Mesenchymal stem cells in allergic diseases: Current status

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Introduction

Allergic diseases have become a global health problem 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, allantoicsums and the therapy of allergic diseases, corticosteroids, antihistamines, allergic skin diseases, allergic rhinitis, and allergic conjunctivitis. In the most prevalent allergic disorders include allergic asthma, tissue (Table 1).4 Hematopoietic, stromal precursor cells found in adult and neonatal tissues (Table 1).4–6 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 neurospheres.30,31 MSCs contribute to the regeneration of damaged tissue resulting from several disease states, including cardiovascular disorders, liver damage, kidney injury, 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 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-β1 (TGF-β1), 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).51,52 Additionally, several researchers have found that MSCs are able to attenuate allergic immune diseases, including asthma, allergic rhinitis, 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...
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.\(^ {65} \) 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 allergic airway in rodents.\(^ {72} \) Currently, inhaled corticosteroids, β2-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 bronchial lavage fluid (BALF).\(^ {75} \) Additionally, MSCs have beneficial effects on severe refractory neutrophil-predominant asthma, which is characterized by a low responsiveness or even resistance to steroids.\(^ {75} \) In contrast, in a study on a feline model, AD-MSCs failed to attenuate airway inflammation (AAI) and airway remodeling.\(^ {70} \) 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.\(^ {79} \) 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.

<table>
<thead>
<tr>
<th>Source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induced pluripotent stem cell</td>
<td>Sun, Y. Q. et al. Stem Cells. (2012)</td>
</tr>
<tr>
<td>GMScs</td>
<td>gingiva-derived MSCs</td>
</tr>
<tr>
<td>HUCB</td>
<td>human umbilical cord blood</td>
</tr>
<tr>
<td>ILC2s</td>
<td>group 2 innate lymphoid cells</td>
</tr>
<tr>
<td>iPSC-MSCs</td>
<td>induced pluripotent stem cell-derived MSCs</td>
</tr>
<tr>
<td>LPS</td>
<td>lipopolysaccharide</td>
</tr>
<tr>
<td>NF-κB</td>
<td>nuclear factor kappa-B</td>
</tr>
<tr>
<td>NOD2</td>
<td>nucleotide-binding oligomerization domain 2</td>
</tr>
<tr>
<td>OVA</td>
<td>ovalbumin</td>
</tr>
<tr>
<td>PBMCs</td>
<td>peripheral blood monocytes</td>
</tr>
<tr>
<td>S-MSCs</td>
<td>skin-derived MSCs</td>
</tr>
<tr>
<td>STC2</td>
<td>stanniocalcins-2</td>
</tr>
<tr>
<td>STAT6</td>
<td>signal transducer and activator of transcription 6</td>
</tr>
<tr>
<td>T-MSCs</td>
<td>tonsil-derived MSCs</td>
</tr>
<tr>
<td>TLR</td>
<td>toll-like receptor</td>
</tr>
<tr>
<td>TCs</td>
<td>telocytes</td>
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the lung tissue and improved bronchial asthma. This relocation might depend on the stromal cell-derived factor-1a/CXCR4 axis. The suppression of TGF-β1 disturbs the migration of murine MSCs induced by CM from cockroach allergen-stimulated human epithelium. Moreover, the aryl hydrocarbon receptor also plays a key role in ameliorating inflammation by regulating MSC recruitment and immunosuppressive potential.

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. The suppression 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. 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. 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. 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. 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. 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. 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

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) legend 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.
Macrophages could be reversed by suppressing TGF-
Moreover, they also demonstrated that such M1/M2 polarization of
however, MSCs did not change the total number of macrophages.
DCs.100
recruitment, antigen-presenting function, and maturation of
as high mobility group box 1 (HMGB1) and IL-25, to suppress the
mouse model over time.63 In mice with asthma, Dai and colleagues
et al.
Asthma is characterized by airway inflammation and remodeling.
In a toluene disocyanate-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.100

Macrophages, a group of highly heterogeneous cells, can alter
their effector function according to different local signals. Gener-
ally, M1 macrophages become activated via IFN-γ and toll-like rece-
ceptor (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 and rescue the impaired of the IL-10, Foxp3, and IL-17 expressions might be caused by the number of AD-MSCs, timing of AD-
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**Allergic skin diseases**

