

## REVIEW ARTICLE

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# The Probable Role of Mesenchymal Stromal/Stem Cells and Their Exosomes in Improving Allergen Immunotherapy

Mahdieh Shadian Zarsabzevar<sup>1</sup>, Kianush Charoghdozi<sup>2,3</sup>, Mohammad Javad Balighi<sup>2</sup>, Yeganeh Khazaei<sup>4</sup>, Amirali Ebrahimpour<sup>4</sup>, Sajad Dehnavi<sup>5,6</sup>, and Mahvash Sadeghi<sup>6,7</sup>

<sup>1</sup> Department of Laboratory Sciences, School of Paramedical and Rehabilitation Sciences, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>2</sup> Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>3</sup> Department of Immunology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>4</sup> Department of Medical Laboratory Sciences, Varastegan Institute for Medical Sciences, Mashhad, Iran

<sup>5</sup> Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>6</sup> Allergy Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>7</sup> Innovative Medical Research Center, MMS. C., Islamic Azad University, Mashhad, Iran

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## ABSTRACT

Allergic asthma considered is a type I hypersensitivity disorder with increasing global prevalence and limited curative options. Mesenchymal stem cells (MSCs) and their exosomes have emerged as promising adjuncts in the control of allergic reactions. MSCs can regulate and shift the inflammatory responses and promote tissue remodeling in the airway tissues. Furthermore, exosomes derived from MSCs contribute to these effects by mediating intercellular communication and delivering bioactive molecules that modulate immune responses. This review discusses current evidence on the immunomodulatory potential and therapeutic benefits of MSCs and their exosomes in the context of allergen-specific immunotherapy (AIT) to enhance efficacy, induce long-lasting tolerance, and address current therapeutic limitations in allergic asthma.

**Keywords:** Allergic asthma; Exosome; Immunotherapy; Mesenchymal stem cell (MSC)

## INTRODUCTION

In recent decades, the prevalence of allergic disorders has increased worldwide, affecting approximately 30% of the population in industrialized nations.<sup>1,2</sup> The major allergic disorders are skin-associated conditions, allergic asthma, allergic rhinitis,

allergic conjunctivitis, and food allergies.<sup>3</sup>

Asthma is a long-term inflammatory disorder defined by airway constriction and inflammation, which can result in long-term changes in airway structure, mostly induced by allergens, infections, and environmental pollutants.<sup>4,5</sup> In case of allergic asthma pathophysiology, a variety of immune cells have been

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**Corresponding Authors:** Sajad Dehnavi, PhD;  
Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: (+98 921) 6828 566, Fax: (+98 51) 3800 2395, Email: [sjd72dehnavi@gmail.com](mailto:sjd72dehnavi@gmail.com)

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Mahvash Sadeghi, PhD;  
Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: (+98 922) 0464 932, Fax: (+98 51) 3800 2395, Email: [mahvashsadeghi8@gmail.com](mailto:mahvashsadeghi8@gmail.com)

identified such as T and B cells, eosinophils, basophils, mast cells, and type 2 innate lymphoid cells (ILC2s), dendritic cells (DCs), and monocytes/macrophages. Primary exposure to allergens has been demonstrated to result in the differentiation of type 2 helper T (Th2) cells and the subsequent production and secretion of specific immunoglobulin E (IgE) antibodies. Subsequent exposures to allergens induce the activation of mast cells and basophils, leading to the release of inflammatory factors and the accelerated recruitment and accumulation of additional inflammatory cells, thereby exacerbating local airway inflammation.<sup>6,7</sup> Structural changes in the airways associated with asthma severity include subepithelial fibrosis, increased airway smooth muscle mass, reduced distance between smooth muscle and epithelium, mucous gland and goblet cell hyperplasia, blood vessel proliferation, and airway edema.<sup>8</sup>

The majority of patients diagnosed with allergic asthma achieve a transient disease control through the administration of a combination of corticosteroids, long-acting  $\beta_2$ -adrenoceptor agonists, and oral leukotriene inhibitors.<sup>9</sup> These pharmaceutical agents have been demonstrated to reduce inflammation and airway remodeling.<sup>5,10</sup> However, due to their inability to reverse established remodeling, many patients continue to experience severe exacerbations or unsuccessful control of their symptoms.<sup>11,12</sup> Consequently, the development of novel therapeutic strategies capable of reversing airway remodeling is imperative to prevent the progressive deterioration of lung function observed in asthmatic patients. In recent years, a promising immunotherapeutic approach has emerged that aims to promote a Th2-to-Th1 shift. The regulatory T cells (Tregs) play a pivotal role in inducing unresponsiveness to allergens.<sup>13</sup> Also, previous studies have indicated that the utilization of mesenchymal stromal/stem cells (MSCs) and their derivatives, including exosomes, as adjunctive or alternative approaches, has yielded encouraging findings.<sup>14</sup>

In this review, we introduced MSCs and their derivatives, especially exosomes, along with allergen-specific immunotherapy (AIT) and compared their potential ability for management of allergic asthma.

## SEARCH METHOD

Keywords including Allergic asthma; immunotherapy; mesenchymal stromal/stem cell

(MSC); and exosome were searched in multiple databases such as Google Scholar, Scopus, Web of Science, PubMed, Science Direct, etc. to reach the references for the present review article.

