Old Friends with Unexploited Perspectives: Current Advances in Mesenchymal Stem Cell-Based Therapies in Asthma

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Abstract
Mesenchymal stem cells (MSCs) have a great regenerative and immunomodulatory potential that was successfully tested in numerous pre-clinical and clinical studies of various degenerative, hematological and inflammatory disorders. Over the last few decades, substantial immunoregulatory effects of MSC treatment were widely observed in different experimental models of asthma. Therefore, it is tempting to speculate that stem cell-based treatment could become an attractive means to better suppress asthmatic airway inflammation, especially in subjects resistant to currently available anti-inflammatory therapies. In this review, we discuss mechanisms accounting for potent immunosuppressive properties of MSCs and the rationale for their use in asthma. We describe in detail an intriguing interplay between MSCs and other crucial players in the immune system as well as lung microenvironment. Finally, we reveal the potential of MSCs in maintaining airway epithelial integrity and alleviating lung remodeling.

Keywords
Mesenchymal stem cells · Asthma · Immune regulation · Experimental asthma · Stem cells

Introduction

Significant progress in our understanding of stem cell biology accompanied by development of technologies enabling the induction of pluripotency in somatic cells opened new ways to develop stem cell-based therapies for currently incurable diseases [1–5]. However, initial optimism was quickly disturbed by ethical dilemmas and significant safety issues. Apart from crucial ethical dilemmas concerning embryonic stem cells, the most controversial issues inhibiting the wider use of adult stem cells and induced pluripotent stem cells (iPCs) relate to their stability and long-term effects of their application [6–13]. In fact, to date, only two stem cell-based therapies were approved by FDA (U.S. Food and Drug Administration) and EMA (European Medicines Agency). These are hematopoietic stem cell transplantation, available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products [14] and limbal stem cell therapy used for for corneal transplant vision recovery, available at: https://www.ema.europa.eu/en/news/first-stem-cell-therapy-recommended-approval-eu [15]. Other stem cell-based therapies are still tested in clinical trials or applied as medical experiments [16, 17]. Therefore, they still represent patients and medical professionals’ unfulfilled dreams rather than a widely available therapeutic option.

This holds true for patients suffering from advanced inflammatory diseases [18–21], poorly healing injuries [22–24], and irreversible tissue/organ damage [25–28], including patients with advanced suboptimally controlled or even uncontrolled respiratory diseases such as acute respiratory distress syndrome (ARDS) [29], idiopathic pulmonary fibrosis [30] and severe persistent asthma with lung remodeling [31–36].

Inhaled corticosteroids (ICS) are the mainstay in asthma therapy as they effectively control symptoms and prevent exacerbations in the majority of patients. Asthmatic airway inflammation can be further alleviated by allergen-specific immunotherapy in allergic asthmatics and biological therapy in patients with severe eosinophil asthma [37–39]. In contrast,
neutrophilic steroid-resistant asthma represents a significant therapeutic challenge. Notably, poorly controlled and uncontrolled asthmatic patients are consuming over half of the healthcare resources planned for asthma management in highly developed countries [40–42]. Therefore, there is still a substantial need for novel effective therapeutic options that may help better manage poorly responding and non-responding asthmatics. Thus, stem cell-based therapies, including mesenchymal stem cells (MSC) and iPSCs, have been proposed as potential therapeutic options in severe asthma. In fact, anti-inflammatory effects of MSCs have been observed and described over 30 years ago [43, 44]; however, our understanding of the mechanisms of their beneficial effects in respiratory diseases remained elusive, making MSCs old good friends with still unexploited potential.

In this review, we summarized the current understanding of the mechanisms of MSC-mediated regulation of inflammatory processes with particular focus on the advances in their beneficial effects in asthmatic lung inflammation.

**Mesenchymal Stem Cells**

The mesenchymal stem cells (MSCs), also referred to as “mesenchymal stromal cells” and “medicinal signaling cells” are multipotent stromal cells [45]. They have been identified and isolated from various human tissues, including adipose tissue [46], bone marrow [47, 48], Wharton’s jelly [49], cord blood [50, 51], amniotic fluid [52, 53], amniotic membrane [54], dental pulp [55], endometrium [56, 57], peripheral blood [58, 59], salivary gland [60], and synovial fluid [61]. Although MSCs harvested from different tissues may slightly differ in their phenotype and functional properties, the minimal criteria for their definition have been proposed by the International Society for Cellular Therapy. According to the consensus, MSCs should: i) be positive for CD29, CD71, CD73, CD90, CD105, CD271 and lack of CD14, CD34, CD45, and human leukocyte antigen-DR isotope (HLA-DR) expression; ii) exhibit plastic adherence; and iii) possess the ability to differentiate in vitro into mesodermal lineage cells, including osteoblasts, chondrocytes, and adipocytes [62, 63]. Despite, substantial morphological and functional similarity among various subsets of MSCs, their differentiation capability, proliferation efficacy, immunomodulatory and regenerative properties may differ depending on their tissue sources. Nowadays, mesenchymal stem cells harvested from adipose tissue, bone marrow, umbilical cord blood, and Wharton’s jelly represent the most extensively described MSCs subpopulations. However, to date, the reports comparing functional properties of MSCs from different sources in the same laboratory conditions are rare [64]. According to available resources, adipose tissue-derived MSCs possess similar or even more potent immunomodulatory properties compared to bone marrow-derived MSCs [65–67]. In contrast, umbilical cord blood-derived and Wharton jelly’s derived MSCs show higher proliferation efficacy than MSCs isolated from bone marrow and adipose tissue [68, 69]. Thus, slightly different functional characteristics of MSCs derived from particular tissues opened scientific debate considering better and worse “candidates” to implement in cell-based therapies.

