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Original Article

Investigating the effect of mesenchymal stem cells on airway hyper-responsiveness in asthma

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ABSTRACT

Asthma is a lung disease characterized by eosinophilic inflammation, mucus secretion, airway hyper-responsiveness (AHR), and airway obstruction. AHR is a crucial factor in asthma. Mesenchymal stem cells (MSCs) have a regulatory effect on the immune response and may be useful in treating asthma. MSCs have low immunogenicity and are considered safe for application. Additionally, a study was conducted to investigate the effect of MSCs on controlling AHR in an asthma model. MSCs were isolated and used to treat asthmatic male BALB/c mice. To produce an animal model of asthma, the mice were sensitized and challenged with OVA. On days 30 and 40, to measure AHR, a Methacholine challenge test was performed to determine the Penh value. AHR was recorded and analyzed. Treatment of asthmatic mice with MSCs resulted in a significant difference ($p<0.05$) in controlling AHR during the MCh challenge test. MSCs are almost non-immunogenic and can be used to treat asthma and control AHR. The use of MSCs as an anti-asthma treatment presents a new and applicable strategy for controlling AHR in asthma.

بررسی تاثیر سلول های بنیادی مزانشیمی بر پاسخ بیش از حد راه هوایی در آسم

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چکیده

آسم یک بیماری ریوی است که با التهاب ائوزینوفیلیک، ترشح موکوس، واکنش بیش از حد راه هوایی (AHR) و انسداد راه هوایی مشخص می شود. AHR یک عامل مهم در آسم است .سلول های بنیادی مزانشیمی (MSCs) اثر تنظیمی بر پاسخ ایمنی دارند و ممکن است در درمان آسم مفید باشند. سلول های بنیادی مزانشیمی ایمنی زایی پایینی دارند و برای استفاده، ایمن در نظر گرفته می شوند. علاوه بر این، مطالعه‌ای برای بررسی تأثیر سلول‌های بنیادی مزانشیمی بر کنترل AHR در یک مدل آسم انجام شد. سلول های بنیادی مزانشیمی، جدا شده و برای درمان موش های سوری نر BALB/c مبتلا به آسم استفاده شدند. برای تولید مدل حیوانی آسم، موش‌ها حساس شده و با OVA به چالش کشیده شدند. در روزهای ۳۰ و ۴۰، برای اندازه گیری AHR، آزمون چالش متاکولین برای تعیین مقدار پن انجام شد. AHR ثبت و مورد تجزیه و تحلیل قرار گرفت . نتیجه درمان موش‌های مبتلا به آسم با سلول‌های بنیادی مزانشیمی، تفاوت معنی‌دار ($p<۰/۰۵$) در کنترل AHR در طول آزمون چالش MCh داشت. سلول های بنیادی مزانشیمی تقریباً غیر ایمنی زا هستند و می توانند برای درمان آسم و کنترل AHR استفاده شوند. استفاده از سلول های بنیادی مزانشیمی به عنوان یک درمان ضد آسم، یک استراتژی جدید و کاربردی برای آن ارائه می دهد.

واژه های کلیدی: آلرژی، سلول درمانی، آسم، ریه، درمان

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INTRODUCTION

Asthma is a chronic lung disease characterized by eosinophilic inflammation, mucus hypersecretion, airway hyper-responsiveness (AHR), and reversible airway obstruction. AHR is a crucial factor in asthma, and certain anti-asthma medications can help control it [1, 2]. Allergies are the leading cause of asthma. The pathophysiology of asthma is influenced by both genetic predisposition and environmental factors that activate the immune response, specifically the Th2 dominant response. One of the major Th2 cytokines is IL-4, which induces IgE isotype switching of B cells. These IgE antibodies can then bind to the FcεRI receptor on the surface of mast cells. Mast cells can be activated by cross-linking FcεRI-IgE with allergens, leading to the release of histamine and other mediators that cause allergic symptoms, such as bronchospasm reactions [3-5].

Mast cells have a regulatory and modulatory effect on the immune response and inflammation, and their immunoregulatory capacity may be useful in the treatment of asthma. MSC therapy is a novel therapeutic approach with immunoregulatory potential for immune response-related diseases, such as asthma. However, MSCs are harvested from various tissues and may affect the pathophysiology of allergic asthma. MSCs have low immunogenicity and may be safe for clinical application [6, 7]. Additionally, this study evaluated the effect of MSCs on controlling AHR in an asthma mouse model.