## MSCs, Their Immunomodulatory Properties and Therapeutic Importance

MSCs have identified as adherent cells that possess the capacity to differentiate into various tissue cells and highly express CD90, CD105, and CD73 as surface markers, while do not express or express low levels of CD45, CD34, CD14, CD79, and human leukocyte antigen (HLA)-DR.<sup>15</sup> MSCs have been intrinsic and inducible potential to balance immune responses and exhibit anti-inflammatory properties. Due to the absence of HLA-DR and costimulatory molecules such as CD80, CD86, and CD40 on the surface of these cells, they can be utilized in allogeneic or xenogeneic applications.<sup>16,17</sup> Various sources are implicated for MSC isolation such as bone marrow (BM), adipose tissue (AT), umbilical cord (UC), Wharton's jelly (WJ), placenta (PL), dental pulp (DP), and lungs.<sup>18-20</sup> A variety of reports have highlighted that, upon systemic administration, MSCs migrate to the inflammatory location through chemotactic absorption that is not yet fully understood.<sup>21</sup> These mechanisms stimulate downstream pathways involved in tissue repair and balance the immune responses through their paracrine activity, which is associated with the secretion of growth factors, cytokines, and chemokines. These factors regulate exert tissue regeneration and have been shown to suppress apoptosis, promote cell proliferation, induce vascularization, and regulate the immune responses<sup>22-25</sup> (Figure 1).

## MSC-based therapy for Allergic Asthma

Multiple lines of evidence have demonstrated that MSCs could potentially modulate inflammatory responses and promote tissue remodeling in the airway tissues of patients diagnosed with allergic asthma.<sup>26-29</sup> Research indicated that systemic administration of MSCs leads to MSC localization within the pulmonary vascular circulation due to their relatively large size.<sup>30</sup> Additionally, MSCs possess the potential to suppress airway inflammation, decrease excessive mucus secretion and hyper-reactivity, promote epithelial cell repair, and alleviate airway obstruction. Notably, they potentially impede the proliferation of airway goblet cells, prevent fibrosis, and diminish subepithelial

collagen accumulation, which effectively reduces or can even reverse airway remodeling.<sup>31-33</sup> Additionally, MSCs have demonstrated satisfactory therapeutic effects for steroid-resistant and chronic asthma in preclinical trials.<sup>34,35</sup>

Also, various studies have highlighted additional findings on the involvement of MSCs in asthma for years.<sup>36-39</sup> Bentley et al found more cells with the MSC phenotype in asthmatic mice's lungs after ovalbumin sensitization.<sup>36</sup> The migration of CM-induced murine MSCs from cockroach allergen-stimulated human epithelium is disrupted by transforming growth factor- $\beta$  1 (TGF- $\beta$ )1 inhibition.<sup>38</sup> Yang et al discovered that large numbers of mouse BM-MSCs transfected with green fluorescent protein exhibited migration toward the lung tissue and alleviated bronchial asthma in an animal model. The hypoxia-inducible factor-1 alpha (HIF-

1 $\alpha$ )/CXCR4 axis, which is derived from stromal cells, may be responsible for this translocation.<sup>37</sup> Additionally, the aryl hydrocarbon receptor (AhR) plays a substantial role in controlling MSC recruitment and immunosuppressive capacity, thereby contributing to the mitigation of inflammation.<sup>39</sup>

MSCs have been shown to regulate local inflammation, reduce tissue damage, and reverse airway remodeling. This effect is achieved by restoring the Th1/Th2 imbalance.<sup>28,40,41</sup> and promoting Th17/Treg balance toward an anti-inflammatory Treg-dominant state,<sup>42</sup> inhibiting DC maturation and antigen presentation,<sup>43</sup> suppressing mast cell degranulation,<sup>44</sup> restraining ILC2-mediated pathology,<sup>45</sup> promoting M1-to-M2 macrophage repolarization,<sup>46</sup> and finally promoting the repair of epithelial injury via paracrine relation or direct cell-cell interface.<sup>47</sup>

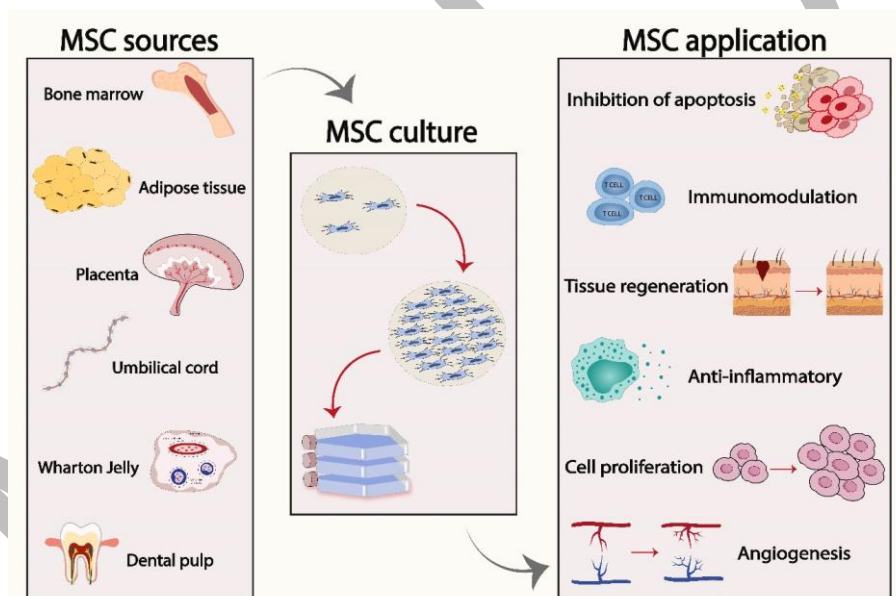


Figure 1. Schematic Representation of Various Sources for MSC Isolation and Applications.

