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Review Article

Mesenchymal stem cells in allergic diseases: Current status

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ABSTRACT

Allergic diseases, which include asthma, allergic skin diseases, allergic rhinitis and allergic conjunctivitis, have already garnered worldwide public health attention over recent decades. Mesenchymal stem cells (MSCs) have gradually emerged as a potential method for treating allergic diseases due to their immunosuppressive characteristics, tissue repair ability and secretion of various biological factors. This potential of MSC-based therapy has been confirmed in clinical and preclinical studies, which report the therapeutic benefits of MSCs for various allergic diseases and explore the antiallergic mechanisms. In this review, we focus on the discoveries and biological mechanisms of MSCs as a therapeutic tool in allergic diseases. We discuss the challenges of conducting MSC studies as well as future directions.

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Introduction

Allergic diseases have become a global health problem^{1,2} and the most prevalent allergic disorders include allergic asthma, allergic skin diseases, allergic rhinitis, and allergic conjunctivitis. In the therapy of allergic diseases, corticosteroids, antihistamines, antileukotrienes and β_2 adrenergic receptor agonists temporarily inhibit inflammation mediators and immune cells.³ However, long-term treatment causes various adverse effects. Drug resistance and intolerance also limit the application in some patients. Therefore, a new therapeutic method is urgently needed for allergic disease treatment.

Mesenchymal stem cells (MSCs) are multipotent, non-hematopoietic, stromal precursor cells found in adult and neonatal tissues (Table 1).^{4–26} The most commonly used sources of MSCs are bone marrow (BM-MSCs), adipose tissue (AD-MSCs) and umbilical cord (UCB-MSCs).²⁷ These cells have tissue repair potential through their self-renewal and differentiation abilities and are increasingly considered regulators of immune responses.^{28,29} MSCs modulate the tissue repair process via differentiation into various types of cells, such as adipocytes, chondrocytes, osteocytes, tenocytes, fibroblasts, cardiomyocytes, skeletal myocytes, and neuroshepatocytes.^{30,31} MSCs contribute to the regeneration of

damaged tissue resulting from several disease states, including cardiovascular disorders,³² liver damage,³³ kidney injury,³⁴ bone diseases^{35,36} and neurological defects.³⁷ For immunomodulation function, MSCs exert an obviously suppressive effect on T cells,^{38,39} B cells,⁴⁰ dendritic cells (DCs)^{41–43} and natural killer (NK) cells,^{44,45} affecting innate and adaptive immunity (Fig. 1). Accumulating data have demonstrated that the action of MSCs on immune cells depends on the secretion of various factors, including tumor growth factor- β_1 (TGF- β_1), IL-10 and prostaglandin E2 (PGE2).^{46–48} The MSC secretome, especially extracellular vesicles (EVs), has exhibited therapeutic benefits in several animal models in recent years.^{49–54}

It is reasonable to speculate that these features make MSCs a potential therapeutic target for inflammatory diseases.⁵⁵ Indeed, MSCs have been broadly administered with advantageous results in various autoimmune diseases, including systemic lupus erythematosus (SLE),^{56,57} graft-versus-host disease (GVHD),^{58,59} multiple sclerosis (MS)⁶⁰ and rheumatoid arthritis (RA).^{61,62} Additionally, several researchers have found that MSCs are able to attenuate allergic immune diseases, including asthma,^{63,64} allergic rhinitis²⁵ and allergic skin diseases (atopic dermatitis and allergic contact dermatitis),^{65–67} indicating that MSCs have an anti-inflammatory function and exert protective effects under different disease-specific inflammatory conditions. Therefore, all of these results suggest that MSC-based therapies could become potential treatments in immune-related diseases.⁶⁸

To understand the current status of MSCs in allergic diseases, we summarized the immunomodulatory properties of MSCs and critically analyzed their therapeutic potential in animal models and

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Abbreviations

AAI	allergic airway inflammation
AD-MSCs	adipose tissue-derived mesenchymal stem cells
AHR	airway hyperresponsiveness
BM-MSCs	bone marrow-derived MSCs
BALF	bronchoalveolar lavage fluid
CM	conditioned medium
COX-2	cyclooxygenase-2
DM	dust mite
DLN	draining lymph node
EVs	extracellular vesicles
EP3	prostaglandin E receptor 3
ECM	extracellular matrix
Foxp3	forkhead box P3

GMSCs	gingiva-derived MSCs
HUCB	human umbilical cord blood
ILC2s	group 2 innate lymphoid cells
iPSC-MSCs	induced pluripotent stem cell-derived MSCs
LPS	lipopolysaccharide
NF- κ B	nuclear factor kappa-B
NOD2	nucleotide-binding oligomerization domain 2
OVA	ovalbumin
PBMCs	peripheral blood monocytes
S-MSCs	skin-derived MSCs
STC2	stanniocalcins-2
STAT6	signal transducer and activator of transcription 6
T-MSCs	tonsil-derived MSCs
TLR	toll-like receptor
TCs	telocytes

clinical trials of allergic asthma, allergic rhinitis, allergic skin diseases and allergic conjunctivitis in this review. We also highlight challenges that need to be overcome before MSC therapy can be used routinely to treat allergic diseases in the clinic.⁵⁵

