DOI: 10.4274/ThoracResPract.2025.s013

MSC-Exosomes as Novel Therapeutics in Asthma and Allergic Airway Inflammation

Sevval Kurt, Ilgin Kimiz-Gebologlu, Suphi S. Oncel

Department of Bioengineering, Faculty of Engineering, Ege University, Izmir, Türkiye

INTRODUCTION: Allergic respiratory diseases, including asthma and allergic rhinitis, are chronic inflammatory diseases that affect millions of people worldwide and constitute a significant health problem.[1] These diseases are characterized by airway obstruction, mucus overproduction, eosinophilic infiltration, and airway hyperresponsiveness, which together lead to impaired respiratory function and reduced quality of life. Despite significant advances in pharmacotherapy, current treatments such as corticosteroids and bronchodilators mainly target symptom control rather than underlying immune dysregulation, often resulting in relapse or steroid resistance.[2] Consequently, there is a growing need for novel, effective, and safe therapeutic strategies that address the root causes of airway inflammation rather than providing temporary relief.

In recent years, extracellular vesicles, particularly exosomes (Exos), have emerged as key mediators of intercellular communication and as promising candidates for next-generation biologics. Exos are lipid bilayer nanosized vesicles (30-150 nm) secreted by almost all cell types, containing proteins, lipids, mRNAs, and microRNAs that reflect the physiological state of their parent cells.[3] Their natural stability, biocompatibility, and ability to traverse biological barriers with minimal immunogenicity confer several advantages over synthetic nanocarriers. Due to their intrinsic targeting capacity and role in cell-cell signaling, Exos are increasingly explored for use in drug delivery, immune modulation, and regenerative medicine.[4] Among various exosome sources, mesenchymal stem cell (MSC)-derived Exos have emerged as highly attractive candidates for cell-free therapies. MSCs are well-known for their immunoregulatory and regenerative capabilities, and their secreted Exos retain most of these biological functions. Importantly, MSC-Exos can interact with immune cells and modulate inflammatory signaling pathways, suggesting their potential as next-generation biotherapeutics in allergic airway diseases.[5]

The immunopathogenesis of allergic airway diseases is mainly driven by the imbalance between Th1 and Th2 immune responses, with Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13 playing central roles in eosinophilic inflammation and immunoglobulin E (IgE) production.[6] MSC-Exos have been shown to mitigate these pathological processes through multiple mechanisms: attenuating Th2-dominated responses, downregulating pro-inflammatory cytokines, and promoting the expansion of regulatory T-cells (Tregs), which are crucial for maintaining immune tolerance.[7] Furthermore, MSC-Exos promotes the polarization of M2 macrophages, a phenotype associated with tissue repair and resolution of inflammation. At the molecular level, Exos derived from MSCs deliver bioactive microRNAs that modulate critical signaling cascades, including NF-κB, STAT6, and MAPK pathways, key regulators of inflammation and immune activation.[8] For instance, microRNAs such as miR-146a-5p, miR-126-3p, and miR-1470 carried by MSC-Exos have been implicated in suppressing inflammatory mediators and restoring immune balance in airway tissues.[6] Through these mechanisms, MSC-Exos effectively attenuate airway hyperreactivity and remodeling,

Corresponding author: Suphi S. Oncel, e-mail: suphi.oncel@ege.edu.tr

leading to functional improvement in preclinical asthma models. MSC-Exos exert their therapeutic effects through multiple mechanisms, including modulation of immune cell activity, suppression of Th2 cytokines, and promotion of Treg and M2 macrophage responses that collectively alleviate airway inflammation (Figure 1).

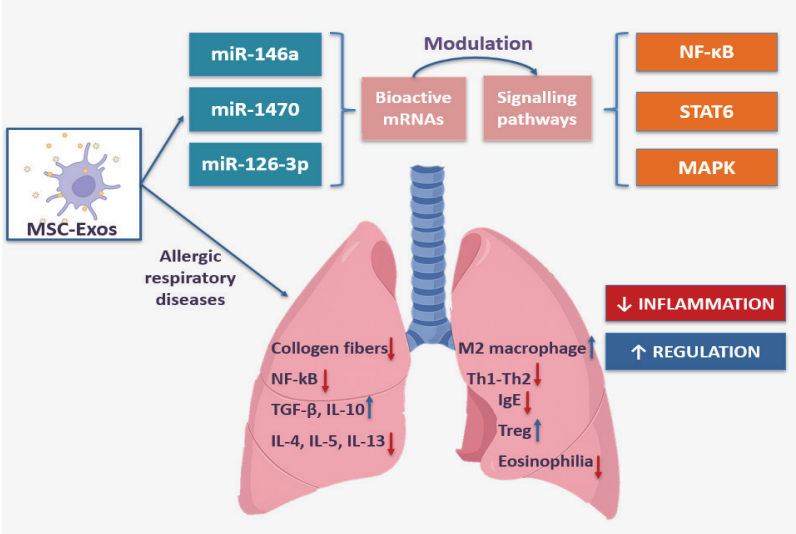

Figure 1. Schematic representation of the therapeutic mechanisms of MSC-derived exosomes in allergic airway inflammation