Interestingly, recently single-cell transcriptomic profiling of the lung allowed to confirm previously reported presence of lung resident mesenchymal stem cells (LR-MSCs) [70, 71]. Although phenotypically similar to bone marrow-derived MSCs, LR-MSCs possess distinct transcriptomic profiles, which may indicate their functional diversity and resulting from the local microenvironmental stimulus. Unfortunately, to date, our understanding of the role of LR-MSCs is minimal. It seems, however, that they can play both either beneficial or pathological roles in lung inflammation dependent on the dynamic changes occurring within local microenvironment. In fact, LR-MSCs represent an important source of growth factors such as keratinocyte growth factor (KGF) [72], fibroblast growth factor-10 (FGF-10) [73], and hepatocyte growth factor (HGF) [74, 75], crucial for the preservation of lung homeostasis. In several pathological conditions, LR-MSCs may serve as regulators of lung inflammation, inhibiting Th17 immune responses and increase T regulatory cell (Treg) activity [72]. On the other hand, transforming growth factor-beta (TGFβ)-triggered activation of the Wnt/β-catenin signaling may lead to differentiation of LR-MSCs towards myofibroblasts. This would indicate to LR-MSCs as cells which after having received some specific signals could contribute to the process of lung remodeling [76]. To date, however, it remains elusive whether this putative profibrotic potential of LR-MSCs can truly play an actual role in asthma pathogenesis [76–78]. Further understanding of the role of LR-MSCs in airway inflammation and remodeling is still warranted as it can open new ways for better asthma management.

Introduction of biotechnological methods, allowing to induce pluripotency by genetic reprogramming of somatic cells and their further maturation towards multipotent stem cells allowed to establish iPSC-derived MSC (iPSC-MSC). Notably, they can be produced by non-integrating episomal methods and acquire the capacity to reproduce without losing their vital functional properties [79, 80]. Therefore, iPSC-MSCs lack the reported weaknesses of natural (tissue-derived) MSCs, namely limited proliferative potential, standardization difficulty, loss of differentiation capacity in the late passage, decrease in therapeutic efficacy during expansion [81, 82]. On the other hand, induction of iPSC-MSC raises concerns about their further stability in clinical settings, e.g. after transplantation. Unfortunately, genetic modifications employed at the iPSC level may lead to oncogene activation resulting in genetic and epigenetic abnormalities and, in consequence, leading to tumorigenesis [83]. Despite these
concerns, iPSC-MSCs hold high therapeutic potential, which has been demonstrated in some preclinical studies [83]. It provides cautious hope for the future application of iPSC-MSCs in clinical settings following careful addressing safety concerns. To date, only two studies on iPSC-MSC-based treatment have been registered in the clinicaltrials.gov database. Mesenchymoangioblast- derived mesenchymal stem cells were tested in steroid-resistant Graft versus Host Disease (GvHD) [84], and acute distress respiratory syndrome in the course of COVID-19 [85].

In fact, according to available preclinical data, iPSC-MSCs reduce both Th2-driven and non-Th2-driven airway inflammation. Similarly to natural MSCs, administration of iPSC-MSCs decreased mucus production and immune cells’ infiltration within lungs as well as interleukin (IL)-4, IL-5, and IL-13 levels in bronchoalveolar lavage fluid (BALF). On the other hand, the limitation of non-Th2-driven inflammation was associated with a significant decrease in TH17 cell infiltration. Importantly, iPSC-MSCs have also been shown to reduce epithelium-derived alarmins, namely IL-33 and thymic stromal lymphopoietin (TSLP) [86–88].

iPSC-MSC represents a significant development of the research on the immunosuppressive activities of MSCs. Nevertheless, iPSC-MSC’s application for the regulation of asthmatic inflammation requires further progress in understanding their long-term stability and function.

**MSC-Mediated Modulation of Immune Responses**

The MSCs may exert diverse immunomodulatory effects upon administration into different inflammatory conditions [89]. MSCs-mediated immune regulation seems to depend strictly on the local microenvironment, usually associated with the disease stage [90, 91]. The numerous reports have presented the MSCs-mediated immunoregulatory effects associated with: i) reduction of CD4+ and CD8+ T cell proliferation, [92] ii) inhibition of monocyte and CD34+ cells maturation towards proinflammatory macrophages and dendritic cells (DCs) [93], iii) recruitment Tregs and induction of effector T cell functional plasticity [94, 95], iv) inhibition of cytotoxicity and proliferation of natural killer (NK) cells [96, 97], and v) limitation of B cells maturation and antibody production [98, 99].

