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Immunomodulatory effect of IL-2 induced bone marrow mononuclear cell therapy on control of allergic asthma

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Abstract
Asthma is a chronic airway disease. Allergic reactions and T helper (h)2 immune response play a key role in asthma occurrence. Cell therapy can control inflammation and remodeling responses in allergic asthma, and cytokines can change this effect. Therefore, in this study, the effect of treated cell therapy with IL-2 to control allergic asthma was studied. Bone marrow cells were extracted and co-cultured with IL-2 and the cells were used via intra-tracheal administration in allergic asthma mice. Levels of IL-4, IL-5, IL-13, Leukotriene B4 and C4, and remodeling factors were measured. At least, a histopathology test of lung tissue was done. Type2 cytokines, leukotrienes, remodeling factors, mucus secretion, goblet cell hyperplasia, peri-bronchial and peri-vascular inflammation were significantly ($p<0.05$) decreased by treating with bone marrow-derived mononuclear cells (BMDMCs) and IL-2-BMDMCs. Treatment with IL-2-BMDMCs could significantly decrease IL-13, transforming growth factor (TGF)-β, HP levels, and mucus secretion ($p<0.05$) compared to BMDMCs treatment. In this study, BMDMCs and IL-2-BMDMCs therapy could decrease inflammation, allergic, and remodeling factors in allergic asthma. Cell therapy with BMDMCs had a strong and notable effect on the control of allergic asthma pathophysiology when co-cultured and used with IL-2.

Introduction

Asthma is a reversible airway disease, which affects more than 350 million people worldwide. Asthma is a multi-factorial disease in which genetic predisposition and environmental trigger factors are the main orchestrate of asthma pathophysiology.[1-3] The main symptoms of asthma are coughing, wheezing, and breathlessness. Th2-associated cytokines [interleukin (IL)-4, IL-5, and IL-13] play a key role in asthma occurrence. Allergic reactions have an important role in the initiation of an asthma attack. IL-4 increases immunoglobulin (Ig)E production which leads

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to the production of allergo-inflammatory mediators. IL-5 increases eosinophil accumulation and inflammation and IL-13 increases mucus secretion and airway obstruction.[4-6]

Bone marrow-derived mononuclear cells (BMDMCs) modulate inflammatory and remodeling processes regardless of allergic asthma. Intravenous administration of BMDMCs attenuate inflammatory and remodeling responses in allergic asthma, and also, promote airway epithelial repair.[7,8]

IL-2 is a T cell growth factor and its receptor (acceptor for T cell growth factor) has two subunits, α and β. The receptor was considered as a signal apparatus responding to cascade driving T cell proliferation. It was speculated that IL-2 deficiency leads to autoimmunity and inflammation. Subsequently, autoimmune and inflammation phenotypes would be noticed when *IL2r*α and *IL2r*β genes (encode α chain [clusters of differentiation (CD25)] and β chain (CD122) of receptor) were genetically depleted.[9-11] Specific CD4+ T cell population expressing CD25 was revealed to essentially regulate immune tolerance (regulatory CD4+ T cells or Treg cells) that are critically activated by IL-2, in health and diseases. IL-2 stimulates Treg activation and via this approach, IL-2 therapy induces immune tolerance without inducing severe immunosuppression, and inhibits the generation of auto-reactive T follicular helper cells (TFH) and TH17 cells.[10,12,13] Therefore, in this study, the effect of BMDMCs that were treated with IL-2 to control allergic asthma pathogenesis through the production of active tolerogenic immune cells and harnessing of allergo-inflammatory and fibrotic factors were done.

Materials and Methods

Extraction of BMDMCs

Bone marrow cells were extracted from male Balb/c mice according to a previously described method[7] and used for administration. Briefly, bone marrow cells were aspirated from the femur and tibia with Dulbecco's modified Eagle's medium, centrifuged, re-suspended in Dulbecco's Modified Eagle Medium (DMEM) and added to Ficoll-Hypaque, and after centrifuging, they were re-suspended in phosphate-buffered saline (PBS) for administration. One day before cell therapy, the cells were treated with IL-2 for 48 h.[14]

Animal preparation and protocol

Thirty-three male Balb/c mice (20–22 g) were kept under standard laboratory conditions (24±1°C, 50±10% humidity, and 12 h light/dark cycle) and randomly assigned to three groups: Ovalbumin (OVA)-induced allergic asthma group, asthma group that was treated with BMDMCs, and asthma group that was treated with IL-2-BMDMCs. OVA-induced allergic asthma mice model was produced according to the previously described method.[2,3,5] Briefly, OVA solution with alum adjuvant was injected for sensitization and for challenge, the OVA solution was nebulized. Treatment with BMDMCs (2×10^6 cells) was done on day 25 via intra-tracheal administration.

