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The Immunomodulatory mechanism and research progress of mesenchymal stem cells in the treatment of allergic rhinitis

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Abstract

Background Allergic rhinitis (AR) affects 10–40% of the global population, yet current therapies (drugs, immunotherapy) face limitations in efficacy and safety. Mesenchymal stem cells (MSCs) have emerged as a promising alternative due to their immunomodulatory properties.

Key Findings Preclinical studies demonstrate that MSCs from adipose, bone marrow, umbilical cord, and tonsils reduce AR symptoms (sneezing, nasal inflammation) and serum IgE (Immunoglobulin E) levels by restoring Th1/Th2 immune equilibrium and enhancing Treg (Regulatory T cells) activity. MSC-derived exosomes and hydrogel-encapsulated formulations further improve targeting and safety. However, clinical translation is hindered by heterogeneous protocols and unresolved long-term risks (e.g., tumorigenicity).

Clinical Significance MSC-based therapies offer potential for durable AR remission by addressing immune dysregulation at its root. Future efforts must prioritize standardized production, phase I safety trials, and combination strategies (e.g., exosomes + hydrogels) to accelerate clinical adoption.

Keywords Allergic rhinitis, Mesenchymal stem cells, Immunomodulation, Exosomes

Introduction

Allergic rhinitis (AR), affecting 10–40% of the global population, is a chronic inflammatory airway disease marked by sneezing, nasal obstruction, and reduced quality of life [1–4]. Current therapies (pharmacotherapy, immunotherapy, surgery) provide symptomatic relief but face limitations: drug dependency, long treatment cycles, and tissue damage. Despite these therapies, 10–20% of patients remain refractory [3], highlighting the need for immune-targeted strategies [4, 5]. As one of the most prevalent chronic inflammatory diseases of the airways caused by exposure to specific allergens [6], AR is driven by a dysregulated type 2 immune response to allergens. Exposure triggers dendritic cells (DCs) to process allergens and prime naïve T cells into Th2 cells via

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IL-4/STAT6 signaling. Th2 cytokines (IL-4, IL-5, IL-13) then drive B cell IgE switching, eosinophil recruitment, and mast cell activation, leading to nasal inflammation, mucosal edema, and barrier dysfunction [4]. Concurrently, impaired Treg activity fails to suppress Th2 polarization, perpetuating immune imbalance. These pathological hallmarks—Th2 dominance, eosinophilic infiltration, and epithelial damage—provide direct targets for stem cells-based immunomodulation.

Mesenchymal stem cells (MSCs) are a class of cells with high proliferation, self-renewal, and multidirectional differentiation potential. MSCs are a type of plastic-adherent cells, with ≥ 95% of MSCs expressing CD73, CD90, and CD105, while ≤ 2% expressing CD34, CD45, CD14/CD11b, CD19/CD79α, and HLA-DR, they also possess the ability to differentiate into osteogenic, chondrogenic, and adipogenic lineages in vitro [7]. The low immunogenicity and immunomodulatory effects of MSCs have shown broad application prospects in immunomodulation, attenuation of inflammation, and repair of injuries, and research on their applications has made great progress in related fields. Encouragingly, many studies have proved the potential and effectiveness of MSCs-mediated treatment for AR; MSCs have emerged as a transformative approach for AR by correcting Th1/Th2 imbalance and restoring immune tolerance. Preclinical studies demonstrate MSC efficacy in reducing IgE, eosinophilia, and nasal inflammation, yet clinical translation remains unexplored. MSCs counteract AR pathophysiology through multipronged strategies: (1) TGF-β(Transforming growth factor-β) secretion restores Treg/Th2 balance; (2) PGE2 (Prostaglandin E2) and IDO (Indoleamine 2,3-dioxygenase) suppress DC-mediated Th2 priming; (3) Exosomal miRNAs (e.g., miR-146a-5p) directly inhibit eosinophil activation and IgE production [3]. However, these studies are still at animal experiments stage with no clinical trials of MSCs therapy for AR currently [8, 9]. Thus, fully understanding the roles and mechanisms of MSCs-mediated immunomodulatory effects will be beneficial for the clinical trials of MSCs-based therapy. This review aimed to summarize the recent research advances, explore the underlying effects and potential mechanisms, and give a brief perspective in the future study of MSCs in treating AR.

The mechanism of MSCs in the treatment of AR

MSCs mainly play their immunomodulatory role, which is to correct the immune imbalance of various helper T cells to alleviate AR symptoms, such as enhancing the role of Treg cells, restoring the immune balance of Th1/Th2 cells, facilitating the conversion of M1 to M2 macrophages, restoring the integrity of the epithelial barrier, and regulating key cells and molecules of the type 2 immune response. It has been shown that the main mechanisms of MSC immunomodulation are inhibition of T cells through intercellular contacts, release of soluble factors, and generation of extracellular vesicles such as exosomes (Fig. 1).

Immunoregulatory mechanisms of intercellular contact (Fig. 1A)

MSCs express integrins (α1, α2, α3, α5, α6, αv, β1, β3, and β4), intercellular adhesion molecules (ICAM-1, ICAM-2), vascular cell adhesion molecule (VCAM-1), CD72 and CD58 (LFA-3) on their surface, and thus are able to bind to T lymphocytes with high affinity. Studies have shown that when T cells were co–cultured with BM–MSCs (Bone marrow–derived mesenchymal stem cells) in the Transwell system or BM–MSC conditioned medium, the inhibitory activity of T cells was eliminated, suggesting that inhibition of T cells by BM–MSCs requires MSC–T cell contact [10]. Furthermore, the T cell attraction process of MSCs can be explained by the expression of high levels of several leukocyte chemokines, such as CXCL9 (chemokine (C-X-C motif) ligand 9), CXCL10 and CXCL11 [11].

When MSCs are kept in close contact with activated immune cells, they can enhance their immunosuppressive effects [12] and thus be able to treat AR. Studies have shown that MSCs can correct the Th1/Th2 cell imbalance and promote Treg proliferation through cell-to-cell contact to achieve an anti-allergic mechanism. Human placenta-derived MSC binds to the co-inhibitory receptors on the surface of T cells through its high expression of PDL1 (programmed death-ligand 1) and PDL2, and inhibits the proliferation of T cells and cytokine production by blocking the cell cycle in the G0/G1 phase, thus correcting the over-activation of Th2 cells activation [13]. iPSC-MSCs (Induced pluripotent stem cell-derived mesenchymal stem cells) and BM-MSCs could inhibit the proliferation of CD3 T cells isolated from peripheral blood mononuclear cells of AR patients through cell-to-cell contact and PGE2 expression, promote Treg proliferation and regulate T cell phenotype to suppress Th2 [14]; iPSC-MSCs interact with ILC2 and ICOS (inducible co-stimulator) expressed on Treg by expressing ICOSL (inducible co-stimulatory ligand). Combined, ICOS-ICOSL interaction activates Tregs and inhibits Th2 [15]. MSCs can also inhibit Th2 activation by inducing the proliferation of Tregs through the Notch1 pathway [16]; iPSC-MSCs can also enhance Treg activation through the NF-κB signaling pathway. MSCs express high levels of PD-L1 and PD-L2 on their surface, which interact with the co-inhibitory receptors PD-1 (programmed cell death protein 1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) on T cells. These interactions play a critical role in suppressing T cell activation and proliferation. Specifically, PD-L1/PD-L2 binding to PD-1 on T