MATERIALS AND METHODS

MSCs culture

MSCs were isolated from the mouse's bone marrow following previously established protocols. Briefly, the bone marrow was flushed out of the cavity and cultured for 5 days. The cells were then re-suspended, passaged, and confirmed [6, 7].

Animal treatment

Male BALB/c mice were kept under standard conditions in the laboratory animal house and were divided into three groups (n = 6): a control group sensitized with PBS and healthy, and two other groups sensitized and challenged with OVA to produce an asthma model [8, 9]. One group received no treatment, while the other was treated with MSCs via bronchial administration on day 25.

Measurement of AHR

To measure AHR on days 30 and 40, we conducted a Methacholine (MCh) challenge test to determine the Penh value under anesthesia. The mice were tracheostomized and intubated separately, and then exposed to PBS aerosol and different MCh concentrations (2, 4, 8, 16, 32 and 64 mg/ml). At least, AHR were recorded and analyzed.

Data analyzing

The data were analyzed using SPSS software version 20 with t-test and Mann-Whitney U test. The results were presented as Mean ± SD using GraphPad Prism. A p-value of less than 0.05 was considered statistically significant.

RESULTS

After creating an allergic asthma mouse model, we measured AHR. According to this study, treating mice with MSCs can control AHR in the MCh challenge test. This control showed a significant difference ($p<0.05$) between days 30 and 40, and on day 40, AHR was better controlled than on day 30 at all MCh concentrations. Graphs created from mouse inhalation in a ventilator showed significant differences between the treated and non-treated groups (Figure 1). Upon analysis of the ventilator graphs, a significant difference was observed between the treated and non-treated groups, as well as between days 30 and 40. For instance, in dose 16 mg/ml, the penh values on days 30 and 40 were 9.4 ± 0.1 and 8.4 ± 0.2, respectively, indicating a significant difference (Figure 2).

DISCUSSION

Asthma is a chronic lung disease that causes bronchial obstruction. The obstruction of airways is caused by the spasm of smooth muscle cells, leading to AHR. Additionally, chronic obstruction of airways is caused by eosinophilic inflammation and mucus released from goblet cells. If these factors persist over time, they may lead to airway remodeling [10, 11]. Therefore, to prevent acute airway obstruction, it is important to control AHR.

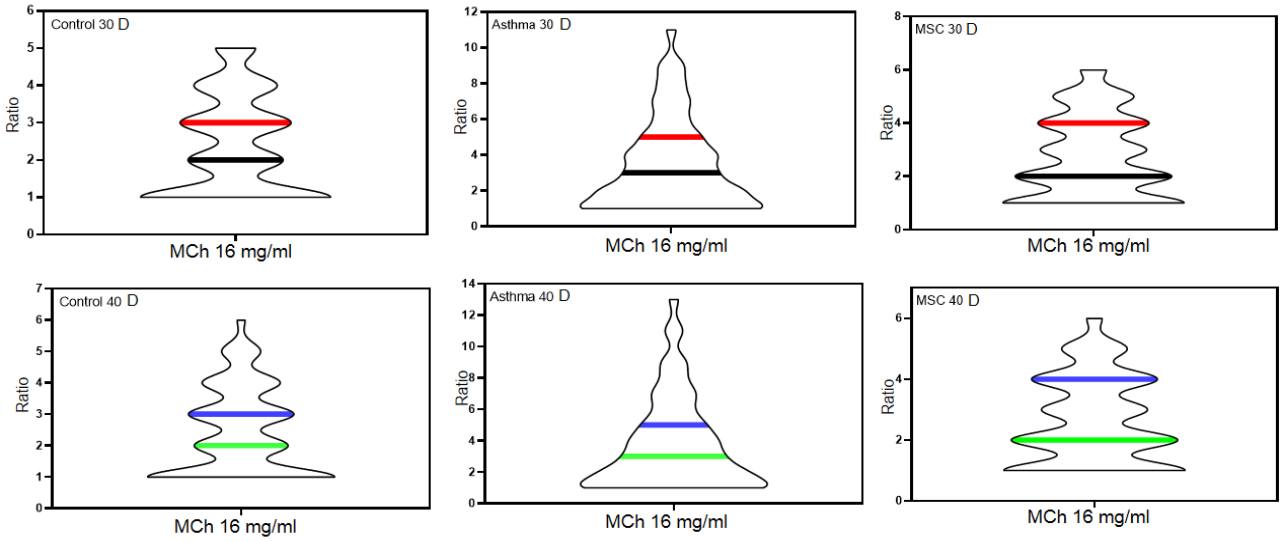

Figure 1. To determinant of AHR, MCh challenge test was done and inhalation graphs of ventilator were showed in MCH 16 mg/ml.