Cytokines measurement

After anesthetization of mice on day 31 by ketamine and xylazine, samples of broncho-alveolar lavage fluid (BALf; 0.8 ml from each mouse) were taken from mice by intubation and the levels of IL-4, IL-5, IL-13 were measured in BALf using enzyme-linked immunosorbent assay (ELISA) kits, according to manufacturer instructions.

LTs Measurement

Leukotriene (LT) B4 and C4 levels were measured in BALf using specific ELISA kits.

Remodeling factors measurement

The content of hydroxyproline (HP) as the main index of collagen fibers deposition in the lung tissue was measured by a colorimetric modified method. TGF-β, as another remodeling factor, was measured in supernatants of lung tissue homogenate described before.[15]

Histopathology

On day 31, the mice were euthanized by CO_2. The left lung of each mouse was removed, fixed, embedded in paraffin, and stained with alcian blue (AB), hematoxylin-eosin (H&E), and periodic acid Schiff stains (PAS). Analysis of lung histopathology was performed with a light microscope. Later, peribronchiolar, perivascular inflammation, goblet cell hyperplasia, and mucus hypersecretion in the airways were determined in lung tissues by the point-counting technique.

Statistical analysis

Experimental tests were repeated three times and results were presented as a mean of three times with standard deviations (SD). The SPSS software version 27 was used for statistical analyses and less than 0.05 was supposed as significant for the *p* value. The graphs were drawn in GraphPad prism (Version 8.3). Data were tested for normality using the KolmogorovSmirnov test. Paired t-test and two-way ANOVA, followed by Tukey's test were used for analyzing data and correlation analysis was carried out using Pearson's method.

Result

ILs

IL-4, IL-5, and IL-13 levels were significantly ($p < 0.05$) decreased by treating with BMDMCs and IL-2-BMDMCs compared to the untreated asthma group (Figure 1). Decreasing of IL-13 level by treatment with IL-2-BMDMCs was significant ($p < 0.05$) compared to BMDMCs treated group, but there is no significant difference ($p > 0.05$) between BMDMCs and IL-2-BMDMCs groups in levels of IL-4 and IL-5.

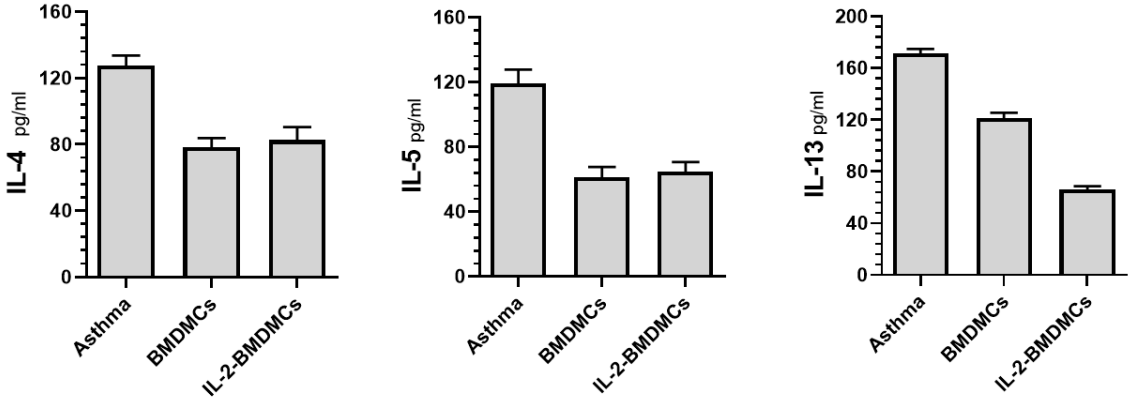

Figure 1. Levels of cytokine in BALf of mice. The levels of cytokines (IL-4, IL-5, and IL-13) in BAL fluid were measured. The levels of IL-4, IL-5, and IL-13 in BALf of BMDMCs and IL-2-BMDMCs groups were decreased compared to the asthma group and IL-13 level in the IL-2-BMDMCs group was significantly decreased in comparison to the BMDMCs group ($p < 0.05$).