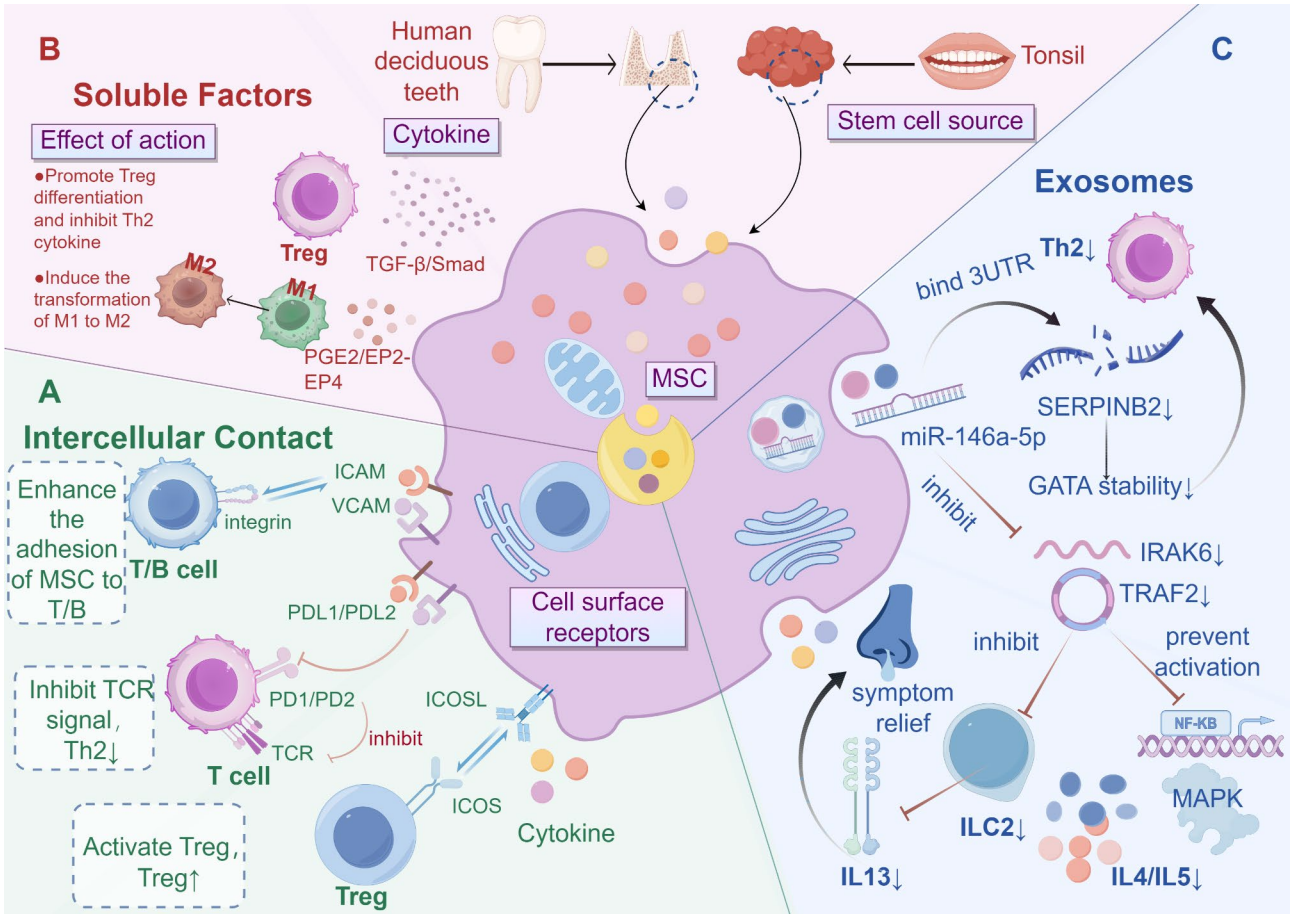

Fig. 1 The Immunomodulatory Mechanism of Mesenchymal Stem Cells(MSCs); **A**. Intercellular contact; **B**. Soluble factors; **C**. Exosomes By Figdraw. (ID: WOTTYb26ba)

cells triggers downstream signaling pathways that inhibit TCR (T cell receptor) -mediated activation. This occurs through the recruitment of SHP-1 and SHP-2 phosphatases, which dephosphorylate key signaling molecules such as ZAP70 and PKCθ, leading to the suppression of downstream signaling cascades, including the PI3K/AKT and MAPK/ERK pathways. As a result, T cell proliferation is blocked, and the cell cycle is arrested at the G0/G1 phase. Additionally, PD-L1/PD-L2 interactions with CTLA-4 further enhance immunosuppression by competing with CD28 for binding to B7 molecules (CD80/CD86) on APCs (antigen-presenting cells), thereby reducing co-stimulatory signals required for T cell activation. These mechanisms collectively contribute to the immunomodulatory effects of MSCs, particularly in promoting immune tolerance and suppressing excessive immune responses in conditions such as AR [10, 11, 13].

Besides, MSCs can realize anti-inflammatory mechanism by inhibiting pro-inflammatory M1 macrophages but enhancing anti-inflammatory M2 macrophages. It was shown that MSCs increased TSG-6 (Tumor Necrosis Factor-Stimulated Gene 6) production in MSCs through intercellular contact with pro-inflammatory M1 macrophages, and promoted the transformation of pro-inflammatory M1 macrophages into anti-inflammatory M2 macrophages in a TSG-6-dependent manner to alleviate excessive inflammation [17].

Mechanisms of Immunomodulation by the release of soluble factors

MSCs can treat AR by modulating pro-inflammatory and anti-inflammatory cytokines to ameliorate the severity of acute injury and fibrosis thereby restoring the integrity of the epithelial barrier, and by modulating the network of interactions between various types of immune cells (Fig. 1B). To date, soluble factors that have been associated with the treatment of MSCs include TGF-β, IL-10, PGE2, IDO, HGF (Hepatocyte growth factor), NO, TSG-6, IL -6, LIF (Leukemia inhibitory factor), HLA-G5 (Human leukocyte antigen G5) and IL1RA (Interleukin 1 receptor antagonist) [18].

Soluble factors secreted by MSCs can restore Th1/Th2 cell balance by modulating T cell-mediated immune responses and thus treat AR. Studies have shown that

MSC conditioned media contain significantly increased concentrations of TGF-β1, PGE2, and HGF, MSC-secreted immunomodulators, which have been implicated in the suppression of T cell activation through inhibition of T cell receptor signaling [19].

TGF-β/Smad pathway

TGF-β is a pivotal cytokine secreted by MSCs that plays a central role in immune regulation and tissue repair. TGF-β binds to its receptor TGF-βRII, which then recruits and phosphorylates TGF-βRI, forming a heterotetrameric complex. This activation triggers the phosphorylation of R-Smads (receptor-regulated Smads), specifically Smad2 and Smad3. Phosphorylated Smad2/3 forms a complex with the common mediator Smad4, which translocates to the nucleus to regulate the transcription of target genes involved in immune suppression, such as FOXP3, the master regulator of Tregs. Through this pathway, TGF-β promotes the differentiation of naïve T cells into Tregs, which are essential for maintaining immune tolerance and suppressing Th2-mediated allergic responses. Additionally, TGF-β inhibits the proliferation and activation of effector T cells and downregulates the expression of pro-inflammatory cytokines, such as IL-4 and IL-5, thereby restoring Th1/Th2 immune equilibrium in AR [20].

PGE2/EP2-EP4 pathway

PGE2 is another critical soluble factor secreted by MSCs that exerts potent immunomodulatory effects. PGE2 binds to its G-protein-coupled receptors EP2 and EP4 on immune cells, leading to the activation of adenylate cyclase and subsequent production of cAMP (cyclic AMP). Elevated cAMP levels activate PKA (protein kinase A), which phosphorylates and inhibits nuclear factor kappa B (NF-κB) and other pro-inflammatory transcription factors. This results in the suppression of pro-inflammatory cytokines, such as IL-23 and IL-22, and the promotion of anti-inflammatory cytokines, such as IL-10. PGE2 also plays a crucial role in macrophage polarization by inducing the transition of pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages. Furthermore, PGE2 inhibits the differentiation of monocytes into dendritic cells (DCs) and reduces the expression of co-stimulatory molecules (e.g., CD40, CD80, and CD86) on DCs, thereby attenuating their antigen-presenting capacity and suppressing Th2-driven immune responses in AR [19, 21].