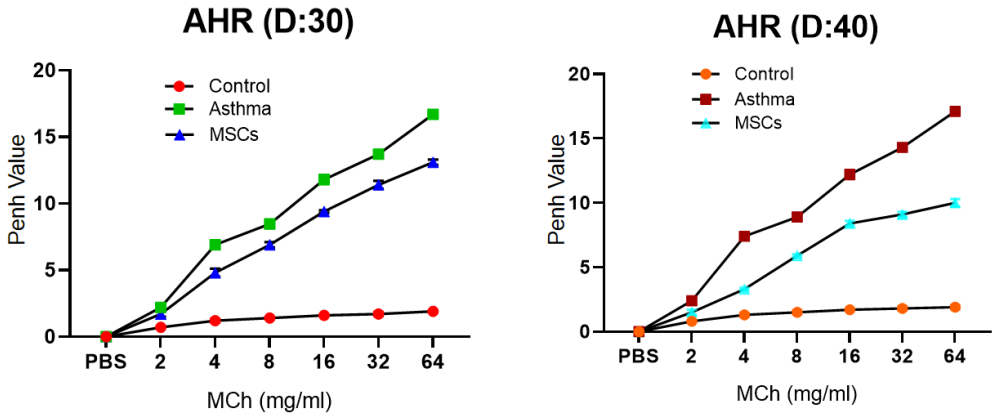

Figure 2. Graphs of analyzed data in all doses of MCh, penh values in days 30 and 40 were presented.

This study achieved this through mesenchymal stem cell therapy. When these cells remain in the airways for a longer period, they can be more effective in controlling AHR. While there are several anti-asthma therapies available, including short-acting and long-acting drugs that can control airway hyper-responsiveness (AHR) and inflammation, many of these drugs have limited efficacy and require frequent administration [12, 13]. Mesenchymal stem cell (MSC) therapy presents a promising long-term treatment option that does not require repeated administration. Because these cells can proliferate and have self-renewal potential, they offer a new approach that does not require higher doses of treatment or repeating therapeutic protocols. In allergic diseases, such as asthma, cell therapy can be used to modulate the immune response, controlling the activation and proliferation of Th2 cells. This therapeutic method can help control immune-related allergic responses in asthma. MSC therapy has been shown to decrease bronchoconstriction and collagen fiber content in the airway [14]. MSCs are a novel therapy developed in regenerative medicine. These cells are highly adaptable and can prevent remodeling in target tissues. Additionally, they aid in repairing lung tissue and reducing lung injury. MSCs, as multi-potent progenitor cells, have immune-modulatory potential [15, 16]. Therefore, using MSC therapy to control AHR in allergic asthma can have a beneficial effect. It was shown that the administration of MSCs systemically can suppress collagen deposition and airway remodeling, reduce the number of goblet cells, and decrease the airway's response to MCh [17, 18]. In this study, the administration of MSCs prevented AHR and resulted in improved airflow in obstructed airways. The immunomodulatory effect of MSCs is considered a new therapeutic approach for allergic diseases, such as asthma, due to their immune-privileged potential. MSC therapy for asthma, via intra-tracheal and/or intra-venous administration, could reduce leukotrienes B4 and C4, which play an important role in the pathophysiology of allergic asthma and airway obstruction [11, 16, 19]. In cases of airway allergic reactions and asthma attacks, immune cell mediators play a dominant role and can cause spasms in the airway smooth muscle cells. One group of these mediators are mast cells. Another group of cytokines, known as Type 2 cytokines, including IL-4 and its upstream cytokines such as IL-33, have a significant impact. IL-33 is a member of the IL-1 cytokine family and affects cytokine network signaling pathways, controlling the production of IL-4. IL-4 stimulates B cells to produce IgE, the main allergic immunoglobulin. IgEs bind to receptors on mast cells and, upon attaching to the allergen, trigger mast cell degranulation. Mediators released from mast cell granules have a strong effect on the spasm of smooth muscle cells, leading to airway obstruction [20]. Although not evaluated in this study, it is possible that MSCs may have an effect on the control of cytokines such as IL-4 and IL-33. Through this pathway, they may be able to regulate the degranulation of mast cells, spasm of airway smooth muscle cells, and AHR. MSC therapy is an innovative immunomodulatory treatment for various immune-related conditions, including allergic asthma. Studies have shown that MSCs have an immunoregulatory effect on both the innate and adaptive immune responses. In one study, it was found that MSCs containing the expression gene of IL-35 were effective in controlling allergo-inflammatory mechanisms, allergic immunopathology, and asthma symptoms in patients with allergic asthma. It was shown that the immunomodulatory effect of MSCs had a synergistic effect with that of IL-35, and together they could mitigate the allergoinflammatory response in asthma. It was also demonstrated that expressing the IL-35 vector inhibits IL-4 and IgE levels, thereby attenuating asthma pathogenesis. Additionally, IL-35 reduces the proliferation of T cells and the allergic immune response of Th2 cells in asthma. In patients predisposed to a high risk of specific IgE-mediated allergic responses to inhaled allergens, dendritic cells with IgE can present aeroallergens and induce allergic inflammation. Therefore, IL-35 prevents the mechanism of allergy and is a therapeutic agent for asthma. IL-35 deficiency gives rise to Th17 cells that are required to maintain AHR after challenge with multiple allergens. It has been reported that MSCs can regulate AHR, and this effect is enhanced in MSCs with the IL-35 gene compared to MSC treatment alone without IL-35 [21].

