (Yu et al., 2024). To sum up, MSCs allowed inflammatory cells to infiltrate and controlled the pathogenic milieu brought on by asthma (He et al., 2024).

Studies on the use of MSC conditioned media (CM): MSCs secrete various cytokines, growth factors and extracellular vesicles into the conditioned medium in which they are grown. Therefore, CMs are expected to have therapeutic effects, and various studies have been conducted to reveal these effects. It was found that systemic administration of CM in repeated dosages can notably decrease pathological injuries through modulation of GATA-3 and T-bet expression in lung tissues and interleukin levels. In contrast, CM administered in a single dose did not provide any beneficial effects (Keyhanmanesh et al., 2018). In asthmatic groups, it was demonstrated that both CM and BM-MSCs altered the synthesis of IL-10 and IL-4 to a level comparable to control rats. Histopathological examination showed that the administration of CM, and particularly mesenchymal stem cells, significantly decreased the amount of lung damage in asthmatic rats (Rahbarghazi et al., 2019) (Table 1). Systemic injection of rBM-MSCs, but not CM, reduced the levels of IL-13, IL-10, IL-4, miRNA155, miRNA133, and pathological changes. The result of the current study demonstrated the potential role of MSCs, but not CM, in decreasing pathological changes during asthma changes, probably through the modulation of miRNA133 and miRNA155 (Ahmadi et al., 2018).

Studies on the use of MSC exosomes: MSC-derived exosomes constitute an important source of the therapeutic effects of MSCs. Therefore, MSC-Exosomes can be used for therapeutic purposes. MSC-Exo can significantly expand spleen-derived lung IL-10-producing IMs and thus contribute to protection against allergic asthma in mice. After intranasal administration of MSC-derived exosomes, lung IM rates increased significantly and high levels of IL-10 were produced (Ren et al., 2021). *In vitro*, hypo-EV therapy enhanced the expression of ZO-1 and E-cadherin proteins and markedly improved the rise in airway cell permeability. Hypo-EV therapies were found to significantly increase caveolin-1 (CAV-1). The positive effects of Hypo-EVs on airway inflammation and remodeling in asthmatic mice were substantially eliminated when CAV-1 was reduced. It was discovered that nebulizing Hypo-EVs could treat other barrier-problem disorders and improve airway epithelial barrier abnormalities in asthma by

Table 1
The effect of MSCs on asthma.

The type of MSC or product being used	The effect of MSCs on asthma	References
hUC-MSCs	hUC-MSCs administration decreased mucus production, inflammation and airway resistance in a mouse model of asthma. hUC-MSCs not only attenuated Th17 cells and Th2 cells, but also enhanced regulatory T cells (Tregs).	(Ahmadi et al., 2017; Kang et al., 2017; Mo et al., 2022).
CM, and MSCs	Histopathological examination showed that the administration of CM, and particularly mesenchymal stem cells, significantly decreased the amount of lung damage in asthmatic rats	(Rahbarghazi et al., 2019).
hypo-EVs and nor-EVs	Compared to Nor-EVs, hypo-EVs were more successful in suppressing the chronic allergic airway remodeling in mice, as evidenced by decreased levels of collagen-1, the pro-fibrogenic markers alpha-smooth muscle actin (alpha-SMA), and the TGF-β1-p-smad2/3 signaling pathway	(Liyang Dong et al., 2021).
iPSC-MSC	Induced pluripotent stem cell-derived *MSC* (iPSC-MSC) transplantation was found to significantly reduce T helper 2 cytokines, attenuate mitochondrial malfunction in epithelial cells and reduce asthma inflammation.	(Yao et al., 2018)
MSCs	Multiple doses of MSCs reduced lung inflammation and remodeling, while inducing immunosuppression in allergic asthma brought on by HDM.	(Castro et al., 2020)