CONCLUSION: Preclinical studies using both systemic and intranasal administration of MSC-Exos have demonstrated significant therapeutic benefits. In murine models of allergic airway inflammation, treatment with MSC-Exos resulted in reduced eosinophilic infiltration, decreased serum IgE levels, and suppression of mucus hypersecretion. These effects were accompanied by enhanced secretion of IL-10 and TGF-β, two key anti-inflammatory cytokines that contribute to an immunosuppressive microenvironment.[9] Collectively, these findings indicate that MSC-Exos can recapitulate many of the beneficial immunomodulatory effects of MSC therapy while avoiding several of the risks associated with live cell transplantation, such as immune rejection or tumorigenicity.

A major advantage of MSC-Exos therapy is its cell-free and safer nature, avoiding risks associated with stem cell transplantation. Due to their nanoscale size, lipid bilayer structure, and endogenous cargo, MSC-Exos can efficiently deliver regulatory molecules to target tissues, outperforming many synthetic nanocarrier systems. Nevertheless, translating these promising preclinical findings into clinical practice requires overcoming several challenges, including standardized isolation and characterization protocols, scalable GMP-compliant production, dose optimization, and rigorous long-term safety evaluation.

Future Perspectives

MSC-Exos represent an innovative and safe therapeutic platform for allergic respiratory diseases such as asthma and rhinitis. By combining the regenerative and immunomodulatory properties of MSCs with the advantages of a cell-free system, they effectively regulate Th2 cytokines and restore immune balance. Future research should prioritize the scalable production and bioengineering optimization of MSC-Exos to enhance their stability, targeting efficiency, and bioactivity. Advances in exosome surface modification, such as ligand conjugation or genetic engineering of parent MSCs, may further improve selective delivery to inflamed airway tissues. Additionally, large-scale clinical trials are necessary to confirm therapeutic efficacy, establish optimal administration routes (e.g., intranasal vs.

systemic), and ensure long-term safety. Beyond allergic airway diseases, the versatility of MSC-Exos may extend to other inflammatory and fibrotic lung conditions, including chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. As understanding of exosome biology deepens and bioengineering techniques advance, MSC-Exos are poised to become a cornerstone of next-generation immunomodulatory and regenerative therapies, bridging molecular biology, nanotechnology, and clinical immunology for transformative outcomes in respiratory medicine.

KEYWORDS: Mesenchymal stem cell, exosomes, allergic diseases, airway inflammation, immunomodulatory therapy

REFERENCES

1. Hough KP, Deshane JS. Exosomes in allergic airway diseases. *Curr Allergy Asthma Rep*. 2019;19(5):26. [Crossref]
2. Iordache A, Balica NC, Horhat ID, et al. A review regarding the connections between allergic rhinitis and asthma-epidemiology, diagnosis and treatment. *Curr Health Sci J*. 2023;49(1):5-18. [Crossref]
3. Kimiz-Gebologlu I, Oncel SS. Exosomes: Large-scale production, isolation, drug loading efficiency, and biodistribution and uptake. *J Control Release*. 2022;347:533-543. [Crossref]
4. Rezaie J, Ajezi S, Avci ÇB, et al. Exosomes and their application in biomedical field: difficulties and advantages. *Mol Neurobiol*. 2018;55(4):3372-3393. [Crossref]
5. Abid AI, Conzatti G, Toti F, Anton N, Vandamme T. Mesenchymal stem cell-derived exosomes as cell free nanotherapeutics and nanocarriers. *Nanomedicine*. 2024;61:102769. [Crossref]
6. Wang M, Zhao N, Wang C, Jin ZB, Zhang L. Immunomodulatory properties of mesenchymal stem cells: a potential therapeutic strategy for allergic rhinitis. *Allergy*. 2023;78(6):1425-1440. [Crossref]
7. Kim SD, Cho KS. Immunomodulatory effects of mesenchymal stem cell-derived extracellular vesicles in allergic airway disease. *Life (Basel)*. 2022;12:(12):1994. [Crossref]
8. Sadeghi M, Mohammadi M, Tavakol Afshari J, Iranparast S, Ansari B, Dehnavi S. Therapeutic potential of mesenchymal stem cell-derived exosomes for allergic airway inflammation. *Cell Immunol*. 2024;397-398:104813. [Crossref]
9. Engeroff P, Vogel M. The potential of exosomes in allergy immunotherapy. *Vaccines (Basel)*. 2022;10(1):133. [Crossref]