Asthma

Asthma, which is an inflammatory disorder, is characterized by airway inflammation and constriction that results in structural changes in the airways, usually in response to allergens, infections, or other pollutants.⁶⁹ During the process of asthma, DCs present allergens to naive T helper (Th0) cells. These Th0 cells differentiate

into type 2 T helper (Th2) cells, which can increase B cell IgE production and eosinophil maturation via associated biological molecules. Additionally, mast cells (MCs) follow IgE-dependent degranulation, Th1 cells become activated, and Th17 cells induce neutrophil recruitment and proliferation via IL-17. The congregation of these cells and their cytokines disturbs the normal functions and proliferation of airway structural-type cells, contributing to allergic airway inflammation (AAI) and airway remodeling.⁷⁰ In recent years, many animal studies have indicated that group 2 innate lymphoid cells (ILC2s), the major sources of Th2 cytokines, may have a role in asthma.^{71,72} Currently, inhaled corticosteroids, β_2 -adrenergic receptor agonists and oral leukotriene inhibitors are administered to control asthma symptoms but do not facilitate the repair of impaired tissue or treat asthma in a radical way.⁷³ Approximately 5–10% of patients with asthma remain symptomatic.⁷⁰

Several studies have shown that MSCs reduce lung inflammation and tissue remodeling in allergic asthma.^{25,74–77} Bonfield *et al.* demonstrated that human BM-MSC treatment was effective and specifically reduced AAI in an eosinophil-predominant asthmatic mouse model established by ovalbumin (OVA) challenge.⁷⁵ Furthermore, in this model, Sun *et al.* showed that treatments with both human induced pluripotent stem cell-derived MSCs (iPSC-MSCs) and human BM-MSCs prevented allergy-specific pathological changes before the challenge phase in the asthmatic model by suppressing the infiltration of inflammatory cells and mucus secretion, which was accompanied by reductions in Th2 immunoglobulin levels in the serum and bronchoalveolar lavage fluid (BALF).²⁵ Additionally, MSCs have beneficial effects on severe refractory neutrophil-predominant asthma, which is characterized by a low responsiveness or even resistance to steroids.⁷⁶ In contrast, in a study on a feline model, AD-MSCs failed to attenuate airway hyperresponsiveness (AHR) in response to an allergen. Interestingly, they still decreased thoracic computed tomographic scan-derived indices of airway remodeling at month 8 after the initial MSC administration, but this difference disappeared at month 12. Such differences in therapeutic benefits in experimental airway models may be related to the differences in complicated genetics and immune systems between cats and rodents.⁷⁷

For years, several studies have reported further research on the mechanism of MSCs in asthma.^{78–81} Bentley *et al.* suggested that significantly increased numbers of cells possessed MSC phenotype in the lung tissues of mice with asthma after OVA sensitization.⁷⁸ In a similar murine model, Ou-Yang *et al.* found that numerous murine BM-MSCs transfected with green fluorescent protein migrated to

Table 1
Overview of the different sources for MSC isolation.

Source	Reference
Bone marrow	Friedenstein, A. J. <i>et al.</i> Cell Tissue Kinet. (1970)
Teeth	Huang, G. T. <i>et al.</i> J Dent Res. (2009)
Periosteum	Yoshimura, H. <i>et al.</i> Cell Tissue Res. (2007)
Synovial membrane	Yoshimura, H. <i>et al.</i> Cell Tissue Res. (2007)
Peripheral blood	Ab Kadir, R. <i>et al.</i> Scientific World Journal. (2012).
Adipose tissue	Yoshimura, H. <i>et al.</i> Cell Tissue Res. (2007)
Scalp tissue	Shih, D. T. <i>et al.</i> Stem Cells. (2005)
Muscle	Yoshimura, H. <i>et al.</i> Cell Tissue Res. (2007)
Lung	Meirelles, L. D. S. <i>et al.</i> Journal of Cell Science. (2006)
Nasal olfactory mucosa	Yang, C. <i>et al.</i> PLoS One. (2015)
Breast milk	Patki, S. <i>et al.</i> Human Cell. (2010)
Endometrial and menstrual Blood	Ulrich, D. <i>et al.</i> Expert Opinion on Biological Therapy. (2013)
Skin	Riekstina, U. <i>et al.</i> Cytotechnology. (2008)
Corneal limbus	Jiang, D. <i>et al.</i> Cell Death Dis. (2016)
Uterine cervix	Eiro, N. <i>et al.</i> Oncotarget. (2014)
Umbilical cord	Seo, M. S. <i>et al.</i> J Vet Sci. (2009)
Placenta	Vellamy, S. <i>et al.</i> World J Stem Cells. (2012).
Fetal blood	Campagnoli, C. <i>et al.</i> Blood. (2001)
Fetal heart	Garikipati, V. N. <i>et al.</i> PLoS One. (2014)
Amniotic fluid	in 'tAnker, P. S. <i>et al.</i> Blood. (2003)
Amniotic membrane	Marcus, A. J. <i>et al.</i> Differentiation. (2008)
Tendon	Rui, Y. F. <i>et al.</i> Tissue Engineering Part A. (2010)
Brain	Meirelles, L. D. S. <i>et al.</i> Journal of Cell Science. (2006)
Thymus	Krampera, M. <i>et al.</i> Stem Cells and Development. (2007)
Kidney	Meirelles, L. D. S. <i>et al.</i> Journal of Cell Science. (2006)
Liver	Meirelles, L. D. S. <i>et al.</i> Journal of Cell Science. (2006)
Pancreas	Guo, X. R. <i>et al.</i> Clin Exp Med. (2015)
Spleen	Meirelles, L. D. S. <i>et al.</i> Journal of Cell Science. (2006)
Induced pluripotent stem cell	Sun, Y. Q. <i>et al.</i> Stem Cells. (2012)
Tonsil	Samivel, R. <i>et al.</i> Am J Rhinol Allergy. (2015)