supplying CAV-1 to decrease p-STAT6 expression (Luo et al., 2024). It was found that giving hUC-MSC migrasomes-recently discovered extracellular vesicles that promote intercellular communication-significantly reduced the symptoms of mucus production and airway inflammation in asthmatic mice. Furthermore, dendritic cell (DC) activation was prevented, and Th2 cytokine production (IL-4, IL-5, and IL-13) was decreased (Gu et al., 2025). It was found that miR-223-3p, which is highly abundant in exosomes, may promote airway remodeling and have protective effects on asthma by regulating the ASC/Caspase-1/GSDMD signaling pathway (Tortosa-Martinez et al., 2023). An inverse relationship was observed between asthma induction and BM-MSC transplantation. A substantial correlation was found between Mmu-miR-21a-3p and the Type IIA immune regulatory activin receptor (Acvr2a). mmu-miR-21a-3p was significantly correlated with immune regulatory activin Areceptor, Type IIA (Acvr2a). Mmu-miR-21a-3p had the opposite correlation with Acvr2a after BM-MSC treatment and asthma. MiR-21a binding sites were present in Acvr2a in both humans and mice. This indicated that the miR-21/Acvr2a axis was conserved between humans and mice. mmu-miR-21a-3p was found to negatively regulate Acvr2a transcript (Tang et al., 2016). In summary, administering MSC-EVs improves a variety of asthma pathology-related factors. Additionally, the source, dosage, frequency, and timing of MSC-EV administration affect the therapy's outcome (Firouzabadi et al., 2024).

Studies on the use of pre-treated MSCs and MSC secretomes: Pre-treatment of MSCs affects the survival time of MSCs, their oxidative-antioxidative systems, their adhesion ability and the cytokines and extracellular vesicles they secrete. Changes in these factors are reflected in the therapeutic effects of MSCs. MSC proliferation, extracellular vesicle release, and self-renewal are all influenced by oxygen content. Therefore, the anti-asthma effect of MSCs can be enhanced under hypoxic conditions. Administration of Hypo-EVs or Nor-EVs notably improved eosinophils, pro-inflammatory mediators (IL-4 and IL-13), and BALF total cells in asthmatic mice. In asthmatic mice, hypo-EVs were often more effective than nor-EVs at reducing airway inflammation. Compared to Nor-EVs, hypo-EVs were more successful in suppressing the chronic allergic airway remodeling in mice, as evidenced by decreased levels of collagen-1, the pro-fibrogenic markers alpha-smooth muscle actin (alpha-SMA), and the TGF-β1-p-smad2/3 signaling pathway. Hypo-EVs inhibited the expression of p-smad2/3, alpha-SMA, and collagen-1 in human lung fibroblasts (HLF-1 cells) that were activated by TGF-β1 *in vitro* (Liyang Dong et al., 2021) (Table 1).

MSC-associated immunomodulatory effects may be enhanced by inflammatory cytokines. For this purpose, studies have been conducted to determine how IFN-γ and tumor necrosis factor-alfa (TNF-α) may affect the therapeutic effects of MSCs. Treg and Th9 cells show anti- and pro- allergic activity, respectively. Th9- and Treg-related parameters did not differ significantly between untreated asthmatic mice and those treated with uninduced MSCs. Compared with the untreated asthmatic group, treatment with IFN-γ-induced MSCs notably decreased lung expression of PU.1 and IL-9 and serum IL-9 levels, and increased lung expression of FOXP3 and serum IL-35 levels. Treatment with TNF-α-derived MSCs significantly reduced serum IL-9 levels and lung expression of IL-9. All examined Treg and Th9-related parameters were substantially impacted by treatment with "IFN-γ+TNF-α"-derived MSCs. Compared with mice treated with uninduced MSCs, serum IL-9 levels were significantly reduced in mice treated with "IFN-gamma+TNF-alpha"-induced MSCs. IFN-γ and "IFN-γ+TNF-α"-treated MSCs were more effective than TNF-α-exposed MSCs (Dong et al., 2021). In comparison to untreated MSC groups, calcitriol-treated MSCs dramatically raised IL-12, TGF-β, and IFN-γ levels in a study. Additionally, MSCs treated with and without calcitriol decreased IL-4 and IL-17 levels more than the asthmatic groups did. Histopathological analysis revealed that, in comparison to the asthma group, calcitriol-treated MSCs decreased the formation of inflammatory cells and the thickness of the bronchial Wall (Ghalavand et al., 2023). Some of the studies that aim to enhance the therapeutic effects of MSCs are based on pre-treatment of MSCs with certain drugs. For this purpose, a study was conducted on the treatment of MSCs with the anti-fibrotic drug serelaxin (RLN). Combined administration of MSC and RLN further reversed OVA-induced airway inflammation and airway/lung fibrosis and further increased MMP-9 levels compared to treatment alone. RLN enhanced MSCs' therapeutic outcomes in a chronic illness context which was most likely due to RLN's capacity to restrict matrix production triggered by TGF-β1 (Royce et al., 2015).