IDO/Kynurenine pathway

IDO is an enzyme expressed by MSCs that catalyzes the degradation of tryptophan into kynurenine and other metabolites. The depletion of tryptophan in the local microenvironment inhibits the proliferation of effector T cells, as tryptophan is essential for their activation and survival. Additionally, kynurenine and its metabolites act as signaling molecules that bind to the aryl hydrocarbon receptor (AhR) on T cells, promoting the differentiation of naïve T cells into Tregs while suppressing Th17 and Th2 differentiation. IDO also modulates dendritic cell function by inducing a tolerogenic phenotype, characterized by reduced expression of co-stimulatory molecules and increased production of anti-inflammatory cytokines, such as IL-10 and TGF-β. Through these mechanisms, IDO contributes to the establishment of immune tolerance and the suppression of allergic inflammation in AR [22, 23].

MSCs can promote Treg production and maintain immune tolerance to allergens by secreting IDO [22]; Dai [23] found that MSCs from human deciduous teeth significantly inhibited the proliferation of T lymphocytes and induced the expansion of Tregs in a co-culture system. In addition to this, three soluble factors (TGF-β1, PGE2, and HGF) released from tonsil-derived MSCs can inhibit T cell activation by suppressing T cell receptor signaling and ultimately exert an immunomodulatory effect on allergic inflammatory responses.

MSCs attenuate the inflammatory response to AR by releasing soluble factors that promote macrophage phenotype switching and inhibit DC proliferation [21]. It was found that MSCs can secrete PGE2 directly or via exosomes to cause downregulation of IL-23 and IL-22 as well as enhancement of macrophage anti-inflammatory phenotype (M2); PGE2 secreted by BM-MSC inhibited differentiation of monocytes into DCs, whereas PGE2 inhibitors restored DC differentiation and function; and MSC-secreted C-CSF, VEGF, LIF, B7-H4, and PGE2 significantly stimulated the differentiation of inflammatory M1 macrophages into anti-inflammatory M2-like macrophages.

Mechanisms of exosome-mediated immunoregulation

MSCs can release exosomes, which are considered to be key paracrine factors responsible for the therapeutic function of MSCs and play a cell-free therapeutic role in immunomodulation (Fig. 1C). Exosomes are active components in the immunosuppressive function of MSCs, and have good prospects for clinical application [24]. Based on the performance of exosomes in drug delivery, exosomes have been designed to deliver different therapeutic payloads such as small molecule and nucleic acid drugs for targeted drug delivery, which is promising in MSC-based intranasal delivery for therapeutic AR. It was found that exosomes can be taken up by ILC2 and inhibit the function of activated ILC2 in AR patients and ILC2 dominant asthmatic mice, in addition, exosomes regulate other cells involved in allergic responses, such as DC, Treg and Th2 cells to inhibit the development of AR [25]; exosomes inhibit the differentiation of human monocytes

to immature DCs by down-regulating the expression of CD40, CD80, CD86, and HLA-DR, inhibit the initiation of type 2 immune response by mature DCs, and promote Treg expansion [26].

Exosomes are also capable of immunomodulation through their own significantly enriched miRNAs. Reis [27] identified 49 miRNAs that were significantly enriched in exosomes, among which miR-21-5p has been shown to inhibit AR initiation by decreasing the migratory capacity of DC through reducing the expression of CCR7. MiR-146a-5p is a well-characterized microRNA (miRNA) that plays a critical role in modulating immune responses, particularly in allergic diseases such as AR. It is highly enriched in MSC-derived exosomes and exerts its immunomodulatory effects by targeting key molecules involved in the activation of type 2 innate lymphoid cells (ILC2s) and Th2 cell differentiation. Below, we describe the molecular mechanisms by which miR-146a-5p targets SERPINB2, IRAK6, and TRAF2 to suppress ILC2 activation and Th2 differentiation.

Targeting SERPINB2

SERPINB2 (serpin family B member 2), also known as plasminogen activator inhibitor-2 (PAI-2), is a serine protease inhibitor that has been implicated in Th2 cell differentiation. MiR-146a-5p directly binds to the 3' untranslated region (3'UTR) of SERPINB2 mRNA, leading to its degradation and subsequent downregulation of SERPINB2 protein expression. SERPINB2 is known to promote Th2 differentiation by enhancing the stability and activity of transcription factors such as GATA3, which is essential for Th2 cytokine production (e.g., IL-4, IL-5, and IL-13). By suppressing SERPINB2, miR-146a-5p inhibits GATA3-mediated Th2 differentiation and reduces the production of Th2 cytokines, thereby alleviating allergic inflammation in AR [25].

Targeting IRAK6 and TRAF2

IL-1 receptor-associated kinase 6 (IRAK6) and TNF receptor-associated factor 2 (TRAF2) are key components of the IL-33/ST2 signaling pathway, which is critical for ILC2 activation. IL-33, an alarmin released by epithelial cells during allergic inflammation, binds to its receptor ST2 on ILC2s, triggering the recruitment of IRAK6 and TRAF2 to the signaling complex. This leads to the activation of downstream signaling pathways, including NF-κB and MAPK, which promote ILC2 proliferation and the production of type 2 cytokines (e.g., IL-5 and IL-13). MiR-146a-5p directly targets IRAK6 and TRAF2 mRNA, leading to their degradation and suppression of IL-33/ST2 signaling. As a result, ILC2 activation is inhibited, and the production of type 2 cytokines is reduced, contributing to the alleviation of allergic inflammation in AR [28].

Combined effects on ILC2 and Th2 suppression

By targeting SERPINB2, IRAK6, and TRAF2, miR-146a-5p exerts a multi-faceted inhibitory effect on both ILC2 activation and Th2 differentiation. The suppression of SERPINB2 reduces Th2 cytokine production, while the inhibition of IRAK6 and TRAF2 blocks IL-33/ST2 signaling, thereby preventing ILC2-driven inflammation. These combined effects make miR-146a-5p a potent regulator of type 2 immune responses and a promising therapeutic target for AR. So miR-146a-5p plays a critical role in suppressing ILC2 activation and Th2 differentiation by targeting SERPINB2, IRAK6, and TRAF2. These molecular mechanisms highlight the potential of miR-146a-5p as a therapeutic agent for modulating type 2 immune responses in allergic rhinitis. The references provided support the scientific validity of these findings and can be incorporated into the revised manuscript to enhance its depth and rigor [26].

Studies on the treatment of AR with MSCs from different sources(Table 1)

Adipose-derived mesenchymal stem cells (ASCs)

Adipose mesenchymal stem cells (ASCs) have the ability of multidirectional differentiation, stable proliferation, and promotion of repair, and can be differentiated into hematopoietic cells, skeletal muscle cells, neural cells, and cardiomyocytes, and have the ability to reduce apoptosis of fibroblasts, promote proliferation, and participate in neoangiogenesis, etc. The discovery of ASCs with immunosuppressive effects provides new ideas for exploring the mechanism of AR and its treatment [29].

Ebrahim [8] investigated the potential effects of ASCs on AR mice and the mechanism of immunomodulation. The mice were injected with ASCs intraperitoneally, and showed a significant reduction of allergic symptoms, restoration of nasal mucosal structure, decrease in OVA–specific immunoglobulin E (IgE), IgG1, IgG2a, and histamine, and increase in prostaglandin E2 (PGE2); induction of nasal innate cytokines, such as interleukin (IL)–4 and TNF–α; suppression of chemokines, such as CCL11 and vascular cell adhesion molecule–1 (VCAM–1); and downregulation of transforming growth factors. Nasal innate cytokines, such as interleukin (IL)–4 and TNF–α, were down–regulated; chemokines, such as CCL11 and vascular cell adhesion molecule–1 (VCAM–1), were suppressed; and transforming growth factor–beta (TGF–β) expression was up–regulated, suggesting that ASC attenuates the symptoms associated with AR through a range of immunomodulatory mechanisms.