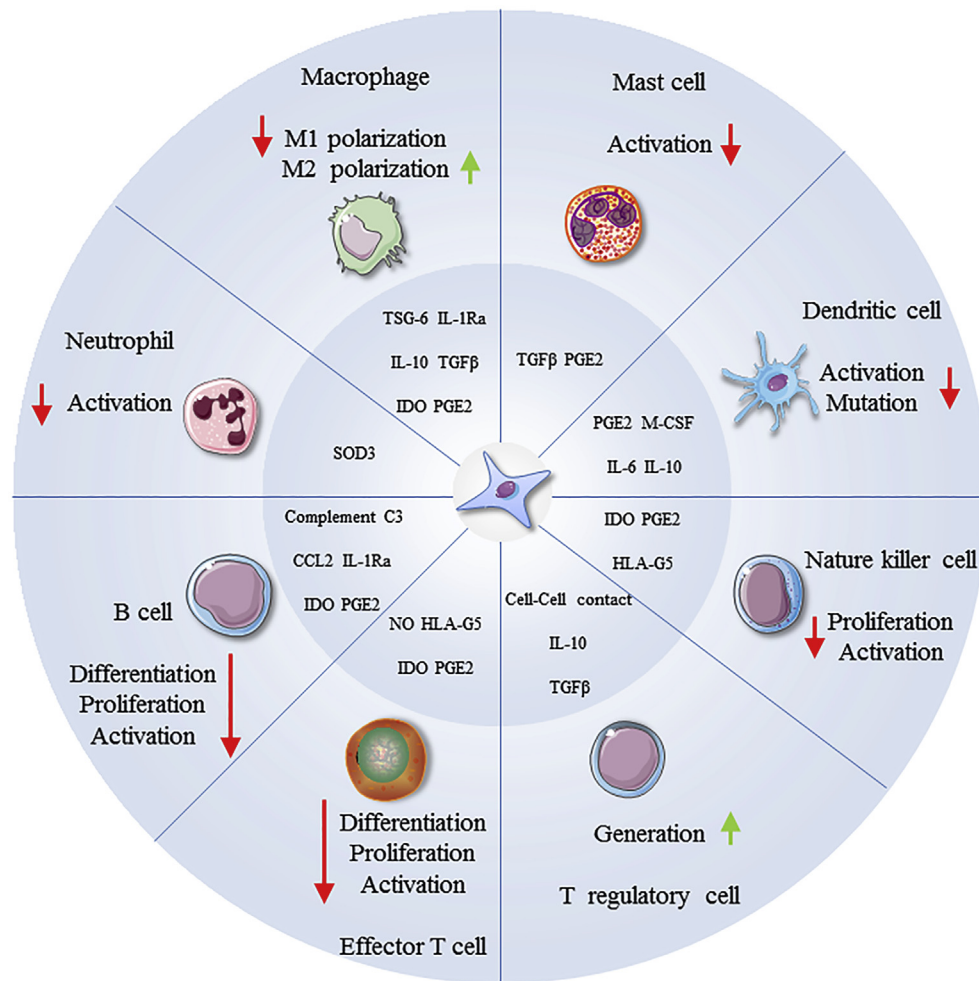


Fig. 1. Immunomodulatory effects of MSCs on immune cells. Inhibition of B and effector T cell differentiation, proliferation and generation; promotion of Treg generation; inhibition of NK cell proliferation and activation; inhibition of DC maturation and activation; inhibition of MC and neutrophil activation; inhibition of proinflammatory M1 macrophage phenotypes but enhancement of anti-inflammatory M2 macrophage phenotypes. The immunosuppressive effects of MSCs are mediated by soluble factors and cell–cell contact. CCL2, chemokine (C–C motif) ligand 2; IL-1Ra, interleukin-1 receptor antagonist; IDO, indoleamine 2,3-dioxygenase; PGE2, prostaglandin E2; NO, nitric oxide; HLA-G5, human leukocyte antigen-G5; IL-6/10, interleukin-6/10; TGF-β, tumor growth factor-β; TSG-6, tumor necrosis factor-α stimulated gene/protein 6; SOD3, superoxide dismutase 3. Red line: suppressive effect; green arrow: stimulatory effect.

the lung tissue and improved bronchial asthma. This relocation might depend on the stromal cell-derived factor-1a/CXCR4 axis.⁷⁹ The suppression of TGF-β1 disturbs the migration of murine MSCs induced by CM from cockroach allergen-stimulated human epithelium.⁸⁰ Moreover, the aryl hydrocarbon receptor also plays a key role in ameliorating inflammation by regulating MSC recruitment and immunosuppressive potential.⁸¹