### Immunoregulation via cell-to-cell interaction

Although not as effective as transplanted MSCs, human induced pluripotent stem cell (iPSC)-MSC-conditioned medium improved lung function and reduced inflammatory conditions in an asthma mouse model, suggesting that both paracrine signaling and direct cell interaction are involved.<sup>48</sup> Co-culturing iPSC-MSCs or BM-MSCs with peripheral blood mononuclear cells (PBMC) from allergic patients increased the growth of anti-inflammatory interleukin-10 (IL-10) and Tregs, while suppressing the proliferation of

lymphocytes and pro-inflammatory mediators such as interferon- $\gamma$  (IFN- $\gamma$ ), IL-4, IL-5, and IL-13.<sup>41</sup> Separation of MSCs and PBMCs in a transwell system eliminated this immunosuppressive effect, demonstrating the importance of direct interaction, and co-cultured BM-MSCs were more successful in suppressing mast cell degranulation, chemotaxis, and production of pro-inflammatory mediators compared with transwell conditions.<sup>44</sup>

The mechanism underlying cell-cell interface involves receptor binding or channel formation. In

iPSC-MSC-T cell co-cultures, activated T cells overexpressed intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) molecules on MSCs, thereby enhancing their adhesion to T cells and suppressing T cell proliferation.<sup>45</sup> Blocking these molecules reversed this effect. Similarly, iPSC-MSCs suppressed ILC2 function in co-cultures by promoting Treg-derived IL-10 through inducible T-cell costimulator (ICOS)-ICOSL interactions. Tunneling nanotubes (TNT) facilitated mitochondrial transfer from iPSC-MSCs to airway smooth muscle and epithelial cells, rescuing mitochondrial dysfunction and reducing inflammation in asthmatic mice.<sup>33,49</sup> Application of MSC membranes for targeted mitochondrial delivery to damaged airway cells is a promising therapeutic strategy.

Paracrine secretion has been reported to be involved in mediating the immunomodulatory effects of MSCs in asthma. Research has highlighted significant alleviation of pathological damage following intratracheal or intravenous administration of MSC-conditioned medium in ovalbumin (OVA)-sensitized rats.<sup>50,51</sup> This process relies on the release of soluble factors and the generation of extracellular vesicles (EVs), highlighting the importance of paracrine mechanisms in MSC-mediated therapeutic outcomes.<sup>52</sup>

#### Immunomodulation via secreted soluble factors

Numerous studies have shown the significant effects of soluble mediators released by MSCs in regulating the immune system<sup>52</sup>. The soluble factors such as TGF- $\beta$ , IL-10, nitric oxide (NO), indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), hepatocyte growth factor (HGF), tissue inhibitor of metalloproteinase 6 (TSG-6), IL-6, human leukemia inhibitory factor (LIF), HLA-G5, and IL-1 receptor antagonist (IL-1RA) have been reported in MSC-based therapeutic approaches.<sup>53–55</sup> According to Park et al, MSC-derived conditioned medium had significantly higher levels of HGF, TGF- $\beta$ 1, and PGE2, which are considered to be immunomodulatory factors released by MSCs and associated with decreased numbers of activated T cells through suppressing T-cell receptor signaling.<sup>56</sup> These mediators are considered to have immunomodulatory properties of tonsil-derived MSCs that influence the allergic inflammatory response.

PGE2 secreted by MSCs has been shown to regulate the immune response of DCs and macrophages. Nemeth and colleagues reported that PGE2 released by BM-

MSCs stimulates IL-10 production by macrophages through prostaglandin EP2 and EP4 receptors.<sup>57</sup> A different research study demonstrated that MSCs may release PGE2 either directly or via EVs, which could increase the anti-inflammatory M2-polarized macrophages and downregulate IL-23 and IL-22.<sup>58</sup> Furthermore, MSCs could strongly polarize M1 macrophages into anti-inflammatory M2-like cells by the release of colony stimulating factor (CSF), vascular endothelial growth factor (VEGF), LIF, B7-H4, and PGE2.<sup>59</sup>

TGF- $\beta$ , a crucial regulator of Foxp3 expression, promotes Treg differentiation along with Th2 suppression.<sup>55</sup> TGF- $\beta$  secreted by BM-MSCs suppresses allergic reactions in the murine model of ragweed-induced allergy. IL-4 and IL-13 activate the signal transducer and activator of transcription 6 (STAT6) pathway, which increases TGF- $\beta$  secretion, decreases IL-4 production, and maintains immunologic balance.<sup>60</sup> In particular, TGF- $\beta$  has been observed to have a detrimental effect on asthma. For example, Zhong and colleagues proved that TGF- $\beta$  increases inflammation by suppressing the TGF $\beta$ 1-Smad2/Smad3 pathway, which reduced airway inflammation in chronic allergic asthma.<sup>61</sup>

IDO released by MSCs has been shown to be essential for Treg production.<sup>62</sup> In addition, MSCs from human exfoliated deciduous teeth were found by Dai et al to significantly decrease T lymphocyte proliferation and increase Treg growth in the co-culture system.<sup>63</sup> However, IDO does not seem to be involved in the suppression of inflammatory responses. AT-MSCs isolated from IDO knockout (KO) mice show immunosuppressive potential on allergic airway inflammatory responses. Furthermore, the therapeutic efficacy of AT-MSCs does not show a significant difference between wild-type (WT) asthmatic mice and IDO-KO asthmatic mice.<sup>64</sup>