Despite an accumulating body of evidence showing the effectiveness of MSCs administration in preclinical and clinical settings, several studies reported failures in their application for immune response modulation in Graft-versus-Host Disease (GVHD) [100], Crohn Disease [101], and Systemic Lupus Erythematosus (SLE) [102]. However, it seems that the lack of desired immunosuppressive effects may be caused by inadequate MSCs “licensing” by the inflammatory mediators and/or untimely cell administration [89, 90]. More specifically, a proper “licensing” (also known in the term “priming” or “preconditioning”) is described as a process to prepare the cells to acquire specific properties in response to particular microenvironment components and conditions. To date, several reports demonstrated that hypoxia [103], TLRs agonists [104, 105], and proinflammatory mediators, including cytokines as crucial stimuli to enhance MSCs’ immunomodulatory and regenerative properties [106–108]. In fact, the presence of cytokines characteristic for non-type two inflammation, interferon-gamma (IFNγ), IL-1α, and IL-1β [20, 94], induces MSC immunosuppressive functions. To date, it remains elusive whether type-2 related cytokines such as IL-4, IL-5, and IL-13 may directly induce regulatory properties of MSCs; however, their effectiveness in limiting Th2-driven inflammation is well established. Under resting conditions, MSCs have been shown to exert antiapoptotic effects and may act as functional “supporters” of various immune cells, such as T cells, B cells, and plasma cells [109]. Interestingly, the MSC polarization towards the proinflammatory phenotype has been observed in cells stimulated with Toll-like receptor (TLRs) agonists, such as a prototypic TLR2 ligand Pam3Cys [104, 110]. Thus, it seems that the immunosuppressive properties of MSCs are induced mainly by the proinflammatory cytokines rather than the constitutive function of these cells [109].

Notably, MSC-mediated interactions leading to the regulation of inflammatory responses are associated with both direct (cell-to-cell dependent) and indirect (soluble factor release dependent) mechanisms (Fig. 1) [111].

**Cell Contact-Dependent Immune-Modulatory Mechanisms**

The processes underlying cell-dependent mechanisms of MSCs-mediated immunosuppression involve a number of immunomodulatory membrane-bound proteins, including costimulatory receptors, membrane-bound cytokines, and small molecules [111–113]. This part will summarize the current understanding of the direct mutual interactions between MSCs and different immune cells.

Attenuation of T cell proliferation and induction of Tregs has been recognized as one of the hallmarks of MSCs immunomodulatory properties. This effect seems to be controlled by IFNγ [94]. In fact, IFNγ signaling in MSCs was shown to induce higher expression of checkpoint proteins, namely programmed cell death-ligand 1 (PD-L1, also known as B7-H1) and programmed cell death-ligand 2 (PD-L2, B7-DC) [95, 114, 115]. Both ligands interact with PD-1 on T and B cells and inhibit their T- cell receptor (TCR) and B cell receptor (BCR)-mediated activation, respectively [116].

In T cells, MSC dependent PD-1 signaling induces reduction of TCR-mediated IL-2 production and, in consequence,
decrease their proliferation and CD4 + CD25+ cell survival. In addition, PD-L1/PD-1 interaction was shown to downregulate Th17 cell activity and to reduce naïve CD4+ T cell differentiation towards Th1 and Th17 cells. The effects of Th17 cell-mediated suppression seems to be regulated by the IL-25/STAT3/PD-L1 axis [117]. In the in vivo settings, a decrease of proinflammatory (Th1/Th17) T cell infiltrate, after MSC administration, is usually associated with an increase in regulatory T cells’ frequency. Recently, MSC mediated PD-1/PD-L1 and ICOS-ICOSL interactions were proposed to play a central role in the induction of conventional T cell plasticity and induction of regulatory like phenotype. MSC induced regulatory like T cells, possess stable immune-suppressive properties, and displayed DNA methylation profiles resembling natural Tregs [118, 119]. It seems that this functional conversion requires direct cell-to-cell interaction. Moreover, MSCs adhesion was shown to be crucial to induce immuno-suppressive effects of MSC derived soluble factors, including lipid mediators such as prostaglandin E2 (PGE2), nitric oxide (NO), cytokines (IL-2, IL-10, TSG-6), and indoleamine 2,3-dioxygenase (IDO); (for more details, please see Soluble Factor Mediated Immumomodulation section) [95, 113, 120–122]. VCAM-1 (vascular cell adhesion protein 1; VLA4- very late antigen 4, ←activation/induction; ↑↑↑ increase; ↓ decrease
direct cellular interaction but after T cell-mediated proinflammatory cytokine conditioning of MSC [125, 126].

**Soluble Factor-Mediated Immunomodulation**

Besides the importance of contact-dependent effects, the vast majority of to date published reports describe MSC-mediated indirect immunosuppressive mechanisms. MSC-derived secretome consists of proteins, small molecules, and extracellular vesicles (EVs), released into extracellular space, acting as orchestrator of immune responses. Here, we summarize current advances in the understanding of the mechanisms of paracrine-mediated immune-modulation [127].

Similarly to previously described cell-dependent mechanisms, MSC licensing by inflammatory cytokines is required to activate their immune-modulatory factors’ secretion. In the presence of IFNγ, MSCs release high amounts of IDO, which metabolizes the degradation of tryptophan to toxic catabolites accumulation, namely kynurenine, L-tryptophan, kynurenic acid, quinolinic acid, and anthranilic acid [122]. However, only the kynurenine impairs the effector function and proliferation of T cells [122]. Notably, the IDO-mediated effect on tryptophan depletion has been identified only locally [89, 127]. Therefore, it seems that cell-to-cell adhesion is required for effect. In addition, IDO activity has been shown to induce monocytes’ differentiation towards IL-10, producing immunosuppressive CD14+CD206+ macrophages (alternatively activated M2 cells), and thus limiting T cell activation and proliferation. Moreover, IDO dependent pathways play a role in CD5+ regulatory B cell (Breg) induction [128]. Similarly to IDO, NO has been proposed as an essential factor in regulating T cell responses that may require direct interaction of MSC and T cells [129]. Furthermore, MSCs involve oxidative stress pathways through inducible cytoprotective enzyme heme oxygenase 1 (HO-1) that catalyzes the heme to biliverdin, which in turn suppresses T cell proliferation [130].