As the recruitment and accumulation of MSCs in the lungs have been demonstrated, it is logical to focus on how these processes work. Nemeth, K. found that Th2-related cytokines activated the signal transducer and activator of transcription 6 (STAT6) pathway in BM-MSCs, thus elevating their TGF-β production, which might contribute to the attenuation of asthma in mice.⁶³ The inhibition of Th2-mediated inflammation may be related to the enhancement of Th1 cell generation. Goodwin, M. and colleagues silenced the interferon-gamma (IFN-γ) gene, a typical marker of Th1 cells, in mice with asthma and found that systemic transplantation of BM-MSCs failed to suppress eosinophils and Th2-related cytokines, indicating that MSCs exert their immunomodulatory function through an IFN-γ-dependent process.⁸² Furthermore, Ge *et al.* confirmed that BM-MSC infusion reversed airway remodeling and

airway inflammation in mice with asthma by upregulating IL-12 expression and downregulating IL-13, IL-4, IgG1, IgE and IgG2a expression.⁸³ Moreover, in patients with asthma, dental follicle MSCs inhibit the proliferation of CD4⁺ T cells and reduce effector and effector memory CD4⁺ T cell numbers, as reported by Genc, D. and colleagues.⁸⁴ In contrast, in animal models, BM-MSCs fail to reduce OVA-induced T cell proliferation. This discrepancy may be due to the different species and the difference between in vivo and in vitro stimulation.⁸² These results illustrate the beneficial effect of MSCs on animals and humans, and the mechanism underlying this effect may involve the regulation of cytokines toward a new Th1/Th2 balance and modulation of T cell proliferation.

It has been confirmed that IL-17 and T regulatory cells (Tregs) have important roles in the development of asthma.^{85–87} Lathrop, M. J. and his colleagues demonstrated that murine BM-MSCs reduced Th2- and Th17-associated secretions in BALF from *Aspergillus* hyphal extract-challenged AAI mice, which indicates the immunomodulatory function of MSCs in the Th2/Th17 balance.⁸⁸ Moreover, Li *et al.* found that human placental MSCs not only decreased IL-17 expression but also significantly enhanced the generation of Tregs and increased the expression of IL-10 and

forkhead box P3 (Foxp3) in rats with asthma.⁸⁹ Similarly, Nemeth *et al.* found a stable increase in the Treg number in an asthmatic mouse model over time.⁶³ In mice with asthma, Dai and colleagues showed that AD-MSC administration could restore the number of Tregs and rescue the impaired of the IL-10, Foxp3, and IL-17 levels.⁹⁰ A similar result was also confirmed by Cho *et al.*⁹¹ Furthermore, Li *et al.* demonstrated that the increase in Tregs driven by MSCs was related to heme oxygenase-1 (HO-1), which is a rate-limiting intracellular enzyme. The overexpression of HO-1 stimulated the generation of Tregs, and its inhibition reduced the number of Tregs.⁹² Kavanagh *et al.* found that the efficacy of human BM-MSCs was blocked after ablating Treg responses. However, despite limited Treg function, MSCs still obviously decreased the pathology in an AAI model.⁶⁴ These results suggest that multiple Treg-dependent and Treg-independent mechanisms of therapeutic action are employed by MSCs.

In addition to T cells, DCs and macrophages play important roles in the development of asthma. DCs, the most effective antigen-presenting cells (APCs), play an important role in driving innate^{93–95} and adaptive³⁸ immune responses by modulating antigen-specific T cell activation.^{96,97} It has been reported that BM-MSCs inhibit the maturation of DCs in the peripheral blood mononuclear cell (PBMC) population of patients with dust mite (DM)-challenged asthma.⁹⁸ Furthermore, Cahill *et al.* found that MSCs induced semimature DCs, which contributed to Treg expansion via Notch signaling in an OVA-challenged murine model.⁹⁹ Duong *et al.* demonstrated that during house DM challenge in mice, MSCs inhibited the activation of airway epithelial cells by elevating the IL-1 receptor antagonist (IL-1ra) level. They also found that the increased IL-1ra level further impaired the IL-1 α autocrine loop and diminished the expression of downstream cytokines, such as high mobility group box 1 (HMGB1) and IL-25, to suppress the recruitment, antigen-presenting function, and maturation of DCs.¹⁰⁰

Macrophages, a group of highly heterogeneous cells, can alter their effector function according to different local signals. Generally, M1 macrophages become activated via IFN- γ and toll-like receptor (TLR) ligands and mainly modulate host defense. M2 macrophages, which are activated via IL-4 or IL-13, exert anti-inflammatory and tissue repair functions.²⁹ Mathias *et al.* found that human umbilical cord blood (hUCB)-MSCs increased the IL-10 production of Tregs through alveolar macrophages to attenuate asthma in an OVA-challenged murine model.¹⁰¹ Furthermore, Takeda *et al.* reported that during allergic AHR, MSCs pretreated with IFN- γ remarkably enhanced the function of CCR2⁺ monocyte and macrophage recruitment through increased chemokine (C–C motif) ligand 2 (CCL2) secretions of MSCs. Then, MSCs enhance the production of IL-10 in these recruited cells to suppress inflammation.¹⁰² Song *et al.* showed that human BM-MSCs provoked a shift from M1 macrophages to M2 macrophages and alleviated asthma; however, MSCs did not change the total number of macrophages. Moreover, they also demonstrated that such M1/M2 polarization of macrophages could be reversed by suppressing TGF- β signaling.¹⁰³ Interestingly, Braza *et al.* further confirmed that macrophages acquired an M2 anti-inflammatory phenotype by phagocytizing MSCs, which in turn attenuated asthma.¹⁰⁴