Tumor necrosis factor-stimulated gene-6 (TSG-6), an important anti-inflammatory factor, suppresses osteoclast activation and mediates the immunomodulatory functions of MSCs.<sup>65</sup> TSG-6, which is secreted by cytokine-stimulated human MSCs, has been highlighted to suppress lung inflammation and facilitate the healing of lung damage by inhibiting the recruitment capability of innate cells.<sup>66,67</sup>

### MSC-derived exosomes

Exosomes (Exo), which are enclosed by a double-lipid membrane and size range from 30 to 150 nm. These nano-sized vesicles, which are released by most cells, play essential parts in intercellular communication. Exosomes transport a variety of biomolecules, such as proteins, glycoproteins, lipids, metabolites, and nucleotide-based structures such as mRNA, miR, siRNA, and DNA.<sup>68,69</sup> Exosomes are biological structures with intrinsic roles that transport biomaterials between origin and target cells in an efficient and safe

route. They play an important role in intercellular communication. They are increasingly being applied as therapeutic agents.<sup>70</sup> The lipid bilayer structure conserves the integrity of the exosomes and helps stabilize their biological activities. Modifying proteins on the surface of exosomes could potentially enhance the exosomes' ability to be recognized and targeted.<sup>71,72</sup> These vesicles and their contents could be taken up by other cells as part of intercellular communication. This makes these vesicles potential therapeutic agents or vehicles for delivering therapeutic agents<sup>73</sup> (Figure 2).

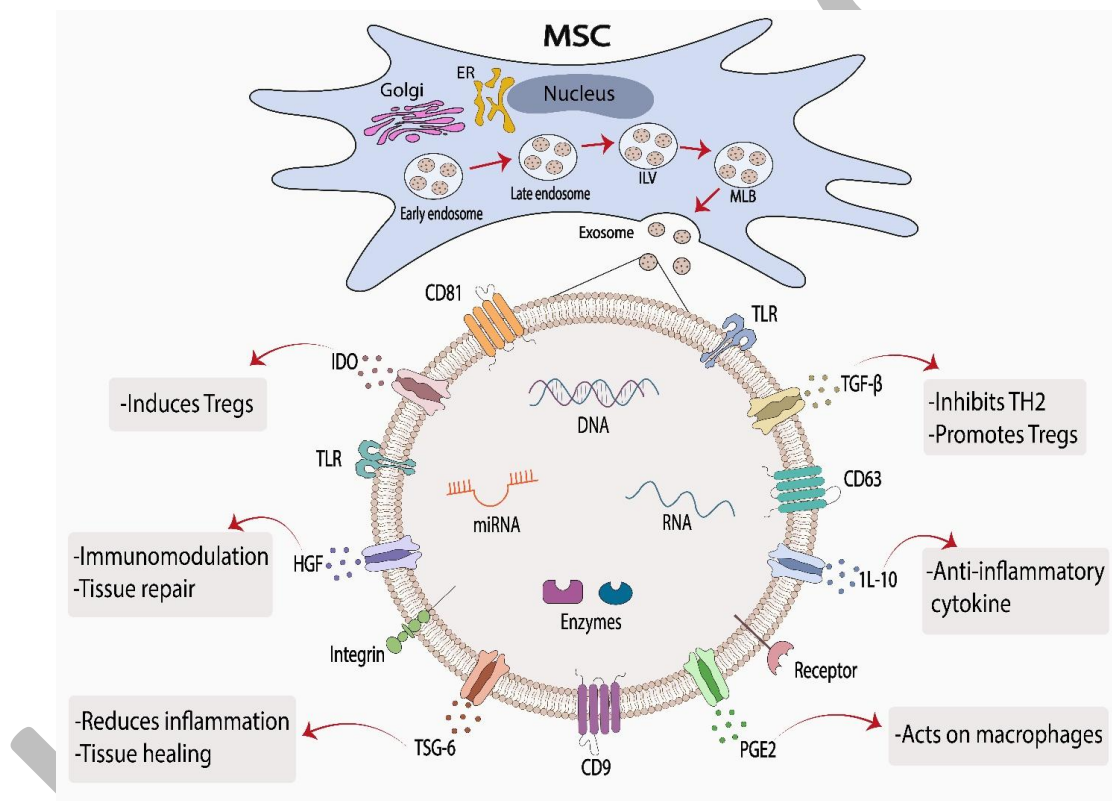


**Figure 2. Immunomodulatory and Immune-regulatory Properties of MSC-Derived Exosomes.**

MSCs have been shown to secrete exosomes, which are considered the primary paracrine factor important in their therapeutic properties. These exosomes have been used in cell-free immunomodulatory therapies.<sup>74,75</sup> MSC-derived exosomes contain various compounds, including cytokines, growth factors, mRNA, siRNA, and miR.<sup>76</sup>