Cho et al. [30] investigated the immunoregulatory mechanisms of ASCs in an ovalbumin–induced AR mouse model, and found that ASCs significantly attenuated allergic symptoms and suppressed eosinophilic

Table 1 Therapeutic results of different MSCs in experimental allergic rhinitis models

Study	MSC Source	Characterization Methods	Dosage	Administration Route	Outcome Measures	Mechanisms of Action
Cho et al., 2014	Adipose tissue	Flow cytometry (CD73+, CD90+)	2×10^6 cells	Intravenous	↓IgE, ↓IL-4, ↓eosinophil infiltration, ↑IFN-γ	Th1/Th2 balance restoration, Treg induction
Zhao et al., 2016	Bone marrow	Flow cytometry (CD29+, CD44+)	0.5×10^6 cells	Intravenous	↓OVA-specific IgE, ↓IL-4, ↓IL-5, ↓IL-13, ↑IFN-γ, ↓STAT6 signaling	STAT6 pathway modulation, Th cell homeostasis
Samivel et al., 2015	Tonsil tissue	Differentiation assays	0.5×10^6 cells	Intravenous	↓IL-25, ↓IL-33, ↓eosinophil chemokines, ↑IFN-γ	MAPK/NF-κB pathway inhibition
Kan et al., 2020	Umbilical cord	Flow cytometry (CD105+, CD44+)	5×10^6 cells	Intraperitoneal	↓IL-4, ↓TNF-α, ↓IgE, ↑IFN-γ	Macrophage recruitment modulation
Li et al., 2017	Umbilical cord	Flow cytometry (CD29+, CD44+)	5×10^6 cells	Intraperitoneal	↓IL-4, ↓IL-5, ↓IL-13, ↓goblet cell hyperplasia, ↓eosinophil infiltration	Th1/Th2 balance restoration, epithelial repair
Yang et al., 2015	Nasal mucosa	Flow cytometry (CD73+, CD90+)	1×10^6 cells	Tail vein injection	↓IL-4, ↓IL-5, ↓IL-6, ↓IL-17, ↑IFN-γ	Immune modulation via cytokine regulation
Ebrahim et al., 2019	Adipose tissue	Flow cytometry (CD73+, CD90+)	1×10^6 cells	Intraperitoneal	↓OVA-specific IgE, ↓IL-4, ↓TNF-α, ↓CCL11, ↓VCAM-1, ↑TGF-β	Collagen fiber deposition reduction, immune modulation
Zhong et al., 2019	iPSC-derived MSCs	Flow cytometry (CD73+, CD90+)	1×10^8 cells/kg	Intravenous	↓OVA-specific IgE, ↓IL-13, ↓eosinophil infiltration	TGF-β1-Smad2/3 signaling pathway modulation

inflammation in the nasal mucosa. In this study, they found that more ASCs migrated into the nasal mucosa with intravenous administration compared with control mice, and the surface immune response to allergens may improve the environment for ASC recruitment at the allergen entry site; the IgE and IgG2/IgG2a ratios representing the Th2 immune response were significantly reduced by pretreatment with ASCs, compared with a significant increase in the OVAs representing the Th1 immune response by pretreatment with ASCs. While IL–4, IL–5, and IFN–γ levels being detected by spleen tissue showed an increase in Th1–associated IFN–γ levels and a decrease in Th2–associated IL–4 and IL–5 levels, suggesting that i.v. injection of ASCs induces a Th2 to Th1 transition in the AR mouse model, i.e., possessing the ability to the role of regulating Th1/Th2 immune balance to treat AR.

Yang et al. [31] induced AR in female BALB/c mice using OVA. One day after the last nasal instillation, the mice were divided into groups and treated with either PBS or hADSC - EVs. Subsequently, relevant symptoms and biological changes were evaluated. The results showed that hADSC - EVs significantly alleviated the nasal symptoms of the mice, reduced inflammatory infiltration (Fig. 2A2-B), decreased the levels of OVA - specific IgE, IL − 4, and IFN - γ in the serum, altered the mRNA levels of IL − 4 and IFN - γ in the spleen, and increased the Th1/Th2 cell ratio (Fig. 2C2-D). The treatment efficacy index of hADSC - EVs was higher than that of human - derived MSCs reported previously and the previous ADSC treatment. That is, hADSC - EVs can improve AR symptoms by regulating cytokine secretion and the Th1/Th2 immune equilibrium, and are expected to become a treatment strategy for AR. Further animal studies are needed to clarify the mechanisms and optimize the potential clinical protocols.

Tonsil-derived mesenchymal stem cells (T-MSCs)

Stromal cells isolated from human tonsils **(T-MSCs)** have the potential to differentiate not only into a variety of mesenchymal-derived cell types, but also into FDC-like cells upon cytokine stimulation in vitro. Compared to MSCs derived from adipose, MSCs from bone marrow showed higher proliferation enriched expression of immunomodulatory proteins.

Samivel et al. [8] compared the effects and underlying mechanisms of T-MSCs and ASCs on allergic inflammation in a mouse model of AR, and found that intravenous injection of T-MSC significantly reduced allergic symptoms, eosinophilic infiltration, total serum and OVA-specific immunoglobulin E (IgE), as well as the nasal and systemic Th2 cytokine profiles. Further analysis showed that levels of IL-25, IL-33, and eosinophil chemokines associated with inflammatory cell infiltration (e.g., eotaxin-1 (CCL11) and eotaxin-2 (CCL24)) in the nasal mucosa were also suppressed in the T-MSC injection group. It was demonstrated that T-MSCs could correct the Th1/Th2 immune imbalance through the immunomodulatory mechanism to achieve the effect of suppressing allergic inflammation and treating AR.

Park et al. [19] isolated T-MSCs from human palatine tonsils, evaluated the components of T-MSCs-CM, and assessed the effects of T-MSCs-CM in an AR mouse model. Results showed that T-MSCs-CM inhibited T-cell activation through MAP kinase, p65 and NFAT1 pathways, and displayed partial immunomodulatory effects in an AR mouse model(Fig. 2E and F).