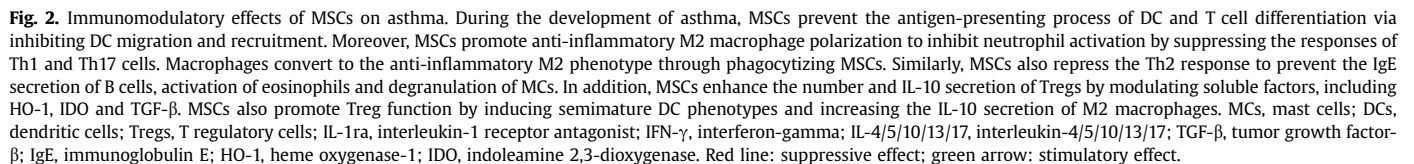
Asthma is characterized by airway inflammation and remodeling.¹⁰⁵ In a toluene diisocyanate-induced asthma model, BM-MSC administration obviously attenuates airway remodeling, which includes decreased goblet cell and airway smooth muscle cell hyperplasia and inhibits the fibrosis of subepithelial basement membranes.¹⁰⁶ Marinas-Pardo *et al.* found that the administration of MSCs in an asthmatic model attenuated contractile tissue remodeling by decreasing α -smooth muscle actin (α -SMA) levels

and extracellular matrix (ECM) deposition.¹⁰⁷ Goldstein *et al.* further demonstrated that human BM-MSCs reduced airway remodeling by inhibiting ECM deposition, specifically by suppressing the production of collagen I, collagen III, and hyaluronan.¹⁰⁸ In addition, Kokubun *et al.* reported that BM-MSCs showed a phenotype similar to that of epithelial lineage cells for repairing airway epithelia and alleviating airway remodeling.¹⁰⁹ Furthermore, Chang *et al.* showed that MSCs could alleviate asthmatic airway remodeling, and the underlying mechanism may be associated with the inhibition of TGF- β 1-induced epithelial–mesenchymal transition.¹¹⁰ Later, Zong *et al.* confirmed that iPSC-MSCs decreased airway remodeling and fibrosis in an asthmatic model through the TGF- β 1-Smad2/Smad3 signaling pathway.¹¹¹

Because the factors secreted by MSCs have been shown to contribute to beneficial therapeutic outcomes in asthma, research on MSC CM is reasonable.¹¹² Accumulating evidence has shown that CM derived from MSCs has therapeutic effects on asthmatic models. Keyhanmanesh *et al.* indicated that the systemic administration of CM modulated the differentiation of Th1/Th2 effector T cells by regulating the levels of T-bet and GATA-3 in an OVA-challenged asthmatic model.¹¹³ After culturing in the BM-MSC CM, monocytes exhibited decreased production of nitric oxide (NO) and secretion of factors such as IL-12 and IL-4. These monocytes also produced more IL-10 and TGF- β . Moreover, the CM altered the proportion of CD68⁺/CD206⁺ cells in the monocyte population. Furthermore, in an OVA inhalation mouse model, the authors confirmed that the administration of these monocytes alleviated the severity of asthma with decreased serum IgE levels and eosinophil counts in the BALF and suppressed nuclear factor kappa-B (NF- κ B) mRNA levels in the lung tissue.¹¹⁴ These findings suggest that MSCs mediate their therapeutic benefits via a paracrine but not a cellular pattern.

The secreted biological factors of MSCs play key roles in their therapeutic function. Many groups have begun to focus on the specific components with therapeutic activity. Recently, EVs, which include exosomes and microvesicles, have been demonstrated to be regulators of a newly identified intercellular communication system that is necessary in different physiological and pathophysiological processes. The EVs of MSCs have been shown to have a beneficial effect similar to that of MSCs themselves in asthma. Cruz *et al.* found that both CM and EVs from human BM-MSCs and mouse BM-MSCs could decrease the severity of AHR and lung inflammation in a mouse model of AAI.¹¹⁵ Similarly, de Castro *et al.* reported that in an OVA-induced asthmatic mouse model, human AD-MSCs and their EVs relieved AHR and airway remodeling but acted differently on Tregs in the BALF, T cells in the lymph nodes, and associated inflammatory molecules. Interestingly, the authors further found that only EVs and not MSCs decreased lung mechanical changes.¹¹⁶ In contrast, some research has reported that human AD-MSCs reduce static lung elastance.^{91,107,117} These differences might be caused by the number of AD-MSCs, timing of AD-MSC treatment and severity of asthma. Exosomes, vesicles ranging in size from 30 to 100 nm, may be a vector for soluble MSC molecules.¹¹⁸ MSC exosomes carry approximately 200 types of proteins with immunosuppressive functions.¹¹⁹ Du *et al.* confirmed that MSC exosomes stimulated the proliferation and immunomodulatory ability of Tregs by enhancing the secretion of IL-10 and TGF- β 1 in PBMCs from patients with asthma.¹²⁰

All of these studies have confirmed the antiallergic properties and therapeutic benefits of MSCs and their EVs in asthma (Fig. 2), suggesting a promising future for their clinical use. In particular, exosomes have the powerful potential to be a better choice for treating allergic disease.