Recent research has shown that mesenchymal stem cell (MSC)-released exosomes have anti-inflammatory, anti-apoptotic, and immunomodulatory properties. These effects are believed to represent novel molecular

pathways through which MSC therapy exhibits therapeutic promise in the treatment of airway allergies.<sup>77-79</sup> Castro and colleagues compared the effectiveness of AT-MSCs and their exosomes in an asthma murine model. They found ameliorated airway inflammatory responses, remodeling, and lung tissue eosinophilia. However, bronchoalveolar lavage fluid (BALF) affected by Tregs and inflammatory mediators, such as IL-4, IL-5, IL-13, and eotaxin, in different ways.<sup>80</sup> Furthermore, Keyhanmanesh and colleagues found that systemic injection of MSC-isolated

conditioned medium (CM) regulates Th1/Th2 balance in mice with OVA-induced asthma via modulation of the transcription factors GATA3 and T-bet.<sup>50</sup> In another study, Dong et al demonstrated that human UC-MSC-isolated exosomes decrease inflammatory responses in severe, steroid-resistant asthma by altering the polarization of macrophages and suppressing tumor necrosis factor receptor-associated factor 1 (TRAF1).<sup>81</sup>

It was discovered that among the most important components, 304 proteins, at least 170 distinct miRs, and numerous mRNA and DNA molecules were transported to target immune cells via MSC-derived exosomes. These molecules regulate the metabolism and function of the target cells.<sup>82–84</sup> MiRNAs have been identified as one of the most prevalent components in mesenchymal stromal cell (MSC)-derived exosomes. Reports indicate that significant levels of the following microRNAs were found in MSC-derived exosome samples: miR-22, miR-100-5p, miR-125b-5p, miR-146a-5p, miR-182, and miR-206.<sup>85–88</sup> More specifically, miRs such as miR-125b-5p, miR-146a-5p, and miR-223 have been related to the modulation of type 2 inflammation in nasal mucosa.<sup>89–93</sup> Lyu et al have shown that miR-146a-5p reduces allergic airway inflammation by inhibiting several genes, including TRAF6 and IRAK1, which are downstream factors of the ST2 signaling pathway. This conversely regulates IL-33/ST2-activated ILC2s.<sup>94</sup> A separate study revealed that the MSC-isolated exosome-derived miR-181a can stimulate the secretion of IL-10 and TGF- $\beta$  in M2 anti-inflammatory macrophages.<sup>95,96</sup> The miR-30b-3p, miR-126, and miR-223-3p are other MSC-isolated exosomal miRs related to the suppression of inflammation.<sup>97–99</sup>

The other mediators that MSC-isolated exosomes transport are important for epithelial cell survival. Programmed cell death protein 4 (PDCD4), tumor suppressor phosphatase and tensin homolog (PTEN) are the targets of the miR-21-5p factor, which has similar effects to miR-126 and miR-135a, two other MSC exosome contents.<sup>100–102</sup>

### MSC-Isolated Exosomes as A Novel Immunotherapy Approach

Exosome-based delivery systems have shown interesting advantages, such as safety, specificity, and stability.<sup>103</sup> Exosomes are bilayer lipid-membrane nanovesicles that are 50–200 nm in size and induce low immune stimulation due to their endogenous nature. Exosomes are widely used as a carrier or delivery

system both in physiological and pathological conditions.<sup>104</sup> In the context of AIT, exosomes could be applied to deliver allergens to immune cells in a controlled manner, potentially increasing the immune tolerance to these allergens and improving the effectiveness and safety of AIT.<sup>105</sup> These nanoparticles are present in a variety of biological fluids, such as plasma, urine, and saliva, and are introduced as part of the paracrine system that transports a group of biological factors, including proteins, enzymes, lipids, and nucleic acids, based on their cell source. Therefore, MSC-derived exosomes have immune-regulatory potential and play a crucial role in immune regulation and maintaining homeostasis.<sup>106,107</sup> An extraordinary benefit for the application of exosomes is their compatibility to be biochemically modified, altered, or enhanced their therapeutic potential. MSC-isolated exosomes could be applied either in systemic or local applications, each of which has advantages and disadvantages.<sup>108</sup> MSC-derived exosomes play an important role in regulating immune responses by exerting their effects through ameliorating the inflammatory functions of T lymphocytes, B lymphocytes, macrophages, DCs, natural killer (NK) cells, and ILCs.<sup>109–113</sup> In recent years, MSC-exosomes have attracted much attention as a result of their interesting ability in tissue repair, suppressing inflammation, inhibiting apoptosis, and increasing cell survival, and finally modulating immune responses.<sup>108,114,115</sup> The modulatory and regulatory potential of MSC-exosomes in reducing allergic airway inflammatory responses has been approved in several studies.<sup>80,116,117</sup> In recent years, the clinical application of MSCs has been assessed both in vitro and in vivo, highlighting a basis for therapeutic applications. Differentiation and activation of allergen-specific CD4<sup>+</sup> Th2 cells are critical to induce isotype switching to the  $\epsilon$  immunoglobulin heavy chain in B lymphocytes and the secretion of allergen-specific IgE antibodies during the sensitization phase. Specific IgE antibodies bind to Fc $\epsilon$ RI on the surface of mast cells and basophils, resulting in the sensitization of cells for further exposure.<sup>118,119</sup> Over-activated Th2 lymphocytes and defective function of Tregs are associated with allergic airway reactions. Additionally, the IL-17 released by Th17 cells promotes neutrophil proliferation and migration, leading to neutrophilic asthma and glucocorticoid insensitivity in severe asthma patients. Multiple lines of evidence revealed that human MSCs prevent steroid-resistant neutrophilic airway