Studies on the use of recombinant MSCs and MSC secretomes: Released into the cytosol or extracellular environment, a variety of metabolic products and mitochondrial constituents can act as damage-associated molecular models and induce inflammation (Marchi et al., 2023). Excreted mitochondrial products and elements may encourage inflammation when associated with damage and suppress inflammation when healthy. In this context, mitochondrial transfer from bone marrow MSCs to damaged epithelial cells may result in reduced acute lung injury in mice. Induced pluripotent stem cell-derived MSC (iPSC-MSC) transplantation was found to significantly reduce T helper 2 cytokines, attenuate mitochondrial malfunction in epithelial cells and reduce asthma inflammation. The formation of tunneling nanotubes (TNTs) occurred between iPSC-MSCs and epithelial cells, and it was discovered that iPSC-MSCs transferred mitochondria to epithelial cells both *in vivo* and *in vitro* using TNTs. Connexin 43 was found to mediate mitochondrial transfer between iPSC-MSCs and epithelial cells, and the modulation of TNT synthesis was significantly influenced by it (Yao et al., 2018) (Table 1). However, administration of iPSC-MSCs before inflammation occured also led to protective effects. Mice treated with human iPSC-MSC systemic injection before developing asthma were shielded from the negative effects of long-term allergic airway inflammation, particularly fibrosis and improved remodeling of the airways (Zhong et al., 2019).

Downregulated miR-138 alleviated the inflammatory response and promoted wound healing in diabetic foot ulcer rats by activating the hTERT and PI3K/AKT pathway. After suppression of miR-138, the level of inflammatory cytokines decreased, while the amount of healing factors and anti-inflammatory increased *in vitro* and *in vivo* (Wang et al., 2022). In a study on whether there is a connection between miR-138 and the effect of MSCs on asthma, binding between miR-138-4p and SIRT1 was determined. SIRT1 was upregulated upon inhibition of miR-138-5p. Inhibition of miR-138-5p caused hMSCs to elicit an attenuated inflammatory response after TNF-α and IL-6 stimulation, leading to the release of histamine and ovalbumin-specific IgG, as well as allergic symptoms in mice. hMSCs with miR-138-5p inhibition demonstrated features of active SIRT1 and repressed the TLR4/HMGB1 pathway (Tang et al., 2021). MSCs transfected to express the *IL-35 gene* were able to control allergic asthma symptoms significantly better than MSCs lacking IL-35 (Bao et al., 2023).

2.1.2. Cockroach extract (CRE)-induced asthma model

For almost 60 years, cockroach allergies have been linked to the onset of asthma. Beginning in the 1990s, the determination of allergens in cockroaches led to the current listing of 20 confirmed allergy categories in the World Health Organization and International Union of Immunological Societies (WHO/IUIS) allergen nomenclature database, and this process is ongoing. Cockroach allergens are used in experimental animal models of asthma and can be administered intranasally, intratracheally and intraperitoneally (Pomes and Arruda, 2023).

While the macrophage M1 phenotype is pro-inflammatory, the M2 phenotype has an anti-inflammatory characteristic. MSCs significantly decreased mRNA levels of IL-1β, NOS2, and IL-6 as M1 markers, while notably increased mRNA levels of selected M2 markers such as FIZZ1, YM-1, and ARG-1. Furthermore, it was shown that aryl hydrocarbon receptor (AhR) signaling notably increased throughout the pathogenesis of asthma. It was also shown that high AhR signaling could alleviate the onset of asthma. The use of an AhR antagonist (CH223191) led to significant inhibition of AhR signaling and increased expression of M2 markers, but elevated expression of M1 markers in the CRE-induced asthma model. MSC were shown to be able to modulate macrophage polarization through activation of AhR signaling during CRE-induced asthma (Cui et al., 2020). MSCs not only had an anti-inflammatory effect in asthma by supporting macrophage polarization towards M2, but also increased tissue regeneration and repair by activating TGF-beta 1 signaling. TGF-β1 signaling was observed to be more activated in MSCs treated with CRE. Transforming growth factor beta 1 had an important effect on the collection of stem cells for tissue regeneration, repair and remodeling. When TbR1 inhibitors or TGF-β1 neutralizing Ab substantially reduced MSC migration, TGF-β1 neutralizing Ab prevented MSC recruitment stimulated by CRE but encouraged inflammation of the airways (Xu et al., 2014). Compared with mice used as controls, the lungs' tissues from mice with asthma exhibited a higher synthesis of active RhoA. Another way that MSCs repair the devastating effects of asthma was through differentiation into damaged epithelial cells and collagen. RhoA-L63 expression promoted MSC development into fibroblasts and myofibroblasts, while differentiation toward epithelial cells was changed by RhoA-19 expression (Ke et al., 2019). In conclusion, MSCs created an anti-inflammatory and regenerative effect in animals with cockroach-induced asthma.