Furthermore, the clinical value of MSCs in AD has been confirmed via clinical trials (phase I/IIa). Kim, H. S. *et al.* found that the transplantation of hUCB-MSCs could significantly decrease the Eczema Area and Severity Index (EASI) score of 55% of patients with moderate-to-severe AD. In addition, the patients administered hUCB-MSCs showed 33% and 50% reductions in the

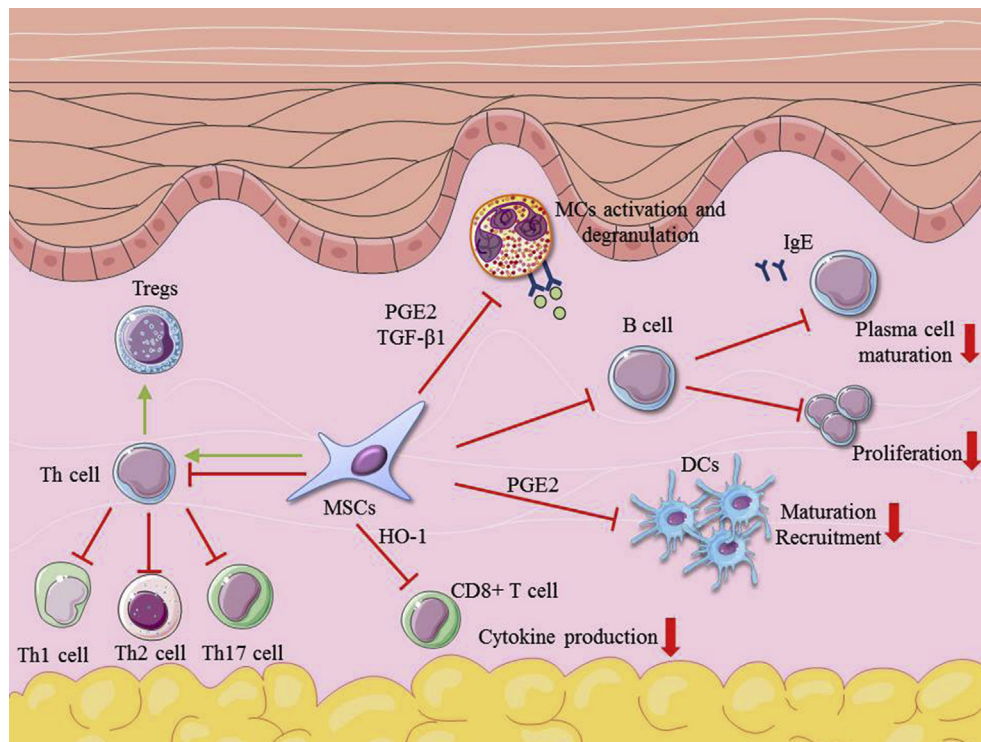


Fig. 3. Immunomodulatory effects of MSCs on allergic skin diseases. During the process of allergic skin diseases, MSCs inhibit DC migration and recruitment via mediating PGE₂. MSCs suppress Th cell differentiation and the responses of Th1, Th2 and Th17 cell, but promote the number and function of Tregs. Moreover, MSCs repress the cytokine production of CD8⁺ T cells and inhibit the proliferation and IgE secretion of B cells. Additionally, MSCs suppress MC activation and degranulation by modulating PGE₂ and TGF-β1. MSCs also suppress DC maturation and recruitment via PGE₂. MSCs inhibit B cell maturation and proliferation via PGE₂. MSCs inhibit CD8⁺ T cell cytokine production via HO-1. Red line: suppressive effect; green arrow: stimulatory effect.

Investigator's Global Assessment (IGA) score and SCORing Atopic Dermatitis (SCORAD) score, respectively. In particular, the pruritus score decreased by 58%. Moreover, the hUCB-MSCs reduced the serum IgE levels and eosinophil count in the patient blood without the occurrence of serious adverse events.¹³⁴ This clinical study was the first to confirm the efficacy and safety of allogeneic MSCs for AD.

Allergic contact dermatitis (ACD)

ACD, a type of dermal inflammation, is caused by a type IV hypersensitivity reaction mediated by T cells due to repeated contact with allergens. In the clinic, ACD is characterized by rash, blisters and itch. During ACD, after the innate immune system recognizes a hapten, secreted proinflammatory cytokines induce activated DCs to migrate to the draining lymph node (DLN), where they stimulate memory and naive T cells via their antigen-presenting function. Finally, effector T cells and proinflammatory molecules contribute to inflammation. Additionally, MC degranulation also plays a key role in the pathological process of ACD.¹³⁵ Despite the obvious advances in intensive treatments for this disease, patients who are resistant to steroids or systemic immunosuppressive agents still have few therapeutic choices. Therefore, several studies have focused on MSC-based therapy due to the immunosuppressive properties of MSCs (Fig. 3).^{67,136–139}