Similarly to small molecules, MSC-derived anti-inflammatory cytokines, namely IL-10, IL-35, and TGFβ, play a central role in indirect immune regulatory mechanisms. The anti-inflammatory properties of IL-10 were recognized as a central mechanism of MSC-mediated regulation of innate and adaptive immune compartments. Its function is associated with downregulation of Th1 and Th17 derived cytokines [94], regulation of HLA-DR, CD80, and CD86 expression on APC and thus induction of their tolerogenic phenotype [131, 132], blocking of NF-κB signaling [133], regulation of IL-1α, IL-1β [134], IL-12p40 [135], IFNγ [136], and TNF-α production [134], among others. Notably, by induction of regulatory T cells and alternatively activated macrophages, MSCs indirectly enhance IL-10 release [93, 137, 138]. In some contrast to IL-10, IL-35 represents a relatively new described cytokine belonging to the IL-12 family [139]; thus, its function remains not fully elucidated. Immune regulatory properties of IL-35 are associated with the selective expansion of Treg and a decrease of Th17 immune response [140]. Moreover, MSC-derived IL-35 promotes the conversion of B cells to IL-10 producing Bregs [141]. However, further studies are needed to better understand the importance of MSC-derived IL-35 in immune regulation, healing, and regeneration. On the other hand, TGFβ may act as both a potent regulator or an activator of innate and adaptive immune responses [142]. Its function depends on the composition of local activating factors (recently reviewed elsewhere [143]). However, it seems that MSC-derived TGFβ contributes to the polarization of activated T cells towards Tregs and promotes their expansion. In addition, recently, TGFβ induced plasticity of Th17 cells towards regulatory phenotype was reported [144]; however, the mechanism remains elusive. In macrophages, TGFβ was shown to regulate NF-κB signaling and thus control their inflammatory response. Moreover, it polarizes monocytes towards M2 alternatively activated cells [145]. On the other hand, however, TGFβ signaling has been found to play a role in lung fibrosis and promotion of Th17 cells in which other MSC-derived factors may further induce functional plasticity [142, 146]. However, complex interplay between different protein and non-protein components of MSC-derived secretome and their effects on immune function needs more attention in the future.

In the past two decades, an additional cellular communication mechanism that involves the transfer of extracellular vesicles (EVs) has been proposed as a soluble factor-dependent mechanism [3, 147, 148]. EVs are classified according to their size and base, available at: http://www.exocarta.org. EVs are characterized by the presence of surface CD9, CD29, CD44, CD63, CD73, CD81, CD105, and CD107. Immune regulatory properties of IL-35 are associated with the selective expansion of Treg and a decrease of Th17 immune response [140]. Moreover, MSC-derived IL-35 promotes the conversion of B cells to IL-10 producing Bregs [141]. However, further studies are needed to better understand the importance of MSC-derived IL-35 in immune regulation, healing, and regeneration. On the other hand, TGFβ may act as both a potent regulator or an activator of innate and adaptive immune responses [142]. Its function depends on the composition of local activating factors (recently reviewed elsewhere [143]). However, it seems that MSC-derived TGFβ contributes to the polarization of activated T cells towards Tregs and promotes their expansion. In addition, recently, TGFβ induced plasticity of Th17 cells towards regulatory phenotype was reported [144]; however, the mechanism remains elusive. In macrophages, TGFβ was shown to regulate NF-κB signaling and thus control their inflammatory response. Moreover, it polarizes monocytes towards M2 alternatively activated cells [145]. On the other hand, however, TGFβ signaling has been found to play a role in lung fibrosis and promotion of Th17 cells in which other MSC-derived factors may further induce functional plasticity [142, 146]. However, complex interplay between different protein and non-protein components of MSC-derived secretome and their effects on immune function needs more attention in the future.
effects of MSC-derived EVs are comparable to entire MSCs. Therefore, they are increasingly recognized as a potential therapeutic factor for inflammatory and degenerative diseases. However, to date, the effects of MSC-derived EVs in the regulation of asthmatic inflammation remain elusive.

**Mechanisms of MSC Mediated Regulation of Asthmatic Lung Inflammation**

Asthmatic airway inflammation should be considered a complex network of interactions between different lung resident cells, immune cells, growth factors, enzymes, cytokines, chemokines, metabolites, and miRNAs [164]. Unfortunately, our understanding of the effects of MSC on this network is significantly restricted due to limitations of used models, namely xenotransplantation models of human MSC into mice or usage of mice cells only (Table 1). However, in this section, we summarize the current understanding of MSC effects on each of the lung’s crucial inflammatory cascade components (Fig. 2).

To date, MSCs-mediated effects on T cell function are the best characterized and are associated with the regulation of their proliferation and functional plasticity [165, 166]. T cell proliferation leads to the formation of high numbers of effector cells [167]. Activated MSCs regulate this process by the production of nitric oxide (NO) and PGE2 [168, 169]. NO synthase (iNOS) [170]. This pathway increases NO levels, which induces S-nitrosylation of transcription factors, metabolic enzymes, and cytoskeletal proteins [171]. In some contrast, PGE2 promotes T cell anergy by the regulation of IL-2 production and IL-2R (CD25) expression on activated cells [117, 172]. In addition, PGE2 has been demonstrated to suppress Th1 differentiation and enhance the induction and differentiation of adaptive regulatory T cells in the lungs [94].