2.1.3. House dust mite (HDM)-induced asthma model

It has been demonstrated that HDMs are significant sources of indoor allergens linked to allergies, including asthma. *D. farinae* (Df), *D. pteronyssinus* (Dp), *B. tropicalis* (Bt), and *E. maynei* (Em) are the most prevalent dust mite species found in the world (Milián and Díaz, 2004). House dust mites are used in experimental animal models of asthma and are administered to the animal intratracheally or intranasally.

Since MSCs have immunomodulatory qualities and the host's ability to tolerate them, they may be used therapeutically to treat asthma, but previous evidence indicates that blood-borne progenitor cells may participate in airway remodeling. MSCs were found to localize to the lungs and rapidly reduce airway inflammation in association with increased T-helper-1 lung cytokines. However, this effect was diminished under constant allergen challenge despite the permanent presence of MSCs. Therapeutic MSC infusion in experimental mouse asthma did not create undesirable side effects and was able to improve airway hyperresponsiveness and contractile tissue remodeling (Marinas-Pardo et al., 2014). hUC-MSC administration alleviated lung type 2 (Type 2 and th2 innate lymphoid cell) inflammation in both diesel exhaust particle (DEP)/HDM-induced and alternaria alternata-induced asthma models. These consequences, however, could only be proven with certain treatment regimens and schedules. *In vitro* co-culture revealed that hUC-MSC down-regulated IL-13 and IL-5 synthesis of peripheral blood mononuclear cells and differentiated mouse Th2 cells taken from people with asthma. Thus, these findings suggested that hUC-MSCs could improve asthma by decreasing the generation of asthmagenic cytokines by effector cells (Shin et al., 2021). However, how many doses of MSCs should be administered is also an important issue. In a study conducted to investigate this, two and three MSC dosages reduced lung inflammation, IL-13, eotaxin and IL-4 levels, CD4+ T cell,

eosinophil and total leukocyte counts in bronchoalveolar lavage fluid, and total leukocyte counts in spleen, mediastinal lymph nodes and bone marrow. Two and three MSC dosages also reduced TGF-β levels and collagen fiber content in lung tissue, but the three-dosage frequency worked better, reducing these parameters to control levels while also reducing alpha-actin content in lung tissue. Multiple doses of MSCs reduced lung inflammation and remodeling, while inducing immunosuppression in allergic asthma brought on by HDM (Castro et al., 2020) (Table 1). In a study, a medium that produced CATT7-MIF-licensed MSCs with elevated VEGF levels (CATT7-MIF MSC CM) greatly accelerated the migration and proliferation of bronchial epithelial wounds *in vitro*. This impact was eliminated by using mitomycin C or blocking VEGFR2. Furthermore, upon HDM exposure, CATT7-MIF MSC CM markedly decreased goblet cell hyperplasia *in vivo*. The application of an anti-human VEGF neutralizing antibody eliminated this impact, confirming that it was VEGF-dependent (Dunbar et al., 2025).