The hapten-induced murine contact hypersensitivity (CHS) model is a common animal model for studying the mechanism of ACD. Lim *et al.* reported that intravenously injected MSCs preferentially migrated into the DLN, where they produced NO to promote T cell apoptosis and ameliorate the CHS reaction.¹³⁶ Kikuchi *et al.* demonstrated that AD-MSCs may decrease IFN-γ but not IL-10

expression to induce the self-limiting course of ACD.¹³⁷ Additionally, our group showed that intravenous injection of human gingiva-derived MSCs (GMSCs) obviously attenuated CHS and reduced the recruitment of DCs, CD8⁺ T cells, Th17 cells and MCs as well as the levels of various inflammatory cytokines. They also boosted the local number of Tregs and the expression of IL-10 in the DLN and allergic ear tissue. Furthermore, we found that GMSCs pretreated with indomethacin, an inhibitor of COX-1/2, blocked the GMSC-mediated suppressive effects on CHS. In vitro, GMSCs directly inhibited DC differentiation and MC activation, and these suppressive effects were reversed by indomethacin. Mechanistically, GMSCs inhibited MC activation partly via the TNF-α/PGE₂ feedback axis.⁶⁷ Recently, Li *et al.* found a similar result, as a regional injection of GMSCs resulted in more obvious CHS mitigation than a systemic infusion during the late phase of CHS. Indomethacin pretreatment dramatically blocked the GMSC-mediated suppressive effects. Moreover, GMSC infusion increased the expression of prostaglandin E receptor 3 (EP₃). Applying an EP₃ agonist obviously alleviated CHS, producing a change similar to that observed with GMSC injection.¹³⁸ Chen *et al.* discovered that silencing stanniocalcin-2 (STC2) in MSCs obviously inhibited the MSC functions involved in suppressing TNF-α and IFN-γ secretion by CD8⁺ T cells. Importantly, STC2 expression knockdown abrogated the therapeutic benefit of MSCs in a CHS murine model. Mechanistically, STC2 is responsible for the MSC-mediated decrease in CD8⁺ cytotoxic type I T cells by modulating HO-1 activity.¹³⁹

Although many results have indicated the benefits of MSC treatment in ACD, further clinical and mechanistic studies are needed to address the current lack of knowledge about MSC-based therapy and ACD.

Allergic rhinitis (AR)

AR, characterized by nasal itching, sneezing, rhinorrhea, and congestion, is a prevalent yet underappreciated inflammatory disease of the nasal mucosa.¹⁴⁰ After allergens are inhaled, DCs in the nasal mucosa present the allergens to T cells in the DLN to cause a Th2-type allergic reaction.¹⁴¹ The release of Th2-related cytokines increases the IgE production of B cells and the recruitment of eosinophils in the nasal tissue. Furthermore, the allergens combine with allergen-specific IgE on MCs, resulting in the secretion of histamine, which contributes to the early symptoms of AR. In addition, the influx of inflammatory cells induced by histamine and TNF- α plays a key role in the late phase of AR.^{142,143} Currently, AR treatment includes mainly MC stabilizers, antihistamines, leukotriene receptor antagonists and steroids. In addition, allergen-specific immunotherapy has the potential to cure AR. However, even with the best pharmacotherapy, approximately 20% of patients with AR remain highly symptomatic; thus, new strategies are required.¹⁴²

In recent years, MSCs have been confirmed to suppress inflammation as a promising therapy for AR. Cho *et al.* found that in a mouse model of AR, AD-MSCs could localize to the nasal mucosa and reduce the infiltration of eosinophils by shifting to a Th1-type response from a Th2-type immune reaction to allergens.¹⁴⁴ Fu *et al.* reported that human iPSC-MSCs regulated T cell phenotypes toward the suppressive Th2 phenotype by inducing Treg expansion, which was associated with PGE2 expression and cell–cell contact.¹⁴⁵ Desai, M. B. *et al.* demonstrated that in contrast to MSCs in allergic asthma, MSCs in an AR mouse model increased inflammatory cytokine production and presented allergens to APCs, which resulted in the promotion, not the inhibition, of lymphocyte proliferation. The authors further confirmed that this antigen-presenting function of MSCs was relevant to enhancing the expression of major histocompatibility complex (MHC)-II and CD86. The different therapeutic effects of MSCs on allergic asthma and AR may depend on the specific disease.¹⁴⁶ Fan *et al.* found that iPSC-MSCs altered the balance between Th1 and Th2 cells, increased the proliferation of quiescent lymphocytes, and enhanced the activation of T cells and Tregs via NF- κ B signaling.¹⁴⁷ Samivel *et al.* reported that tonsil-derived MSCs (T-MSCs) significantly attenuated allergic symptoms in an AR mouse model. Furthermore, the administration of T-MSCs inhibited Th2-associated factors and IgE production in B cells. Additionally, the levels of IL-25, IL-33 and eosinophil chemokines related to inflammatory cell infiltration, such as eotaxin-1 (CCL11) and eotaxin-2 (CCL24), were suppressed in the nasal mucosa.¹⁴⁸ Yang *et al.* showed that ecto-MSCs migrated to inflamed nasal tissue and attenuated the pathological change. Furthermore, MSCs enhanced the Th-1 immune response by upregulating IFN- γ levels, while they inhibited the Th-2 immune response by downregulating IL-4, IL-5 and IL-10 expression in an AR mouse model.¹⁰ Similar therapeutic benefits and mechanisms have also been confirmed for BM-MSCs.^{148,149} Furthermore, Li *et al.* found that hUCB-MSCs inhibited histamine secretion and macrophage recruitment at the inflammatory site in rats with AR.¹⁵⁰