inflammation via reducing the numbers of Th17 cells, and the levels of IL-17A cytokine, and phosphorylated STAT3 or p-STAT3.<sup>28,35</sup> Various studies have shown that MSCs promote the expansion of Treg cells in vivo.<sup>42,61,120–122</sup> by producing several secretory factors, such as TGF- $\beta$ , IDO, and PGE2.<sup>120,121</sup> Involvement of DCs in allergic reactions is primarily associated with presenting allergens and activating naive T cells. Activated T cells differentiate into the Th2 subset in response to DC-released cytokines and further IgE production and IgE-mediated reactions are resulted by Th2-associated mediators.<sup>123–125</sup> MSCs could potentially suppress antigen processing and presentation of DCs through targeting the activation of mitogen-activated protein kinases, leading to impaired T-cell activation in vivo.<sup>126</sup> Additionally, MSCs promoted DCs toward a functionally tolerogenic phenotype and induced and activated Treg cells in a mouse model of allergic airway inflammation. Macrophages are a heterogeneous population of phagocytic innate cells that actively participate in the pathological and repair-associated pathways in allergic asthma. M1 macrophages, also

called classical or pro-inflammatory phenotype, can be primed by cytokines including IFN- $\gamma$ , granulocyte-macrophage colony-stimulating factor (GM-CSF) or tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which enhances the ability of antigen processing and presentation along with phagocytosis. Conversely, alternative M2 macrophages are polarized by IL-4 and IL-13 exposure and exhibit anti-inflammatory phenotype. Using human MSCs has been shown to significantly elevate the alveolar macrophage population and suppress asthma reactions in an OVA-induced mouse model.<sup>127</sup> In addition, the number of IL-10-secreting monocytes/macrophages was elevated in the lung tissue following IFN- $\gamma$ -treated MSCs-isolated exosome administration in the animal model of allergen-induced airway inflammation, and IFN- $\gamma$  stimulation was considered as a crucial mechanism for increased inhibitory potential of MSCs.<sup>128</sup> Hence, MSC exosomes are highlighted as interesting therapeutic approaches in various pathological conditions, especially asthma, allergic rhinitis, and autoimmune diseases<sup>113,129–133</sup> (Figure.3).

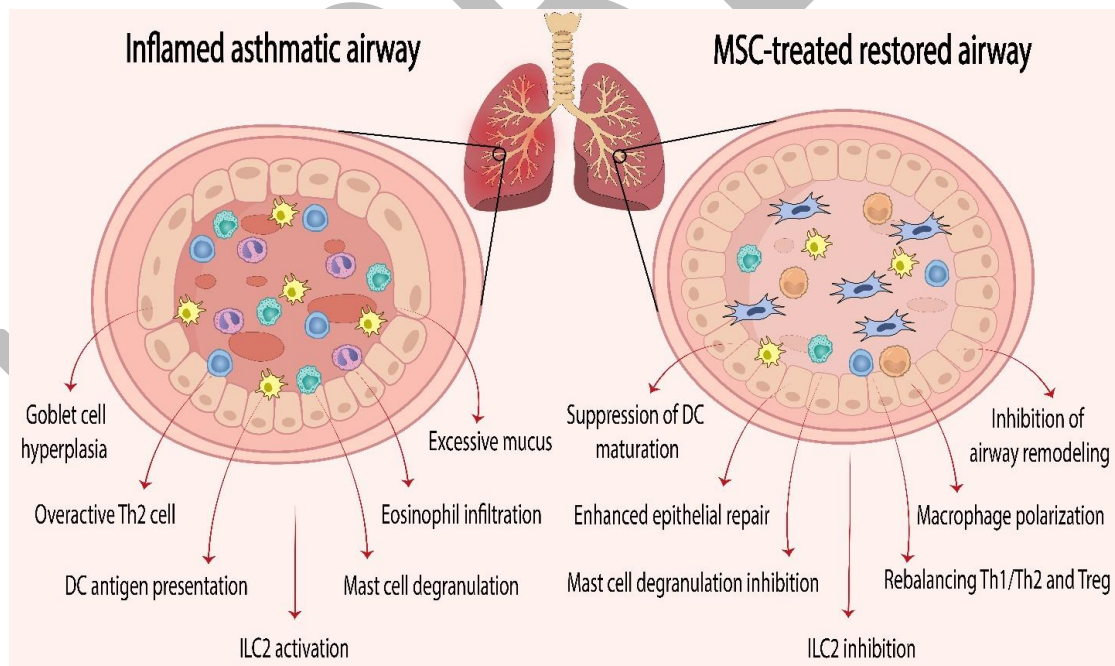


**Figure 3. Schematic Representation of the Immune State in Inflamed Asthmatic Airways Compared With MSC-Treated Airways.**