LTs

LTB4 and LTC4 levels were significantly ($p < 0.05$) decreased by treating with BMDMCs (99.6 ± 5.7 and 185.3 ± 44.2 ng/ml, respectively) and IL-2-BMDMCs (97.7 ± 4.4 and 179.3 ± 50.1 ng/ml, respectively) compared to untreated asthma group (163.4 ± 8.2 and 334.2 ± 28.6 ng/ml, respectively) (Figure 2). There is no significant difference ($p > 0.05$) between BMDMCs and IL-2-BMDMCs groups in LTB4 and LTC4 levels.

Remodeling

Levels of TGF-β and HP were significantly ($p<0.05$) decreased by treating with BMDMCs and IL-2-BMDMCs compared to the non-treated asthma group (Figure 2). Decrease of TGF-β and HP levels by treating with IL-2-BMDMCs was significant ($p<0.05$) compared to the BMDMCs treated group.

Histopathology

Mucus hypersecretion, goblet cell hyperplasia, eosinophilic bronchial, and vascular inflammation were significantly ($p < 0.05$) reduced by treating with BMDMCs and IL-2-BMDMCs compared to the untreated asthma group (Figure 3). Reduction of mucus hypersecretion by treating with IL-2-BMDMCs was significant ($p < 0.05$) compared to BMDMCs treated group, but there is no significant difference ($p > 0.05$) between BMDMCs and IL-2-BMDMCs groups in goblet cell hyperplasia, eosinophilic bronchial, and vascular inflammation.

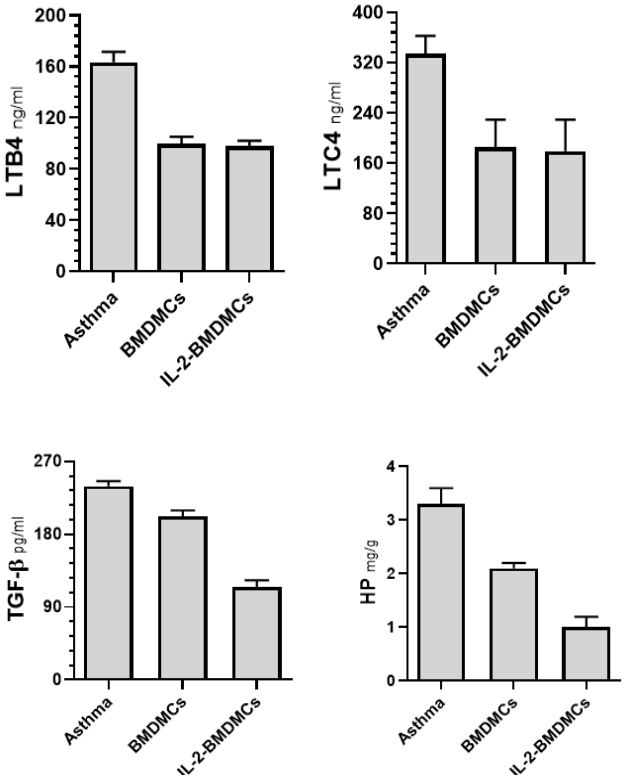

Figure 2. Levels of LTs and remodeling factors. The levels of LTB4, LTC4 and also HP and TGF-β as remodeling factors were measured. The levels of LTB4, LTC4, HP, and TGF-β in BMDMCs and IL-2-BMDMCs groups were decreased compared to the asthma group and HP and TGF-β in the IL-2-BMDMCs group were significantly decreased in comparison to the BMDMCs group ($p < 0.05$).

Discussion

Asthma is a reversible airway disease that causes substantial medical and financial burdens in more than 350 million people worldwide. Allergic asthma has common characteristics such as high serum IgE, excessive activation of Th2, and increased cellular infiltration. Th2-associated cytokines (IL-4, IL-5, and IL-13) play a key role in asthma occurrence.[16,17] The interaction between BMDMCs and Th2 cells leads to a decrease in IL-4 secretion, which can promote IgE synthesis and allergic response initiation. IL-5 can promote the development of eosinophils, and eosinophils can induce