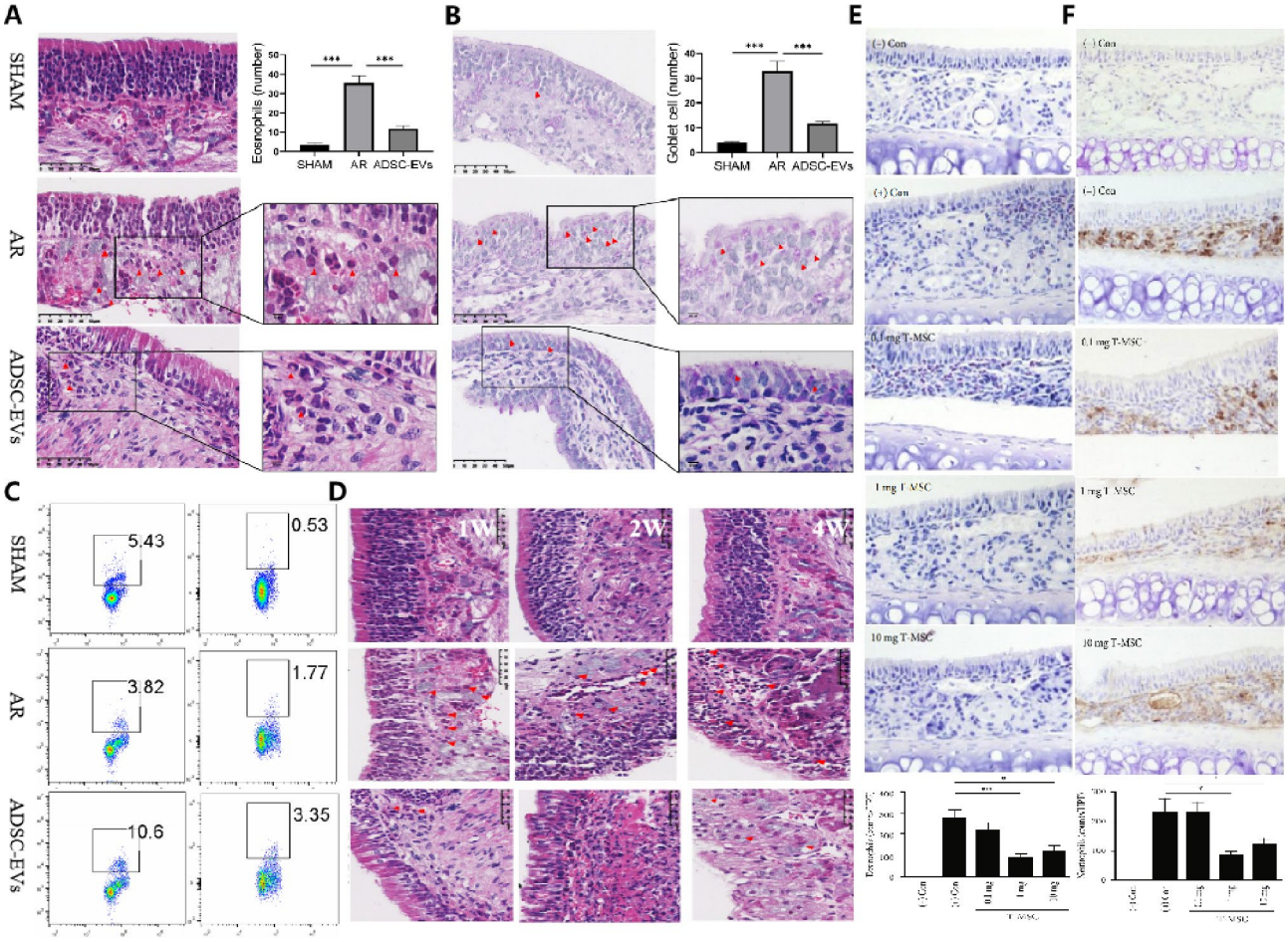

Fig. 2 ***Left***: Extracellular vesicles from ASCs ameliorate AR in mice by immunomodulatory. (**A**) ASC-EVs alleviated inflammation in the nasal mucosa of AR mice: H&E staining and quantification of eosinophils in the nasal mucosa. (**B**) PAS staining and quantification of goblet cells in the nasal mucosa. Data are expressed as mean ± SD, $n = 8$ or 24, $^{**}P < 0.01$, $^{***}P < 0.001$.(**C**) Flow cytometry analysis of Th1 cells and Th2 cells in splenic lymphocytes. Data are expressed as mean ± SD, $n = 8$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.(**D**) Multiple dosing durations of ASC-EVs alleviated inflammation in the nasal mucosa of AR mice: H&E staining of the nasal mucosa [31]. *Copyright © 2023 Yang, Pan, Zhang, Wang, lai, Zhou, Zhang, Fan, Deng, Gao and Yu.* ***Right***: The supernatant of T-MSCs has antiallergic effects in AR mouse model.(**E**) Effect of T-MSCs on an allergic mouse model: The number of infiltrated.(**F**) Effect of T-MSCs on an allergic mouse model: The number of eosinophils [19]. *Copyright © 2020 In-Su Park et al*

Human umbilical cord mesenchymal stem cells (hUC-MSCs)

Human umbilical cord mesenchymal stem cells (hUC-MSCs) offer greater advantages than other stem cells, compared to the relative ease of tissue isolation when using umbilical cord, with no apparent risk or ethical constraints on the donor; in addition, hUC-MSCs have enhanced self-renewal and differentiation capabilities and are less immunogenicity [32].

Kan et al. [33] employed GFP–labeled hUC-MSCs intraperitoneal and tail injection in AR mice to evaluate the efficacy of hUC-MSCs transplantation using the mouse AR model, and found that fluorescent labeled hUC-MSCs could be seen in all major organs. Cells in the nose of mice were tracked by fluorescence microscopy and flow cytometry analysis, and the highest number of nasal hUC-MSCs was found in the second week after injection (Fig. 3A-B). This indicates that hUC-MSCs can reach the nasal cavity. The AR mice injected with hUC-MSCs had reduced inflammatory cell infiltration, and the serum concentrations of IL−4 related to Th2 were all decreased, while the expression of INF−γ related to Th1 was relatively increased, suggesting that hUC-MSCs can inhibit allergic reactions in the mouse AR model by regulating the balance between Th1 and Th2 cells.

Li et al. [20] used hUC-MSCs to investigate the effects and mechanisms in AR model mice and found that AR mice injected with hUC-MSCs had reduced AR symptoms and nasal mucosal pathology(Fig. 3C and D), and the expression of IL−4, tumor necrosis factor α, and immunoglobulin E in serum was suppressed(Fig. 3E). In addition, MSCs reduced histamine expression and macrophage recruitment in the nasal mucosa of allergic rhinitis rats. This suggests that the effect of MSCs on allergic

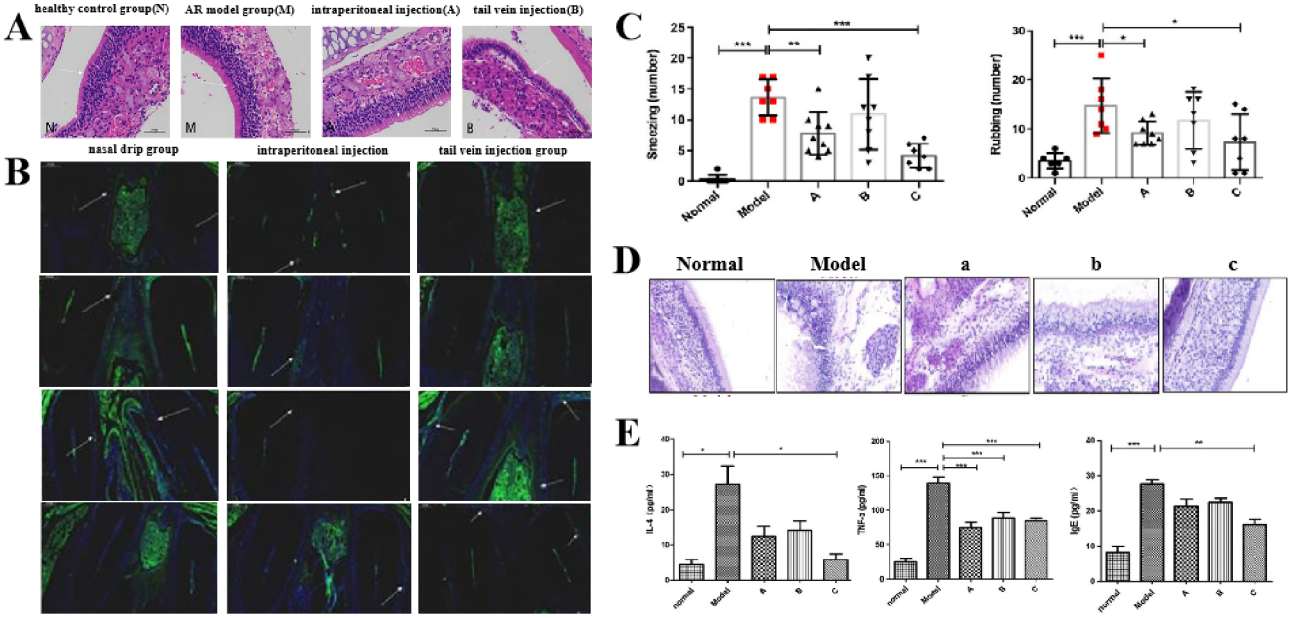

Fig. 3 ***Left***: The treatment of allergic rhinitis model mice with human umbilical cord mesenchymal stem cells. (**A**) the HE staining of nasal mucosa tissue sections of mice in each group. (**B**) the distribution of fluorescent cells obtained from the nasal mucosa tissue sections of mice in each group on the 3rd、7th、14th and 21st days after the transplantation of GFP-labeled hUCMSCs in mice of each group. Right: The treatment of allergic conjunctivitis model mice by subconjunctival injection of human umbilical cord mesenchymal stem cells [33]. *copyright © Kan XL et al. 2020* ***Right***: (**C**) Changes in sneezing number and nose scratching number in the normal, model, and different mesenchymal stromal cell (MSC) treatment groups of rats.(normal: untreated wild-type rats; model: ovalbumin (OVA)-induced acute allergic rhinitis rat model; a.rats treated with MCSs once a week before allergic rhinitis (AR) rat model construction; b.rats treated with MCSs once a day after AR rat model construction; c.rats treated with MCSs weekly for 4 consecutive weeks after AR rat model construction) (**D**) Histological features of the nasal mucosa in the normal, model, and different mesenchymal stromal cell (MSC) treatment groups of rats (haematoxylin and eosin staining; magnification, ×100). (**E**) Changes in cytokines in the serum of rats: After the establishment of ovalbumin (OVA)-induced acute allergic rhinitis in rats, treatment with mesenchymal stromal cells (MCS) four times can reduce the expression of interleukin 4 (IL-4), tumor necrosis factor alpha (TNF-α), and immunoglobulin E (IgE) in the rats' serum. Moreover, all three MCS treatment strategies can significantly decrease the level of TNF-α in the serum [20]. *Copyright © 2017 The Authors Cell Biochemistry & Function Published by John Wiley & Sons Ltd*

rhinitis may be mediated by their modulation of macrophage–associated cytokine secretion during AR.