Although T cells acquire their effector function towards antigen presentation by antigen-presenting cells (APC) upon TCR and costimulatory molecule engagement, they may retain functional plasticity and acquire additional cytokine-producing capacities upon re-stimulation [173]. Interestingly, MSC may directly induce functional plasticity by the epigenetic reprogramming of Th17 cells. In fact, the interaction between IFNγ and TNF-α activated MSCs and Th17 cells via CD56 – CCR6 (CD196) receptors induces IL-10 production and histone H3K4me3 methylation in the FOXP3 locus promoter with subsequent suppression of RAR-related orphan receptor C (RORC) [174]. Consequently, Th17 cells lose their immune-activatory properties and acquire suppressive (regulatory) functions. Furthermore, MSCs have been shown to regulate the expression of Th2 cytokines, namely IL-4, IL-5, and IL-13 [36, 175–183]. However, it needs to be addressed whether observed regulation may represent a consequence of T cell plasticity or is a consequence of Th2 cell anergy and in consequence apoptosis. Notably, a manifestation of disease symptoms considered extensively as hallmarks of asthma is directly or indirectly related to the overproduction of IL-4, IL-5, and IL-13 [184, 185]. More specifically, IL-4 synergistically with IL-13 induces the antibody class switching towards immunoglobulin E (IgE), produced by B cells [184], whereas IL-5 plays a key role in the survival, differentiation, degranulation, and recruitment of eosinophils to the site of inflammation [184, 186]. In mice that lack IL-4, IL-5, IL-13 reduction of asthma symptoms was observed in the Ova-Alum experimental model. Thus, administration of MSC may block the initial steps of allergic sensitization cascade through regulation of Th2-related cytokines [165, 177, 178, 187–189]. Nevertheless, it became clear that activated MSC may enhance regulatory T cell activity and induce the production of anti-inflammatory cytokines, namely IL-10 and TGFβ, in both direct and indirect mechanisms. It seems that soluble factor-mediated mechanisms are sufficient to induce regulatory effector functions of Treg, while direct cell-to-cell interaction is needed for their expansion [36, 165, 178, 190, 191]. Nonetheless, the mechanistic of MSC-Treg interactions remain poorly understood and are likely to be complex and dependent on the local lower airway microenvironment.

Dendritic cells (DCs) are referred to as a professional antigen-presenting cell (APC) linking innate and adaptive immune responses. Therefore, they are recognized as central players in the inflammatory cascade [192, 193]. It seems that MSC may directly regulate DC maturation and differentiation from monocytes and CD34+ progenitors through PGE2 dependent mechanism [194]. Notably, immature or semi-mature DCs possess tolerogenic properties and may regulate T cells’ proinflammatory responses and induce Treg maturation. In contrast to immature DCs, mature cells from asthmatic patients present high expression of costimulatory molecules, namely CD80 and CD86, and possess high T cell stimulatory properties [132, 195]. In fact, they are involved in the polarization of T cell responses towards Th1/Th17 or Th2 cells and thus may support both eosinophilic and non-eosinophilic (neutrophilic) lung inflammation [164, 180, 181, 193]. Importantly, however, MSCs were shown to decrease the above-described properties by regulation of DC expression of costimulatory molecules and proinflammatory cytokine secretion. In addition, MSC decreases the release of CC chemokine ligand (CCL)17 and CCL22 chemokines by dendritic cells and, thus, regulate T cell responses within the lung [196].