Allergic conjunctivitis (AC)

AC, the most common mucosal allergic disease, is characterized by symptoms of chemosis, eyelid swelling, sneezing and itching.¹⁵¹ General therapies, including antihistamines, intranasal corticosteroids and antileukotrienes, have good effects that alleviate AC symptoms. Allergen immunotherapy is a potential choice for patients with poor responses to novel treatments. However, the adverse effects of these therapies and the treatment of patients

with inadequately controlled AC are still large challenges. Therefore, exploring more effective therapies is urgently needed.

Our group found that the local instillation of CM from BM-MSCs stimulated by TNF- α (MSC-CMT) dramatically mitigated the clinical signs of experimental AC induced by ragweed pollen.¹⁵² We also found that MSC-CMT obviously decreased the amount of inflammatory cells and the levels of related molecules, such as NF- κ B p65, TNF- α and IL-4.¹⁵² Moreover, in vitro, MSC-CMT also decreased MC activity and the IgE level in B cells and alleviated the vascular hyperpermeability induced by histamine.¹⁵² In vivo, MSC-CMT also suppressed the secretion of IgE and histamine, recruitment and activity of MCs, and hyperpermeability of vessels in the conjunctiva.¹⁵² Our group also demonstrated that the beneficial outcomes were blocked by a COX2-specific small interfering RNA. These results indicate that the antiallergic effect of MSC-CMT in AR might be mediated by COX2.¹⁵²

Conclusion

The accumulated studies suggest a potential future for the clinical application of MSCs, especially in allergic diseases. In the future, many allergic diseases, such as asthma, rhinitis, dermatitis, conjunctivitis, and anaphylaxis, will benefit from MSC administration. As our experimental knowledge of MSCs expands, the therapeutic strategy might ultimately be uniquely tailored for allergic disease. In some diseases, MSCs have a weak inhibitory effect on the remodeling process due to lower levels of specific biological molecules and growth factors,^{107,153–155} and more powerful therapeutic MSCs are thus required. Abreu *et al.* found that the serum from an asthmatic mouse model induced apoptosis and the secretion of anti-inflammatory mediators from MSCs. These MSCs had a stronger therapeutic effect, further attenuated AAI and airway remodeling and promoted lung function.¹⁵⁶ In other diseases, the specific mechanism underlying the beneficial outcomes produced by MSCs might be more complex, requiring a combination of pretreated MSCs. MSCs with the erythropoietin gene¹⁵⁷ and high angiopoietin-1 expression¹⁵⁸ or combined with serelaxin¹⁵⁹ and simvastatin^{160,161} could enhance the efficacy of modulating the remodeling process and AHR in allergic airway disorders. Similarly, in an AD mouse model, MSCs pretreated with superoxide dismutase 3 could promote a therapeutic effect by modulating immune cell activation.¹⁶² In addition, administering both MSCs and telocytes (TCs) has high efficacy in an asthmatic mouse model because of the supportive function of the TCs.¹⁶³

For most clinical trials and fundamental studies with MSCs, ex vivo culture is usually needed. However, the culture conditions do not have any standard and might change the regeneration, proliferation and differentiation abilities of MSCs.¹⁶⁴ Moreover, the cell senescence and aging might also influence the therapeutic effect of MSCs.^{165,166} Additionally, the risk of MSC transformation is controversial¹⁶⁷ but must be taken into consideration during MSC-based therapy.

Replacing MSCs with the targeted delivery of MSC-derived EVs (MSC-EVs) might be feasible. The more significant efficacy in the treatment and clinical diagnosis of MSC-EVs compared with that of MSCs has attracted considerable attention. Compared with MSCs, MSC-EVs, which are more convenient to store and manage, have weaker immunogenicity and graft rejection.^{168,169} Moreover, MSC-EVs are better than any other promoter or inhibitor because they are not diluted in intra- or extracellular spaces. An increasing number of studies have shown that MSC-EVs have the powerful potential to interfere with cancer development, alleviate immune-related diseases and promote the regeneration of various organs.^{49,170–173} Regardless of the treatment modality used, all treatments must be confirmed to be safe, efficient, economical,

easily produced, and conveniently used in clinical practice without adverse effects.

Underlining the nature of the present research on MSC treatments is necessary. There is still much to explore regarding the therapeutic efficacy of MSCs derived from various tissues in different allergic diseases. The long-term efficacy and duration of local or systemic MSC transplantation are still not clear. The risk of adverse events during MSC in vitro culture still needs to be prevented. However, as long-term safety data and the number of therapeutic efficacies in the clinic accumulate, more effective approaches that can benefit patients with allergic disorders that cannot be cured with conventional treatments are possible. Generally, although MSCs have been demonstrated to have potential therapeutic value in allergic diseases, enhancing their immunomodulatory functions remains difficult. Future studies need to investigate better dosing and application methods in pharmacodynamic studies and subsequent clinical trials to bring MSC-based therapies into the clinic.

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Conflict of interest

The authors have no conflict of interest to declare.

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