## Immunotherapy for Allergies

AIT, also known as desensitization, is defined as a process consisting of repeated administrations of allergens and is designed to promote tolerance in atopic patients.<sup>134</sup> AIT has been utilized for a century as a desensitization treatment for allergic conditions, and it signifies a potentially curative and targeted therapeutic approach. The mechanisms underlying AIT's effectiveness encompass very early desensitization, modulation of T and B cell responses along with their respective antibody isotypes, and the inhibition of eosinophil, basophil, and mast cell migration into tissues, as well as the release of their mediators. Regulatory B cells (Bregs), which produce IL-10, TGF- $\beta$ , and IL-35, function as immunoregulatory cells that elicit anti-inflammatory responses against activated lymphocytes.<sup>135,136</sup> Tregs are recognized as crucial modulators of immune mechanisms involved in peripheral tolerance to allergens. The transition of allergen-specific effector T cells into a regulatory phenotype seems to be a significant occurrence in fostering a robust immune response to allergens and achieving favorable results in AIT.<sup>118</sup> Tregs can control and modify the pathogenesis of allergic diseases. Treg cells diminish the inflammatory characteristics and the ability of DCs to activate effector Th1, Th2, and Th17 cells, while simultaneously fostering the emergence of tolerogenic DC phenotypes. In these mechanisms, DCs are crucial, as they possess the unique ability to generate robust immune responses against harmful pathogens while also preserving a state of tolerance toward harmless substances, thereby safeguarding the body's integrity in an environment replete with pathogens and possible allergens.<sup>137,138</sup> Naturally occurring forkhead box P3 (FoxP3) + CD4<sup>+</sup> CD25<sup>+</sup> Treg cells, along with inducible type 1 Treg (Tr1) cells, play a significant role in modulating allergen-specific immune responses through various mechanisms. These mechanisms can be outlined as follows: the inhibition of DCs that facilitate the development of effector T cells; the suppression of effector T helper cells, including Th1, Th2, and Th17 subsets; the reduction of allergen-specific IgE levels while promoting the production of IgG4; the inhibition of mast cells, basophils, and eosinophils; and the prevention of effector T cell migration into tissues.<sup>13,118</sup> In summary, the mechanism of action of AIT involves the induction of immunologic tolerance, as evidenced by increased levels of IL-10, TGF- $\beta$ , Breg and Treg cells. In addition, the production of IgG4 antibodies is

increased, which act as inhibitors of IgE activation by Fc epsilon receptor I (Fc $\epsilon$ RI) on mast cells and basophils and Fc $\epsilon$ RII on B cells.<sup>139,140</sup>

## Subcutaneous Immunotherapy (SCIT) and Sublingual Immunotherapy (SLIT)

AIT is the only allergy treatment that provides long-term symptom relief for allergy sufferers. The most commonly used route of allergen administration is subcutaneous injection, generally considered the gold standard, followed by sublingual or oral administration of allergen preparations.<sup>141</sup> SCIT is a viable option for managing allergic rhinitis and allergic asthma; however, it does entail a minor yet significant risk of potentially severe and life-threatening anaphylactic reactions. In contrast, SLIT is typically regarded as having a superior safety profile compared with SCIT. A notable distinction between SCIT and SLIT lies in the quantity of allergen that is administered. To reach a comparable level of efficacy, SLIT necessitates at least 50–100 times more allergen than SCIT.<sup>142,143</sup> While the safety profile of SLIT seems to surpass that of SCIT, findings from certain studies and meta-analyses indicate that the effectiveness of SCIT could be superior and more immediate compared with SLIT in pediatric patients suffering from allergic asthma.<sup>144</sup> The choice between SCIT and SLIT is influenced by various factors, such as the availability of products, financial considerations, the patient's capacity to regularly visit the clinic, individual patient traits, and the preferences of both the physician and the patient, among others.<sup>145</sup> SLIT may also be considered if SCIT results in systemic reactions.<sup>146,147</sup>

## MSC Exosomes Vs. SCIT and SLIT

SCIT is linked to invasive and extended injections, along with a heightened risk of serious local and systemic reactions, which can reduce patient adherence. Consequently, needle-free methods, such as SLIT, may present a compelling alternative that enhances patients' readiness to accept and persist with the immunotherapy regimen.<sup>148</sup> During SLIT, allergens are taken up by Langerhans-like dendritic cells residing in the sublingual mucosa. However, because of the limited effectiveness in delivering allergens to these cells, SLIT necessitates doses that are 50 to 100 times greater than those used in SCIT.<sup>107</sup> SCIT and SLIT present notable disadvantages following biological application, such as toxicity, diminished targeting capability, and swift circulatory clearance. Exosomes, which are endogenous

vesicles ranging from 30 to 120 nm, transport protein and nucleic acid cargoes without encountering any of the previously mentioned issues.<sup>149</sup> These small extracellular vesicles are endogenous carriers, suggesting that they are safer than other synthetic particles. Exosomes are therefore powerful drug delivery systems.<sup>150</sup> The acquisition of plentiful and scalable exosomes derived from MSCs presents a significant challenge for clinical applications. The prospective use of MSC-derived exosomes in the treatment of allergic diseases has garnered heightened interest among researchers. These exosomes possess the ability to modify the functions of diverse innate and adaptive immune cells through the delivery of biological microRNAs or active proteins. However, the use of MSCs in therapeutic contexts is still constrained by several limitations in clinical environments, including the necessity for fresh preparation, the risk of off-target effects associated with intravenous administration, and difficulties in traversing certain physiological barriers, such as the blood-brain barrier.<sup>113</sup>

### Current Limitations, Mechanistic Rationale, and Future Perspectives for Clinical Translation

Despite the growing body of evidence that highlights the immunomodulatory and anti-inflammatory effects of MSCs and MSC-derived exosomes in allergic conditions, it is crucial to acknowledge several significant limitations when evaluating the existing literature. Primarily, most of the studies conducted to date have utilized animal models of allergic asthma and allergic rhinitis.<sup>151,152</sup> Although these models offer important mechanistic insights, they fail to completely mirror the complexity, variability, and prolonged immunological responses seen in human allergic diseases. As a result, the translational significance of numerous preclinical discoveries is still questionable.