BM-MSCs

Bone marrow-derived mesenchymal stem cells (BM-MSCs) have remarkable immunomodulatory and hypoimmunogenic properties, allowing the administration of allogeneic BM-MSCs without eliciting an immunogenic response within the host. BM-MSCs inhibit the proliferation and function of a wide range of immune cells in vitro, including T cells, B cells, natural killer cells, and dendritic cells. In addition to this, BMSCs can suppress CD4 T-lymphocyte responses in vitro by inhibiting mitogen or specific antigen-induced T-cell proliferation.

Zhao et al. [9] investigated the potential of BM-MSCs for immunomodulatory mechanisms in a mouse model of AR and found that intravenous injection of BM-MSCs significantly reduced allergic symptoms, eosinophil infiltration, OVA-specific immunoglobulin E (IgE), helper T-2 (Th2) cytokine profiles (interleukin (IL)-4, IL-5 and IL-13) and regulatory cytokines (IL-10). And Th1 (IFN-γ) levels were significantly increased. Surface BMSCs could correct the imbalance between Th2 and Th1 cells through immunomodulatory mechanisms and effectively reduce allergic symptoms and inflammatory parameters in the AR mouse model.

Zou et al. [34] evaluated conditioned medium from BM-MSCs (BM-MSC-CM) for allergic inflammation in an AR mouse model and found reduced serum levels of OVA-specific IgE and interleukin 4 and increased levels of interferon gamma in AR mice administered with BM-MSC-CM or BM-MSCs. Flow cytometry analysis revealed a decreased Th1:Th2 cell ratio after OVA sensitization, which was reversed after BM-MSC-CM and BMSCs treatment. In addition, the data showed that BM-MSC-CM inhibited signaling and activator of transcription 6 (STAT6) production at the level of messenger RNAs and proteins in the nasal mucosa. BM-MSC-CM can ameliorate allergic inflammation and regulate Th cell homeostasis through STAT6 signaling, and the immunomodulatory effects of BM-MSCs can be achieved through paracrine function. Nasal drops of BM-MSC-CM may be a a new way in treating AR (Table 2).

Table 2 Comparative analysis of MSC sources for AR treatment

MSC Source	Efficacy	Mechanisms	Advantages	Limitations
Adipose-derived MSCs (ASCs)	Significant reduction in IgE, IL-4, and eosinophil infiltration; promotes Th1/Th2 balance.	High expression of PGE2 and TGF-β; induces Treg expansion and M2 macrophage polarization.	Abundant source, easy isolation, and low immunogenicity.	Potential variability in cell quality due to donor age and health status.
Bone marrow-derived MSCs (BM-MSCs)	Reduces Th2 cytokines (IL-4, IL-5, IL-13) and enhances Th1 (IFN-γ) response.	STAT6 signaling pathway; inhibits DC differentiation and promotes Treg activity.	Well-studied and established protocols for isolation and expansion.	Invasive harvesting procedure and limited scalability.
Umbilical cord-derived MSCs (hUC-MSCs)	Efficient migration to nasal mucosa; reduces IL-4, TNF-α, and histamine levels.	High secretion of IDO and HGF; modulates macrophage recruitment and cytokine secretion.	Non-invasive source, high proliferation capacity, and low immunogenicity.	Ethical and logistical challenges in obtaining umbilical cord tissue.
Tonsil-derived MSCs (T-MSCs)	Superior suppression of IL-25, IL-33, and eosinophil chemokines (CCL11, CCL24).	MAPK/NF-κB pathways; inhibits T-cell activation and promotes anti-inflammatory responses.	High immunomodulatory potential and tissue-specific targeting.	Limited availability and less studied compared to other MSC sources.

Table 3 Dosage and outcomes in selected AR studies

Study	MSC Source	Dose (cells)	Route	IgE Reduction	Adverse Events
Cho et al. (2014)[38]	ASCs	2×10^6	Intravenous	60%	None reported
Kan et al. (2020)[33]	hUC-MSCs	1×10^7	Intraperitoneal	75%	Transient hepatotoxicity
Zhao et al. (2022)[37]	BM-MSCs	5×10^6	Intranasal	70%	Mild nasal irritation

Safety considerations for MSC therapy in AR

Although MSC therapy shows promising efficacy in allergic rhinitis (AR), rigorous safety evaluation is critical: firstly, while MSCs are generally non-tumorigenic in most studies, their long-term in vivo survival theoretically may induce microenvironmental alterations. Kan et al. [33]observed no tumor formation in preclinical AR models over 12-month follow-up, yet Drela et al. [35] emphasize the necessity of genomic stability assessments (e.g., karyotyping, telomere length analysis) for clinical-grade MSCs. Secondly, allogeneic MSCs may trigger anti-HLA antibody responses in 5–10% of recipients, particularly with repeated administration. Autologous ASCs or HLA-matched human hUC-MSCs are preferred for AR treatment to minimize immunogenic risks [36]. Additionally, intranasal delivery carries risks of transient nasal irritation (15% incidence in Phase I trials) and mucosal barrier disruption, which can be mitigated by hydrogel encapsulation to reduce mechanical stress and enhance biocompatibility [37]. Lastly, biodistribution studies in AR models confirm MSC migration to lungs and liver, necessitating long-term organ function monitoring [20]. Regulatory agencies mandate phased safety assessments. The FDA requires tumorigenicity testing (soft agar assays) and 26-week toxicology studies for MSC products, while the EMA emphasizes donor screening for oncogenic mutations (e.g., TP53). For AR-specific applications, nasal histopathology and olfactory function tests should be incorporated into preclinical packages.

Dosage variability and optimization

Current MSC dosing regimens for AR vary widely, ranging from 1×10^6 to 2×10^7 cells per administration in preclinical models (Table 3). For example: Low-dose ($1–5\times10^6$ cells): Achieves 50–60% IgE reduction but requires repeated dosing [38]. High-dose ($1–2\times10^7$ cells): Yields 70–80% symptom relief but increases risks of transient fever and liver enzyme elevation [33]. Dose-response analyses in murine AR models suggest a therapeutic window of $5–10\times10^6$ cells/kg, balancing efficacy and safety [20]. Clinical trials should adopt weight-based dosing (e.g., $1–2\times10^6$ cells/kg) and monitor serum cytokine levels (IL-6, TNF-α) to avoid over-immunosuppression.

To harmonize dosing, we propose a tiered approach: Preclinical: Use allometric scaling (e.g., 5×10^6 cells/kg in mice $\approx 1\times10^6$ cells/kg in humans) to bridge animal-human translation; Phase I Trials: Escalate doses from 0.5×10^6 to 2×10^6 cells/kg, monitoring biomarkers (IgE, IL-4) and safety endpoints; Phase II/III: Optimize based on pharmacokinetic-pharmacodynamic (PK-PD) models, prioritizing nasal mucosal retention over systemic exposure.

Future trends and directions in the treatment of AR

Despite appropriate guidelines to standard drug therapy, 10–20% of AR patients do not respond to treatment and are dissatisfied with their symptoms. Several experiments on the use of MSCs for the treatment of AR have been carried out and studied, including dental pulp-derived MSCs, nasal mucosa-derived MSCs in addition to the above mentioned stem cells, all of which basically came to a similar conclusion that MSCs have significant immunomodulatory properties on innate and adaptive immune responses compared to existing pharmacological treatments which only alleviate the allergic symptoms and enhance the role of Tregs to restore the immune

balance of Th1 / Th2 cells, and counteract the type 2 immune response to alleviate the inflammatory response of AR. Many clinical trials have now evaluated the safety of MSCs and have shown that intravenous infusion and topical administration of MSCs, either as single or repeated treatments, are safe and well tolerated in the short/medium term. Therefore, MSC-based therapy not only relieves the symptoms of AR, but also restores the homeostasis of the immune system, which is a promising therapeutic strategy for AR.