CONCLUSION

MSCs are almost non-immunogenic due to their embryonic state. Therefore, the use of MSCs to treat asthma is a viable option, as demonstrated in this study, which showed a significant effect on the control of AHR and the evaluation of breathing output in asthmatic mice. Therefore, the use of MSCs as a treatment for asthma presents a new and applicable strategy and is a useful method for controlling AHR in asthma. These cells can also be used as a delivery system for certain genes, but further research in this field is necessary.

ETHICS

Approved.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

[1] Roxbury CR, Lin SY. Efficacy and safety of subcutaneous and sublingual immunotherapy for allergic rhino conjunctivitis and asthma. Otolaryngologic Clinics of North America. 2017; 50(6): 1111-19. **doi:10.1016/j.otc.2017.08.011**

[2] Virchow JC. Allergen immunotherapy (AIT) in asthma. Seminars in Immunology. 2019; 46: 101334. **doi:10.1016/j.smim.2019.101334**

[3] Isik E, Fredland NM, Freysteinson WM. School and community-based nurse-led asthma interventions for school-aged children and their parents: a systematic literature review. Journal of Pediatric Nursing. 2019; 44: 107-14. **doi:10.1016/j.pedn.2018.11.007**

[4] Xuan X, Sun Z, Yu C, Chen J, Chen M, Wang Q. et al. Network pharmacology-based study of the protective mechanism of conciliatory anti-allergic decoction on asthma. Allergologia et Immunopathologia (Madr). 2020; 48: 441-9. **doi:10.1016/j.aller.2019.12.011**

[5] Sopo SM, Bersani G, Del Vescovo E, Gelsomino M. Disagreement between guidelines regarding the third step of asthma drug therapy for school-age children. Allergologia et Immunopathologia (Madr). 2020; 48: 789-91. **doi:10.1016/j.aller.2019.12.004**

[6] Huang M, Mehrabi Nasab E, Athari SS. Immunoregulatory effect of mesenchymal stem cell via mitochondria signaling pathways in allergic asthma. Saudi Journal of Biological Sciences. 2021; 28: 6957-62. **doi:10.1016/j.sjbs.2021.07.071**

[7] Hou C, Sun F, Liang Y, Mehrabi Nasab E, Athari SS. Effect of transduced mesenchymal stem cells with IL-10 gene on control of allergic asthma. Allergologia et Immunopathologia (Madr). 2023; 51(2): 45-51. **doi:10.15586/aei.v51i2.789**

[8] Cheng C, Mehrabi Nasab E, Athari SS. Survey of immunopharmacological effects of botulinum toxin in cell signaling of bronchial smooth muscle cells in allergic asthma. Allergologia et Immunopathologia (Madr). 2022; 50(3): 93-100. **doi:10.15586/aei.v50i3.549**