Similarly to DCs, macrophages possess antigen-presenting capacities, and due to their pleiotropic biological activities, they may orchestrate both adaptive and innate immune responses. Macrophages can be polarized towards two distinct phenotypes, namely M1 (classically activated) and M2 (alternatively activated) cells [197–200]. M1 macrophages are
| Source and number of MSC | Route of MSC administration | Type of experimental asthma model | Mice strain | Histological outcome and respiratory mechanics | Immunomodulatory outcome or proposed mechanism | Reference |
|--------------------------|-----------------------------|---------------------------------|-------------|-----------------------------------------------|-----------------------------------------------|-----------|
| Mice ADMSCs (0.3×10^6 cells) | Intranasally | Intranasal challenge with HDM extract (100 μg/tune) | BALB/c | ↓ airway hyperresponsiveness ↓ immune cell infiltration ↓ total leukocytes number in BALF ↓ goblet cells hyperplasia ↓ airway contractile tissue remodeling ↓ extracellular matrix mass ↓ eosinophils in BALF, whereas greater after BMMSCs administration | ↓ IgE in BALF ↑ IFNγ, IL-12, FGF in BALF | [35] |
| Mice BMMSCs (0.5×10^6 cells) | Intravenously | Intraperitoneal injection of 0,5 μg OVA and 400 μg of potassium alum adjuvant; nebulization with aerosolized OVA (2,5% in NaCl) | BALB/c | ↓ IgE in BALF ↑ IFNγ, IL-12, FGF in BALF | ↓ peribronchial inflammatory cell infiltration (IN, IV) ↓ goblet cells (IN, IV) ↓ colagen deposition and concentration (IN, IV); whereas IN to a greater extent ↓ total leukocytes number in BALF ↓ goblet cell hyperplasia ↓ airway epithelial thickness (only IN) ↓ bronchial hyperreactivity compared ↓ airway eosinophilia ↓ macrophages count in BALF ↓ bronchial mucus secretion ↓ neutrophils, eosinophils, lymphocytes count in airway ↓ goblet cell hyperplasia ↓ airway epithelial thickness (only IN) ↓ bronchoconstriction ↑ OVA-specific IgG2 ↑ CD4+:CD25+:Foxp3+: cells in lungs and spleens; Tregs dependent mechanism ↑ IDO and TGFβ gene in lung tissue ↑ M2 gene in serum | [165] |
| Mice ADMSCs (1×10^6 cells) | Intravenously | Intraperitoneal injection of 0,5 μg OVA in 2mg of aluminum hydroxide in 200 μL PBS; an intranasal challenge with 1 μg/μL of OVA (in PBS) | C57BL/6 | ↓ allergen-specific IgE immune response ↓ IL-4, IL-13 in BALF and restimulated spleen cells ↑ IL-10 in BALF and restimulated spleen cells ↑ CD4+:CD25+:Foxp3+: cells in lungs and spleens; Tregs dependent mechanism ↑ OVA-specific IgG1, IgG1/IgG2 ratio ↑ OVA-specific IgG2 ↑ CD4+:CD25+:Foxp3+: cells in mLNs ↑ IL-10 in BALF and restimulated spleen cells ↑ IDO and TGFβ gene in lung tissue ↑ M2 gene in serum | ↓ peribronchial inflammation ↓ bronchial hyperreactivity compared ↓ airway eosinophilia ↓ macrophages count in BALF ↓ bronchial mucus secretion ↓ neutrophils, eosinophils, lymphocytes count in airway ↓ goblet cell hyperplasia ↓ airway epithelial thickness (only IN) ↓ bronchoconstriction ↑ OVA-specific IgE, IgG1, IgG1/IgG2 ratio ↑ OVA-specific IgG2 ↑ CD4+:CD25+:Foxp3+: cells in mLNs ↑ IL-10 in BALF and restimulated spleen cells ↑ IDO and TGFβ gene in lung tissue ↑ M2 gene in serum | [175] |
| Mice BMMSCs (0.5×10^6 cells) | Intravenously | Percutaneous injection with 25 μg/μl of Der f extract in PBS; an intranasal challenge with 6,25 μg/μl of Der f extract in PBS | BALB/c | ↓ CD3+CD4+ T cells in the thymus ↓ M2 muscarinic receptor expression ↓ O M2 muscarinic receptor expression ↓ IL-4, IL-5, IL-13, IL-17 by lung CD4+ cells ↓ IFNγ and IL-10 by lung CD4+ cells ↓ M2 alveolar macrophage phenotype through COX2/PGE2 dependent signaling | ↓ CD3+CD4+ T cells in the thymus ↓ M2 muscarinic receptor expression ↓ O M2 muscarinic receptor expression ↓ IL-4, IL-5, IL-13, IL-17 by lung CD4+ cells ↓ IFNγ and IL-10 by lung CD4+ cells ↓ M2 alveolar macrophage phenotype through COX2/PGE2 dependent signaling | [177] |
| Human ADMSCs (0.1×10^6 cells) and their EVs (0.7 μg) | Intravenously | Intraperitoneal injection with 1 μg/μl of OVA (adjuvant-free, in saline); intratracheal administration with 1 μg/μl of OVA (in saline) | C57BL/6 | ↓ total IgE in serum ↓ airway hyperresponsiveness ↓ immune cell infiltration ↓ total leukocytes number in BALF ↓ eosinophils count in BALF ↓ IL-4, IL-5, IL-13 by lung CD4+ cells ↓ IFNγ and IL-10 by lung CD4+ cells | ↓ M2 muscarinic receptor expression ↓ O M2 muscarinic receptor expression ↓ IL-4, IL-5, IL-13, IL-17 by lung CD4+ cells ↓ IFNγ and IL-10 by lung CD4+ cells ↓ M2 alveolar macrophage phenotype through COX2/PGE2 dependent signaling | [178] |
| Mice BMMSCs (1×10^6 cells) | Intravenously | Intranasal induction with 0.5 μg/μl and 0.1 μg/μl of HDM extract | BALB/c (H2d) | In the acute model: ↓ airway lymphocytes, neutrophils, eosinophils, monocytes count ↓ mucus secretion ↓ peribronchial eosinophilia, the mast cells count ↓ AHR | In the acute model: ↓ total IgE in serum ↓ IL-5, IL-13 in BALF ↓ IFNγ in BALF ↓ IL-5-IL-13, eotaxin in BALF | [179] |
Table 1 (continued)