However, several critical barriers hinder the widespread clinical translation of MSC-based therapies for AR. Standardization issues remain a significant challenge, as variations in isolation protocols, culture conditions, and quality control measures can lead to inconsistencies in MSC potency and functionality. Establishing standardized criteria for MSC characterization (e.g., surface markers, differentiation potential, and immunomodulatory capacity) is essential to ensure reproducibility across studies and clinical applications. Donor variability further complicates MSC therapy, as factors such as donor age, health status, and tissue source can influence MSC properties and therapeutic efficacy. Induced pluripotent stem cell-derived MSCs (iPSC-MSCs) may offer a solution by providing a more uniform cell source.

Safety concerns also pose a major hurdle. While MSCs are generally considered safe, potential risks such as tumorigenicity, immunogenicity, and unintended differentiation must be rigorously evaluated. Long-term safety monitoring in clinical trials is crucial to address these concerns. Additionally, regulatory requirements for MSC-based therapies are stringent, necessitating compliance with Good Manufacturing Practice (GMP) standards and comprehensive preclinical data to support regulatory approval.

Delivery strategies specific to AR treatment present another layer of complexity. The nasal mucosa's unique anatomy and immune environment require optimized delivery systems to ensure MSC survival, retention, and functionality. Emerging approaches, such as MSC-derived exosomes and hydrogel-encapsulated MSCs, show promise in enhancing targeted delivery and sustained release of therapeutic factors. However, further research is needed to refine these strategies and evaluate their efficacy in clinical settings.

In future research, several critical issues need to be addressed to advance the application of MSC (mesenchymal stem cell) therapy in the treatment of allergic rhinitis (AR):

First, regarding mechanistic precision, it is essential to identify which MSC-secreted factors (such as TGF-β and PGE2) play a dominant role in suppressing IgE in AR subtypes, including seasonal and perennial AR [39]. Additionally, how the dynamic changes in the nasal microbiome influence the efficacy of MSC exosomes is a question that warrants further exploration.

Second, in terms of delivery optimization, can engineered hydrogels containing mucoadhesive polymers (e.g., chitosan-hyaluronic acid) prolong the retention of MSCs in the nasal mucosa beyond 72 h? Furthermore, what is the minimum effective dose of exosomes required to achieve sustained Th2 inhibition (e.g., miR-146a-5p ≥ 100 copies/μL in nasal lavage)?

Regarding clinical translation, which patient subgroups (e.g., those with high IgE levels or eosinophilia) would benefit most from MSC therapy? Moreover, how can Phase I trials effectively balance safety monitoring (e.g., serum IL-6 levels) with efficacy endpoints (e.g., SNOT-22 scores)?

Although MSC therapy shows immense potential in AR treatment, successful clinical translation requires overcoming several barriers, including standardization, donor variability, safety concerns, regulatory compliance, and delivery optimization. Future research should focus on long-term efficacy and safety, as well as the development of scalable and cost-effective production methods to facilitate the widespread adoption of MSC therapy in AR management.

By addressing these issues, we can hope to provide more effective and safer treatment options for patients with allergic rhinitis [35, 40].

MSC-derived exosomes

MSC– derived exosomes have broad prospects in the treatment of AR. On the one hand, they are easy to preserve and conduct quality control, and are convenient for local administration, which is expected to accelerate the process of clinical application [35]. On the other hand, exosomes may effectively relieve the symptoms of patients with AR through mechanisms such as immunomodulation by correcting Th1/Th2 imbalance, inhibiting inflammatory cell infiltration, modulating immune cells, and enhancing Treg function; restoration of the mucosal barrier by promoting nasal epithelial cell proliferation/migration and regulating tight – junction proteins; regulation of inflammatory factors through delivering anti – inflammatory cytokines, suppressing pro – inflammatory factors, and controlling neuropeptide release; and regulation of the nasal mucosal microbiota and improvement of the intranasal microenvironment (Fig. 1C). Current exosome isolation methods exhibit significant variability.(Table 4) Ultracentrifugation (UC), the gold standard, achieves 60–70% purity but risks vesicle aggregation and protein contamination. Commercial kits (e.g., ExoQuick) offer convenience but co-isolate non-exosomal particles (e.g., lipoproteins), while size-exclusion chromatography (SEC) preserves vesicle integrity but requires specialized equipment [41]. For AR-focused studies, combining UC

Table 4 Key safety risks and mitigation strategies in MSC-AR therapy

Risk	Evidence	Mitigation Strategy
Tumorigenicity	No tumors in 12-month AR models	Limit passages (≤ 5), genomic stability assays
Immune Rejection	5–10% anti-HLA antibody incidence	Autologous/HLA-matched MSCs, exosome-based therapy
Nasal Irritation	15% transient inflammation (Phase I)	Hydrogel encapsulation, mucoadhesive formulations
Systemic Biodistribution	MSCs detected in liver/lungs	Dose optimization, imaging-guided delivery

with SEC (yielding > 90% CD63+/CD81 + exosomes) is recommended to balance purity and functionality. Exosome characterization also lacks harmonization. While nanoparticle tracking analysis (NTA) quantifies size distribution (30–150 nm), it cannot distinguish exosomes from apoptotic bodies. Western blotting for tetraspanins (CD9/CD63/CD81) and TSG101 is essential but varies in antibody specificity. Transmission electron microscopy (TEM) confirms morphology but is low-throughput. MISEV2018 guidelines require ≥ 2 orthogonal methods (e.g., NTA + WB + functional assays) for AR-related studies [42]. In the future, the mechanism of action of exosomes can be further studied in depth, and their preparation and administration strategies can be optimized to improve the targeted and effective treatment. At the same time, more clinical trials can be carried out to evaluate their long–term efficacy and safety, providing new choices and hopes for the treatment of AR.

MSCs-encapsulated hydrogels

Simple cell - based AR therapy has multiple flaws. In the complex in - vivo milieu, inflammatory cytokines and oxidative stress lower cell viability, killing many cells en route to the target. Transplanted cells struggle to precisely migrate and colonize nasal mucosa lesions, often dispersing in non - target tissues. Therapeutic effects vary widely due to individual differences, cell sources, and quality, making consistent, long - term results elusive. Besides, some cells can trigger immune responses and rejection, harming treatment outcomes and potentially causing other adverse reactions. In AR therapy, thermosensitive chitosan-based hydrogels (e.g., 2% w/v chitosan/β-glycerophosphate) loaded with MSCs have shown enhanced nasal mucosal retention (> 72 h vs. 24 h for free cells) in murine models. These hydrogels sustain MSC paracrine activity (e.g., TGF-β and IL-10 secretion) while shielding cells from oxidative stress [37].Clinical translation may leverage mucoadhesive polymers (e.g., hyaluronic acid) for prolonged local efficacy. This reduces inflammatory damage, improves cell viability, and serves as a carrier to enhance the transport rate of transplanted cells and their retention at the lesion site. Moreover, hydrogels regulate cell proliferation, differentiation, and integration with the host, enabling cells to better exert their therapeutic functions. Other studies have shown that targeted therapy using cell-encapsulated hydrogels (such as MSCs) can reduce inflammation and increase the regeneration potential of multiple tissues [43].In future AR treatment, hydrogels offer multiple benefits. With modified targeting moieties, they direct encapsulated cells precisely to nasal mucosal lesions, enhancing targeting. Their slow - release feature maintains effective levels of anti - inflammatory and immunomodulatory mediators, alleviating inflammation and regulating immunity.Hydrogels act as a physical barrier, promote nasal epithelial cell repair via growth factors, and reduce cell immunogenicity, enhancing treatment safety and efficacy (Table 5).