[9] Jiang J, Mehrabi Nasab E, Athari SM, Athari SS. Effects of vitamin E and selenium on allergic rhinitis and asthma pathophysiology. Respiratory Physiology & Neurobiology 2021; 286: 103614. **doi:10.1016/j.resp.2020.103614**

[10] Tanaka H, Komai M, Nagao K, Ishizaki M, Kajiwara D, Takatsu K. et al. Role of interleukin-5 and eosinophils in allergen-induced airway remodeling in mice. American Journal of Respiratory Cell and Molecular Biology. 2004; 31(1): 62-68. **doi:10.1165/rcmb.2003-0305OC**

[11] Booth BW, Sandifer T, Martin EL, Martin LD. IL-13-induced proliferation of airway epithelial cells: mediation by intracellular growth factor mobilization and ADAM17. Respiratory Research. 2007; 8: 51.

[12] Ouyang Y, Miyata M, Hatsushika K, Ohnuma Y, Katoh R, Ogawa H. et al. TGF-beta signaling may play a role in the development of goblet cell hyperplasia in a mouse model of allergic rhinitis.

Allergology International. 2010; 59(3): 313-19.
doi:10.2332/allergolint.10-SC-0172

[13] Samitas K, Delimpoura V, Zervas E, Gaga M. Anti-IgE treatment, airway inflammation and remodelling in severe allergic asthma: current knowledge and future perspectives. European Respiratory Review. 2015; 24(138): 594-601. **doi:10.1183/16000617.00001715**

[14] Yin J, Yan F, Zheng R, Wu X, Athari SS**.** Immunomodulatory effect of IL-2 induced bone marrow mononuclear cell therapy on control of allergic asthma. Allergologia et Immunopathologia (Madr). 2023; 51(1): 110-15. **doi:10.15586/aei.v51i1.746**

[15] Cruz FF, Borg ZD, Goodwin M, Sokocevic D, Wagner DE, Coffey A. et al. Systemic administration of human bone marrow derived mesenchymal stromal cell extracellular vesicles ameliorates aspergillus hyphal extract induced allergic airway inflammation in immunocompetent mice. Stem Cells Translational Medicine. 2015; 4(11): 1302-16.
doi:10.5966/sctm.2014-0280

[16] Lathrop MJ, Brooks EM, Bonenfant NR, Sokocevic D, Borg ZD, Goodwin M. et al. Mesenchymal stromal cells mediate aspergillus hyphal extract-induced allergic airway inflammation by inhibition of the Th19 signaling pathway. Stem Cells Translational Medicine. 2014; 3(2): 194-205.
doi:10.5966/sctm.2013-0061

[17] Hu X, Yu SP, Fraser JL, Lu Z, Ogle ME, Wang JA. et al. Transplantation of hypoxia preconditioned mesenchymal stem cells improves infarcted heart function via enhanced survival of implanted cells and angiogenesis. Journal of Thoracic and Cardiovascular Surgery. 2008; 135(4): 799-808.
doi: 10.1016/j.jtcvs.2007.07.071

[18] Urbanek K, de Angelis A, Spaziano G, Piegari E, Matteis M, Cappetta D. et al. Intratracheal administration of mesenchymal stem cells modulates tachykinin system, suppresses airway remodeling and reduces airway hyperresponsiveness in an animal model. Plos One. 2016; 11(7):e0158746.
doi:10.1371/journal.pone.0158746

[19] Lin YD, Fan XL, Zhang H, Fang SB, Li CL, Deng MX. et al. The genes involved in asthma with the treatment of human embryonic stem cell-derived mesenchymal stem cells. Molecular Immunology. 2018; 95: 47-55.
doi:10.1016/j.molimm.2018.01.013

[20] Zhang R, Yin Z, Pan J, Zhai C, Athari SS, Dong L. Effect of transfected induced pluripotent stem cells with Decorin gene on control of lung remodeling in allergic asthma. Journal of Investigative Medicine 2023, Vol. 71(3): 235-43.
doi:10.1177/10815589221140590

[21] Bao ZH, Gao F, Athari SS, Wang H. Immunomodulatory effect of IL-35 gene-transfected mesenchymal stem cells on allergic asthma. Fundamental & Clinical Pharmacology. 2023; 37(1): 116-124. **doi:10.1111/fcp.12823**