| Source and number of MSC | Route of MSC administration | Type of experimental asthma model | Mice strain | Histological outcome and respiratory mechanics | Immunomodulatory outcome or proposed mechanism | Reference |
|--------------------------|------------------------------|----------------------------------|-------------|-----------------------------------------------|-----------------------------------------------|-----------|
| Mice ADMSCs (1×10⁶ cells) | Intravenously | Intraperitoneal injection with 0.1% OVA (in PBS); challenge with aerosolized 2.5% OVA (in PBS) | BALB/c | | | |
| Human UCMSCs (0.3×10⁶, 0.6×10⁶ cells) | Intravenously | Intranasal sensitization with 75 μg OVA and 10 μg Poly(I:C); Intranasal challenge with 50 μg OVA and 10 μg Poly(I:C) | BALB/c | | | |
| Human BMSCs (1×10⁶ cells) | Intravenously | Intraperitoneal injection with 10 μg OVA and 1.5 mg of Al(OH)₃ (100 μg total volume); an intranasal challenge with 1% weight/volume OVA in PBS | C57BL/6 | | | |
| Human ADMSCs, UCMSCs BMSCs (1×10⁶ cells) | Intravenously | Intraperitoneal injection with 50 μg OVA with 2 mg aluminium hydroxide gel; intranasal administration with 50 μg OVA | Balb/c | ADMSC-, UCMSC- and BMSC-mediated effect: | ADMSC-, UCMSC- and BMSC-mediated effect: | [187] |
| Mice ADMSCs (0.2×10⁶ cells) | Intravenously | Intraperitoneal injection with 20 μg OVA with 1 mg of alum as an adjuvant; nebulization OVA (1% in saline) | C57BL/6 WT, IFN-γ/−/−; IFN-γR−/−; CCL2−/− | | | |
| Mice BMSCs (2×10⁶ cells) | Intravenously | Intraperitoneal injection with 100 mg of OVA in 9% aluminum hydroxide hydrate Intratracheal | C57BL/6 | | | |
| Source and number of MSC | Route of MSC administration | Type of experimental asthma model | Mice strain | Histological outcome and respiratory mechanics | Immunomodulatory outcome or proposed mechanism | Reference |
|-------------------------|-----------------------------|----------------------------------|-------------|-----------------------------------------------|-----------------------------------------------|-----------|
| Mice BMMSCs and ADMSCs (0.1×10⁶ cells) | Intratracheally | Intranasal induction with 1 μg/μl of HDM extract in PBS | C57BL/6 | BMMSC-mediated effect: | ↑ IFNγ, and IFNγ/IL-4 (mRNA) ratio; shift from Th2 to Th1 response | [191] |
| Human BMMSCs (1×10⁶ cells) | Intravenously | Intraperitoneal injection with 50 μg OVA with 2 mg aluminum hydroxide gel; an intranasal challenge with 50 μg OVA | NOD/SCID | AHR ↓ | ↑ CD4+CD25+Foxp3 cells frequency in T lymphocytes in lungs | [204] |
| Mice BMMSCs (0.25×10⁶ cells) | Intravenously | Intraperitoneal sensitization with 10 μg/0.1 ml OVA in alum adjuvant; a challenge with 1% aerosolized OVA (in PBS) via airways | BALB/c | immune cells infiltration in the lungs ↓ | ↑ CD4+CD25+Foxp3 cells frequency in T lymphocytes in lungs | [212] |
| Mice BMMSC (0.5×10⁶ cells) | Intratracheally | Intraperitoneal injection with 100 μg OVA in 1.3 mg aluminum hydroxide (in PBS); nebulization with 2.5% OVA (in PBS) | Balb/c | neutrophils, eosinophils, monocytes count in BALF ↓ | ↑ IL-12 in serum and BALF | [211] |

ADMSCs- adipose tissue-derived mesenchymal stem cells; AHR-airway hyperresponsiveness; BALF- bronchoalveolar lavage fluid; BMMSCs- bone marrow-derived mesenchymal stem cells; CD(4,8,11b,25,163)- custer of differentiation 4, 8, 11b, 25, 163; CCL(2,11,24)- chemokine (CC motif) ligand 2, 11, 24; CCR2- CC chemokine receptor type 2; COX2- cyclooxygenase 2; CXCL15- chemokine (CXC motif) ligand 15; CXCR4- CXC chemokine receptor type 4; DCs- dendritic cells; EVs- extracellular vesicles; FGFb- basic fibroblast growth factor; Foxp3- forkhead box p3; HDM- house dust mite; IDO- indoleamine 2,3-dioxygenase; IFNγ- interferon gamma; IgE, G1, G2- immunoglobulin E, G1, G2; IL-1α, 4, 5, 6, 9, 10, 12, 13, 17, 25- interleukin 1α, 4, 5, 6, 9, 10, 13, 17, 25; ILCs- innate lymphoid cells; iNOS- inducible nitric oxide synthase; Ly6G- lymphocyte antigen 6 complex locus G6D; KC- keratinocyte derived chemokine; LMSCs- lung derived mesenchymal stem cells; MCA- MSCs- mesenchymoangioblast-derived mesenchymal stem cells; MHCII- major histocompatibility complex class II; PBS- phosphate buffered saline; MIP-1α- macrophage inflammatory protein 1α; mLNs- mediastinal lymph nodes; MMP9- matrix metalloproteinase 9; OVA- Ovalbumin; SDF-1- stromal-derived factor 1; TGFβ- transforming growth factor-beta; TNFα- tumor necrosis factor-alpha; UCMSCs- umbilical cord blood-derived mesenchymal stem cells; VEGF- vascular endothelial growth factor; WT- wild type; Ø no effect observed; ↑ an increase/ improvement; ↓ a decrease/ limitation
recognized as immune stimulatory cells producing high amounts of proinflammatory cytokines (including TNF-α, IL-1, IL-6, IL-12, and IL-23), chemokines (such as CCL5, CCL8, CXCL2, and CXCL4), polarizing T cell responses towards Th1 and Th17, and possess high antigen presentation capacity. In contrast, M2 macrophages possess immune regulatory/repairatory properties with high secretion of anti-inflammatory IL-10, IL-35, TGFβ, IL-1 receptor antagonist (IL-1RA), CCL16, CCL18, and CCL22, the ability for induction of regulatory T cells, and lack of cytotoxic activity [187, 201–203]. However, due to their capability to support Th2 response, their role in allergic lung inflammation remains not fully elucidated. Interestingly, MSCs were shown to support macrophages’ alternative activation in the IL-10 and/or TGFβ related mechanism [98, 204]. In fact, an accumulating body of evidence indicates the central role of alveolar macrophages in the MSCs-mediated immunosuppression in the asthmatic lung. It seems that the MSC-induced M2-derived immunosuppression supports induction of regulatory T cells within the lungs [204]. However, the mechanisms of MSC-macrophage mutual interactions need to be elucidated in the future.