**Atopic dermatitis (AD)**

AD, commonly known as atopic eczema, is a typical dermal inflammatory disorder characterized by eczematous cutaneous lesions and severe pruritus. Approximately 20% of children and 10% of adults suffer from AD. These patients, especially those with the moderate-to-severe type, usually have depressive and anxious emotions related to sleep disturbance. Acute AD is mediated by Th2 and Th22 cells, whereas chronic AD is caused by Th1-driven inflammatory responses. In addition to T cells, DCs, which are abundant in AD lesions, enhance the presentation of allergens and the reactions of T cells. After exposure to an allergen, MC degranulation, eosinophil and lymphocyte accumulation, and associated inflammatory molecules contribute to inflammatory processes in the skin. Regional corticosteroids are still the first-line therapy for acute AD flares. Despite the improvement and usage of advanced treatments, including biologically targeted drugs, AD cannot be treated radically. The authors further confirmed that MSCs inhibited B cell differentiation, T cell activities and cytokine production, which resulted in a beneficial effect. Additionally, Kim et al. found that subcutaneous injection of nucleotide-binding oligomerization domain 2 (NOD2)-activated hUCB-MSCs showed powerful therapeutic benefits in AD and inhibited the infiltration and degranulation of MCs via increased production of PEG2 and TGF-β1. Moreover, Shin et al. found that human AD-MSCs not only inhibited the function of MCs but also clearly suppressed the proliferation and maturation of B cells via cyclooxygenase (COX)-2 signaling in an experimental AD animal model. Orciani et al. reported that compared with MSCs derived from the skin (S-MSCs) of healthy people undergoing surgery for epidermal cysts, S-MSCs from the lesional skin of AD patients secreted more Th1/Th17 cytokines, whereas the levels of Th2 factors were reduced. This finding suggests that MSCs modulate the Th1/Th17 balance in AD patients. Furthermore, Cho et al. demonstrated that human AD-MSC-derived exosomes were able to reduce pathological symptoms, including the clinical score, the numbers of MCs, CD86+ cells, and CD206+ cells in the dermal tissue, and the mRNA levels of associated inflammatory factors in AD mouse models.

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 expression of lymph node and cutaneous tissues was also inhibited.
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. 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 naïve 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. 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).

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. Kikuchi et al. demonstrated that AD-MSCs may decrease IFN-γ but not IL-10 expression to induce the self-limiting course of ACD. 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. 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. 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 1 T cells by modulating HO-1 activity.

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. 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. 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. Currently, AR treatment includes mainly MC stabilizers, antihistamines, leukotriene receptor antagonists and steroids. In addition, allergenspecific 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.

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. 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. 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.

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-kB signaling. Samivel et al. reported that tansil-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. 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. Similar therapeutic benefits and mechanisms have also been confirmed for BM-MSCs. Furthermore, Li et al. found that hUCB-MSCs inhibited histamine secretion and macrophage recruitment at the inflammatory site in rats with AR.

Allergic conjunctivitis (AC)

AC, the most common mucosal allergic disease, is characterized by symptoms of chemosis, eyelid swelling, sneezing and itching. 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. We also found that MSC-CMT obviously decreased the amount of inflammatory cells and the levels of related molecules, such as NF-κB p65, TNF-α and IL-4. Moreover, in vitro, MSC-CMT also decreased MC activity and the IgE level in B cells and alleviated the vascular hyperpermeability induced by histamine. In vivo, MSC-CMT also suppressed the secretion of IgE and histamine, recruitment and activity of MCs, and hyperpermeability of vessels in the conjunctiva. Our group also demonstrated that the beneficial outcomes were blocked by a COX2-specific small interfering RNA. These results indicate that the antiergic effect of MSC-CMT in AR might be mediated by COX2.

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, 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 AA and airway remodeling and promoted lung function. In other disorders, the specific mechanism underlying the beneficial outcomes produced by MSCs might be more complex, requiring a combination of pretreated MSCs. MSCs with the erythropoietin gene and high angiopeptin-1 expression, or combined with serelaxin or simvastatin, 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.

In addition, administering both MSCs and telocytes (TCs) has high efficacy in an asthmatic mouse model because of the supportive function of the TCs.

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. Moreover, the cell senescence and aging might also influence the therapeutic effect of MSCs. Additionally, the risk of MSC transformation is controversial 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. 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. 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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