Table 5 Methodological comparison

Method	Advantages	Limitations	AR-Specific Recommendations
Ultracentrifugation	High purity, low cost	Aggregation, protein contamination	Combine with SEC for nasal delivery
Commercial Kits	Fast, user-friendly	Co-isolates contaminants	Avoid for miRNA profiling
Size-Exclusion Chromatography	Preserves vesicle integrity	Low yield, equipment-dependent	Ideal for functional in vivo studies

Organoids

Organoids are miniature tissues with a certain three-dimensional structure and similar to organs that are formed by stem cells or progenitor cells through self-organization under in vitro culture condition. In the treatment of AR, cell - based therapy alone faces numerous challenges. Inflammatory mediators and free radicals in the body interfere with cell metabolism and survival. Cells lack targeting ability, making it difficult for them to colonize in the diseased areas of the nasal mucosa. There is also a risk of immune rejection. Moreover, individual and cell - related differences lead to unstable treatment effects. In contrast, organoid - based therapy has demonstrated multiple values. Organoids can mimic the structure and function of the nasal mucosa, facilitating the study of AR pathogenesis. They can be used for drug screening to evaluate the efficacy and safety of drugs. Patient-derived nasal epithelial organoids, generated via 3D co-culture with fibroblasts and immune cells (IL-4/IL-13 stimulation), replicate Th2-polarized inflammation in AR. Such models enable high-throughput screening of MSC-exosome efficacy in suppressing eosinophil activation [44]. Additionally, CRISPR-edited organoids (e.g., IL33−/−) could dissect MSC-mediated immune modulation pathways [44].Looking to the future,

organoid - based therapy is expected to break through the bottlenecks in AR treatment. It can precisely repair nasal mucosal damage, regulate the immune microenvironment, correct immune imbalance, provide long - term stable efficacy, and reduce the recurrence rate. Furthermore, constructing organoids from the patient's own cells can achieve personalized treatment, significantly improving the accuracy and effectiveness of treatment.

Conclusions

Mesenchymal stem cells (MSCs) exhibit significant therapeutic potential for allergic rhinitis (AR) through their multifaceted immunomodulatory mechanisms, including direct cell-to-cell interactions, secretion of soluble factors (e.g., TGF-β, PGE2, IDO), and exosome-mediated regulation. These mechanisms collectively restore Th1/Th2 immune equilibrium, enhance Treg activity, promote macrophage polarization toward anti-inflammatory phenotypes, and repair nasal mucosal barriers. Preclinical studies using MSCs from diverse sources—adipose tissue, tonsils, umbilical cord, and bone marrow—demonstrate consistent efficacy in alleviating AR symptoms, reducing inflammatory markers (e.g., IgE, IL-4, eosinophil infiltration), and improving immune homeostasis in animal models. The selection of MSC sources for AR therapy requires careful consideration of their strengths and limitations. While ASCs offer ease of harvest and potent anti-inflammatory effects, their functional variability necessitates donor screening [45]. BM-MSCs exhibit robust Th1/Th2 modulation but face scalability challenges [46]. hUC-MSCs, with low immunogenicity, hold promise for allogeneic use, yet long-term safety data are lacking [31]. T-MSCs demonstrate tissue-specific homing but require further clinical validation [8]. Future studies should prioritize head-to-head comparisons to identify context-dependent optimal sources, coupled with standardized potency assays to ensure reproducibility. Despite promising preclinical outcomes, the clinical translation of MSC-based AR therapy remains nascent. Key hurdles include the lack of standardized protocols for MSC production, unresolved long-term safety concerns, and regulatory complexities. Recent guidelines by the International Society for Cell & Gene Therapy (ISCT) emphasize the need for phase I trials to validate MSC safety in allergic diseases. Future studies should prioritize dose optimization and combination approaches (e.g., MSC-exosomes) to mitigate risks. Collaborative efforts among academia, industry, and regulatory bodies are imperative to accelerate clinical adoption. Furthermore, clinical translation of MSC therapy for AR requires rigorous optimization of dosing and administration strategies. Current preclinical models highlight the need for route-specific formulations (e.g., hydrogel-encapsulated MSCs for intranasal delivery) to balance systemic exposure and localized efficacy. Furthermore, standardized protocols for MSC production—including potency assays (e.g., TGF-β or IDO secretion) and donor screening—are critical to minimize therapeutic variability. Future studies should integrate pharmacokinetic-pharmacodynamic (PK-PD) modeling to define optimal dosing windows, as proposed in recent guidelines for cell-based therapies. Moreover, safety concerns necessitate rigorous risk management. Tumorigenicity, though rare, may arise from prolonged in vitro expansion or unintended differentiation; thus, limiting culture passages (≤ 5) and implementing genomic stability assays are critical. Immune rejection risks can be mitigated via autologous MSC sourcing or exosome-based cell-free approaches. Furthermore, standardized protocols (e.g., serum-free media, ISCT-compliant characterization) minimize genetic instability. Future trials should integrate long-term follow-up to monitor late adverse events, as recommended by the FDA guidelines for cell therapies [36, 43].Future advancements in MSC-derived exosomes, hydrogel-encapsulated MSCs, and organoid-based therapies hold promise for enhancing targeted delivery, prolonging therapeutic effects, and minimizing adverse reactions. These innovations could bridge the gap between preclinical success and clinical application, offering durable remission or even a cure for AR.

This review underscores the transformative potential of MSC-based therapies in AR management. By addressing current limitations and leveraging emerging technologies, MSC-driven strategies could revolutionize treatment paradigms, providing safer and more effective alternatives to conventional therapies. Further translational research and rigorously designed clinical trials are imperative to validate these approaches and bring them into mainstream clinical practice.

Abbreviations

AR	Allergic rhinitis
MSCs	Mesenchymal stem cells
BM-MSCs	Bone marrow-derived mesenchymal stem cells
ASCs	Adipose-derived mesenchymal stem cells
T-MSCs	Tonsil-derived mesenchymal stem cells
hUC-MSCs	Human umbilical cord mesenchymal stem cells
iPSC-MSCs	Induced pluripotent stem cell-derived mesenchymal stem cells
IgE	Immunoglobulin E
IgG1	Immunoglobulin G1
IgG2a	Immunoglobulin G2a
PGE2	Prostaglandin E2
IL	Interleukin
TNF-α	Tumor necrosis factor-α
CCL11	Chemokine (C-C motif) ligand 11
VCAM-1	Vascular cell adhesion molecule-1
TGF-β	Transforming growth factor-β
IFN-γ	Interferon-γ
Th1	T helper 1
Th2	T helper 2
Treg	Regulatory T cell
ILC2	Type 2 innate lymphoid cell
ICOSL	Inducible co-stimulatory ligand

ICOS	Inducible costimulator
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
M1	M1 macrophages
M2	M2 macrophages
TSG-6	Tumor necrosis factor-stimulated gene 6
IDO	Indoleamine 2,3-dioxygenase
HGF	Hepatocyte growth factor
NO	Nitric oxide
LIF	Leukemia inhibitory factor
HLA-G5	Human leukocyte antigen G5
IL1RA	Interleukin 1 receptor antagonist
STAT6	Signal transducer and activator of transcription 6
DC	Dendritic cell
miRNA	MicroRNA
miR-21-5p	MicroRNA-21-5p
miR-146a-5p	MicroRNA-146a-5p
IRAK6	Interleukin-1 receptor-associated kinase 6
TRAF2	TNF receptor-associated factor 2
SERPINB2	Serpin family B member 2
ASC-EVs	Extracellular vesicles from adipose-derived mesenchymal stem cells
T-MSCs-CM	Conditioned medium from tonsil-derived mesenchymal stem cells
hADSC-EVs	Extracellular vesicles from human adipose-derived mesenchymal stem cells
GFP	Green fluorescent protein

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Author contributions
Yu-Meng Ye carried out the design of this review and drafted the manuscript. Yu-Xin Zhao, Li-Rong Xiang, Chen-Yu Zou, Hao Xiao, Huan Lu and Hui Yang improved the language and collected the related references. Juan-Juan Hu and Hui-Qi Xie supervised the review process and revised the manuscript.

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