2.2. In vitro studies

Some of the studies investigating the effect of mesenchymal stem cells on asthma are *in vitro* studies. How these *in vitro* studies are organized is up to the creativity of the individual. MSCs and Tregs are powerful immune modulators. The development of asthma is significantly influenced by Treg proliferation and abnormal function. MSC exosomes were found to increase TGF-β1 and IL-10 from peripheral blood mononuclear cells (PBMCs), thus promoting the immunosuppressive capacity and proliferation of Tregs. In this study, antigen-presenting cells (APCs), not the CD4+T cells-dependent pathway, were shown to be the likely mechanism involved in MSC exosome-mediated regulation (Du et al., 2018). The underlying reason for this may be that MSCs have high levels of miR-1470 because it was shown that exosomal miR-1470 of MSCs can increase the proportion of CD4+CD25+FOXP3+ regulatory T cells in patients with asthma. In addition, mechanistic studies indicated that miR-1470 can improve the up-regulation of P27KIP1 by specifically aiming for the *c-Jun mRNA*'s 3' region. Mimic transfection of miR-1470 notably increased the proportion of CD4+CD25+FOXP3+Tregs in CD4+T cells. siRNA-mediated suppression of P27KIP1 inhibited the increase in the proportion of CD4+CD25+FOXP3+ Tregs induced by miR-1470 overexpression. This shows that miR-1470 stimulates the differentiation of CD4+CD25+FOXP3+ Tregs through P27KIP1 (Zhuansun et al., 2019). MSCs suppressed the proliferation of PBMCs exposed to DM (Dust mite) in allergic asthmatic subjects, but not in allergic subjects without asthma. MSCs prevented the maturation of dendritic cells but did not affect regulatory T cells (Kapoor et al., 2012).

Airway smooth muscle (ASM) cells play an important role in the pathogenesis of asthma through cellular changes. ASM has the capacity to contribute to symptoms of asthma, such as asthmatic hyperplasia (proliferative phenotype), inflammation (synthetic phenotype), and bronchoconstriction (contractile phenotype). In this context, how a healthy airway smooth muscle cell becomes diseased is important. The synthesis functions of ASMs in culture from non-asthmatic and asthmatic donors differ. These differences include increased production of extracellular matrix proteins, proinflammatory mediators, and adhesion receptors. ASMs taken from asthmatic subjects are capable of modifying their environment, actively participating in repair processes, and functionally responding to changes in their microenvironment (Wright et al., 2013) . Therefore, joint studies on MSCs and ASMs are important in revealing the effect of MSCs on asthma. Exosomes derived from AD-MSCs can be efficiently taken up by ASMs. Exosomal miR-301a-3p significantly suppressed platelet-derived growth factor-BB (PDGF-BB)-derived proliferation and migration of ASMs, increased apoptosis and decreased secretion of inflammatory factors. The 3`UTR region of *STAT3* was the direct target of MiR-301a-3p.

The increased expression of STAT3 reversed exosomal miR-301a-3p's repressive impact in ASMs stimulated by PDGF-BB. Expression of STAT3 and miR-301a-3p were negatively correlated in samples from asthmatic patients. It was found that exosomal miR-301a-3p produced from AD-MSCs may significantly ameliorate PDGF-BB-induced inflammation and remodeling of ASMs by targeting STAT3 (Feng et al., 2022).

3. Limitations and risk factors for the use of MSCs in asthma treatment

Very promising results have been obtained for the use of MSCs in asthma treatment and no negative side effects of MSC applications other than mild fever have been detected. All MSCs, especially UC-MSCs, reduce mucus production, inflammation, airway resistance, IgG1 and IgE levels and provide tissue healing. However, the donor's age, the *in vitro* culture conditions, the storage time, the injection period, and the timing of the injection are some of the variables that could adversely impact the treatment's outcome if this is not taken into account.

4. Conclusion

Asthma is an inflammatory respiratory disease, in which tissue structure is impaired. MSCs suppress the inflammatory response caused by asthma and provide tissue remodeling and repair. Such studies are based on the direct use of MSCs, recombinant MSCs and pretreated MSCs, the use of their conditioned media and their exosomes. In studies on the direct use of MSCs, AD-MSCs, BM-MSCs and UC-MSCs can be used. We believe that the best results are obtained from UC-MSCs. When we compare the use of MSCs and MSC conditioned media, the direct use of MSCs gives better results. When we compare Hypo-EVs with Nor-EVs, Hypo-EVs give better results. When we compare normal MSCs with recombinant MSCs, it can be said that recombinant MSCs generally give better results. Of course, it should not be forgotten that the recombinantly modified gene is also important.

As a result, the use of MSCs in asthma treatment is promising and it is important to take this information into consideration when determining which MSCs to use.

Conflict of interest: The author declares that he has no conflict of interests.

Informed consent: The author declares that this manuscript did not involve human or animal participants and informed consent was not collected.

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