Airway epithelial cells play a central role in innate immune function as the first line of defense against biological, physical, and chemical stressors. Moreover, activated epithelial cells play a central role in inflammatory cascade by releasing inflammatory mediators, namely cytokines and chemokines [193, 205, 206]. The function of epithelial barrier depends
directly on the expression of proteins building tight connections between epithelial cells referred to as tight junction (TJ) proteins [186]. Disruption of their function is currently recognized as a hallmark of asthma [184, 185, 207]. Moreover, differentially regulated expression of tight junction related genes may be observed in distinct asthma phenotypes [186]. More specifically, reduced zonula occludens-1 (Zo-1) and Claudin 18 expression are typical for all asthma phenotypes, while the upregulation of Claudin 4 and Claudin 7 seems to be specific only to neutrophilic airway inflammation [186, 208]. By some contrast, Claudin 1, Claudin 5, and Claudin 7 expression were downregulated only in the eosinophilic phenotype [186]. Thus, the personalized targeting of particular tight junction proteins may be a useful therapeutic option for individual asthma phenotypes. In fact, impairment of epithelial integrity, observed in asthma, results in barrier leaking, leading to the intensified inflammatory response [205, 206]. Unfortunately, to date, the influence of the MSCs on the epithelial barrier function remains elusive. Notably, disrupted epithelial barrier integrity and uncontrolled lung inflammation may partially contribute to the development of the combination of irreversible structural changes within the lung tissue referred to as airway remodeling [209]. Mucus overproduction, smooth muscle hyperplasia, and increased collagen deposition, resulting in airflow obstruction contribute to the clinical manifestation of a disease. Although some of the concepts explain airway remodeling development to some degree, to date, available therapies do not allow to alleviate its progress [210]. However, several studies reported that MSC administration attenuates airway remodeling by limiting goblet cell hyperplasia, epithelial thickness, subepithelial smooth muscle hyperplasia, and inhibit collagen deposition [35, 211–214]. Notably, the mechanism underlying the mentioned beneficial effects of MSCs remains elusive. Increased deposition of collagen fibers (collagen I, III, V, XI) to extracellular matrix seems to be strongly related to the secretion of profibrotic factor from eosinophils, such as TGF\(\beta\) [215, 216]. In addition, TGF\(\beta\) promotes the release of matrix metalloproteinase 9 (MMP-9), which subsequently contributes to extend collagen deposition [217]. Nevertheless, the loss or augmentation of MMPs activity, also through inadequate control by their tissue inhibitors (TIMPs) results in fibrosis development. Thus, the maintaining or restoring of a balance between MMPs and TIMPs activity seems to prevent remodeling development [218]. Notably, both intranasal and intravenous administration of MSCs causes the increased activity of MMP-9 suggesting activation of compensatory processes [88]. Interestingly, TGF\(\beta\) may act as a regulator of MSCs mediated immunosuppression; however, MSCs decrease the level of TGF\(\beta\) within the lung tissue and thus may limit lung remodeling [204]. Therefore, implementation of mesenchymal stem cells may hold great promise for preventing pathological tissue reconstructions observed in inflammed lung remodeling. Unfortunately, the mechanism underlying the mentioned beneficial effects of MSCs remains elusive and need further research.

### Conclusions

The accumulating body of evidence confirms the beneficial effects of MSCs in different preclinical asthma models. The vast majority of published studies utilized the xenotransplantation of human MSC into mice. Notably, the model possesses critical weaknesses resulting from some of the MSC-derived mediators’ restricted species function. On the other hand, however, mice MSCs may not fully cover the human MSC function. Indeed, these issues represent a significant obstacle to understanding the mechanisms by which MSCs regulate asthmatic lung inflammation and postpone their use in clinical practice. However, according to the clinical trials database (http://clinicaltrials.gov) first clinical trial was performed to assess the safety, tolerability, and efficacy of allogeneic human mesenchymal stem cells infusion in a total of 6 patients with mild asthma [219]. The study was terminated as the first cohort was completed. Unfortunately, to date, the results are not yet available.

In summary, we do not claim that stem cell-based therapies should or will replace currently used effective first-line treatment in asthma. However, stem cells can become an attractive and relatively safe option for helping those patients who failed to satisfactorily respond to conventional treatment.

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### Availability of Data and Material

Not applicable.

### Author Contributions

MT and AE wrote the manuscript. MT designed and prepared figs. AE and MM revised manuscript.

### Declarations

**Ethical Approval** The content of the manuscript is original and it has not been published or accepted for publication, either in whole or in part, in any form. No part of the manuscript is currently under consideration for publication elsewhere.

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

**Conflict to Participate** Not applicable.

**Conflict for Publication** Not applicable.
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