A significant limitation is the large heterogeneity in published research. MSCs from different origins, such as bone marrow, adipose tissue, umbilical cord, placenta, and induced pluripotent stem cells, may have different biological characteristics and therapeutic effects.<sup>153</sup> Moreover, direct comparisons between studies are challenging and can lead to conflicting results due to variations in cell culture conditions, exosome isolation techniques, dosing protocols, administration methods, and outcome assessment methods. Also, the current evidence is further limited in strength and generalizability by the relatively small sample

sizes used in many experimental studies.<sup>154,155</sup>

Despite these limitations, the commonalities of the immunological mechanisms of AIT and MSC-based therapies provide a strong argument for their potential combination. AIT induces immune tolerance via stimulation of Tregs and Bregs, enhanced production of IL-10 and TGF- $\beta$ , inhibition of allergen-specific Th2 responses, and formation of blocking antibodies. Likewise, MSCs and their exosomes exhibit extensive immunoregulatory effects such as enhancing Treg populations, promoting the differentiation of tolerogenic dendritic cells, suppressing Th2- and Th17-mediated inflammation, regulating macrophage polarization, and promoting the synthesis of anti-inflammatory cytokines. This mechanistic convergence indicates that MSC-based approaches may enhance the tolerogenic pathways activated by AIT, potentially improving the establishment and maintenance of long-term immune tolerance.<sup>156,157</sup> On the other hand, exosomes derived from MSCs appear to have their own unique strengths as free-standing therapeutic interventions. Because of their ability to deliver immunomodulating proteins, lipids, and microRNAs to affect immune cell signaling, exosomes can bypass several limitations related to live-cell therapy.<sup>158,159</sup> As such, they have attracted increasing attention as adjuvants that can help modulate allergen-specific immune responses through AIT. Nonetheless, there is not enough clinical or experimental data to confirm the superior effect of such an approach yet.

In the context of translational clinical approaches, several challenges continue to emerge. While MSCs are generally considered safe and exhibit minimal immunogenicity, concerns persist regarding their long-term safety, biological variability, non-specific immunomodulation, and the risks associated with repeated MSC administration. Although exosomes have the potential to mitigate some safety concerns linked to cellular therapy, further research is needed to better understand the biodistribution and pharmacokinetic properties of these nanoparticles.<sup>160,161</sup>

Standardization presents itself as a major barrier toward the clinical translation of therapies. MSC-based therapy manufacturing can be heterogeneous with regard to production methods, donor characteristics, culture conditions, exosome purification protocols, storage, potency assessment, and purity. Such heterogeneity may significantly influence the efficacy of the treatment.<sup>162,16</sup> Therefore, it is necessary to develop

standardized approaches and validate quality control standards to facilitate future clinical progress.<sup>164</sup>

Regulatory hurdles continue to pose challenges during the implementation process. Some of the major challenges include GMP (Good Manufacturing Practice)-scale production, batch-to-batch reproducibility, product characterization, potency testing, and existing regulatory pathways for these products, which have yet to be fully optimized. Also, there is a lack of clinical data. Currently, a small number of clinical studies have been performed using MSC-based therapies in allergic diseases. More importantly, few studies have been conducted to assess the potential of MSCs or their derivatives (exosomes) as an addition to AIT.<sup>161,165</sup>

Further research is required to identify the mechanisms by which MSCs, exosomes, and allergen-tolerizing pathways interact to define the appropriate doses for the treatment as well as to standardize the process of producing the products. This is critical in identifying whether these treatments can be used in conjunction with allergen immunotherapy.

### Concluding Remarks

MSCs and their exosomes demonstrate significant potential as adjuncts to AIT for allergic asthma. MSCs, derived from diverse tissue sources, exert anti-inflammatory effects through both direct cell-cell interactions and paracrine signaling, including the release of soluble factors and extracellular vesicles. These mechanisms collectively restore immune balance by shifting Th2-dominant responses toward Th1 and Treg phenotypes, suppressing dendritic cell maturation, blocking mast cell degranulation, and polarizing M1 phenotype to M2. In addition, preclinical studies have shown that MSCs and their exosomes exhibit strong immunomodulation and anti-inflammatory effects that can help suppress allergic airway inflammation and restore tolerance in the immune system. These findings suggest that MSC-based approaches may represent promising adjunctive strategies to improve allergen immunotherapy (AIT). At the same time, there is no proven evidence showing improvements in treatment efficiency, reduction in treatment time, or enhancement in treatment safety associated with using MSCs or their exosomes.

Despite these advances, translating MSC and exosome therapies into clinical practice requires further investigation. MSC therapy presents potential side

effects, including immunogenicity and graft rejection. The requirement for fresh preparation and the challenges associated with intravenous delivery, such as off-target effects and crossing physiological barriers like the blood-brain barrier, further complicate its clinical application. MSC-derived exosomes have emerged as a cell-free alternative to MSC therapy, offering several advantages over their cellular counterparts. MSC-derived exosomes are easier to store and manage, exhibit lower immunogenicity, and have a reduced risk of graft rejection. Their ability to act as natural nanodelivery systems enables targeted delivery of therapeutic molecules, reducing potential side effects associated with systemic delivery.

Future directions should focus on optimizing delivery methods, ensuring safety and efficacy, and standardizing production protocols. In addition, studies should focus on elucidating the precise molecular mechanisms underlying their immunoregulatory actions, exploring synergistic effects with AIT, and conducting robust clinical trials to validate their therapeutic benefits in diverse asthma phenotypes, including steroid-resistant cases. Collectively, the integration of MSCs and their exosomes with established immunotherapeutic strategies holds significant promise for achieving long-term disease control and improved quality of life for patients with allergic asthma.

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### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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No data was used for the research described in the article.

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The authors declare that they have not use AI-generated work in this manuscript.

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