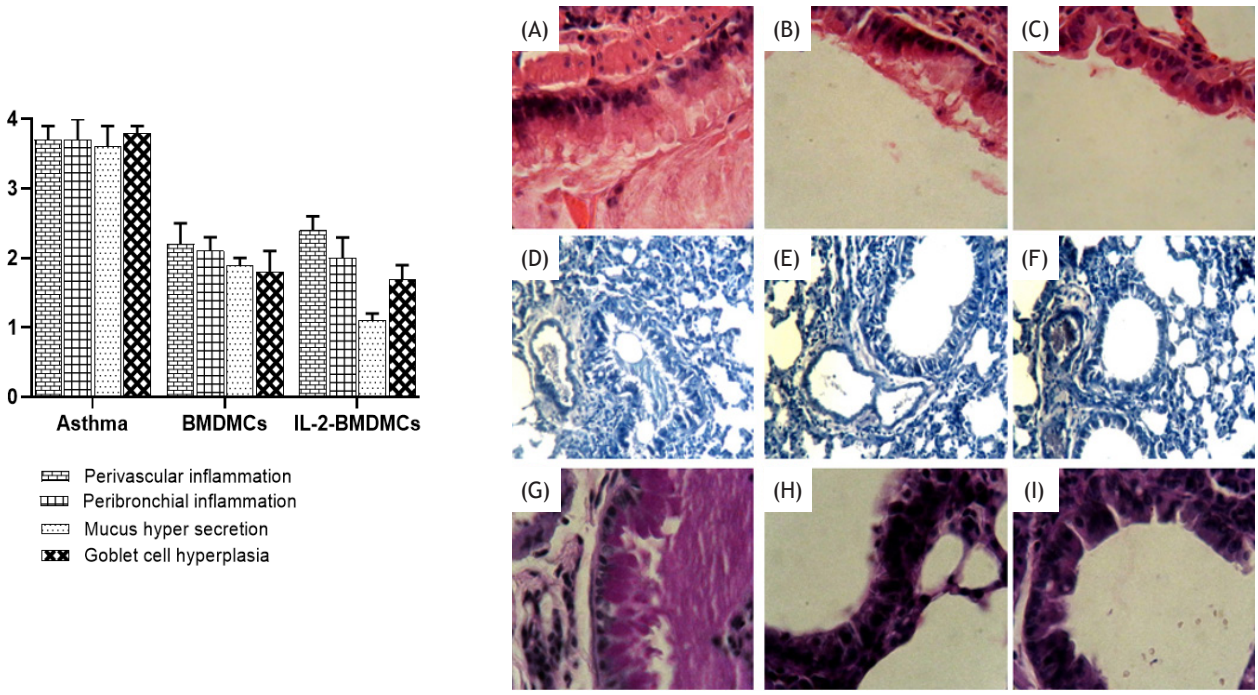

Figure 3. Lungs histopathology. Lung tissues were fixed and stained with H&E (sections in the first line), alcian blue (sections in the second line), and PAS (sections in the third line). Afterwards, the peri-bronchiolar, peri-vascular inflammation, goblet cell hyperplasia, and mucus secretion were evaluated (at 400× magnification in H&E and PAS section and 100× magnification in AB). Peri-bronchiolar and peri-vascular inflammation, goblet cell hyperplasia, and mucus secretion were decreased in BMDMCs (B, E, H) and IL-2-BMDMCs (C, F, I) groups compared to the asthma group (A, D, G). Mucus secretion in the IL-2-BMDMCs group was significantly decreased in comparison to the BMDMCs group ($p<0.05$).

the chemokine to promote the recruitment of Th2 cells, damage the lung epithelial cells by the secretion of an eosinophil-derived neurotoxin, cationic proteins (eosinophil peroxidase), and major basic protein.[16,18] Immunomodulation through cell administration was regarded as a novel therapeutic approach for many immune-related diseases due to their anti-inflammatory and immune-privileged potential. Additionally, cell therapy via immune cells can re-balance the immune response and suppress the pathology of airway allergic inflammation.[16,19] Therefore, modulation of immune response in allergic diseases such as asthma by cell therapy, may inhibit the Th2 cells activation and proliferation, and this therapeutic method can be used as a treatment of immune-related allergic and inflammatory response in asthma. In our study, mucus hypersecretion, goblet cell hyperplasia, eosinophilic bronchial, and vascular inflammation were controlled by treating with BMDMCs and IL-2-BMDMCs. IL-2-BMDMCs reduced mucus hypersecretion strongly compared to BMDMCs treatment and this showed that co-treatment with IL-2 could notably control mucus production and is beneficial in harnessing airway obstruction by mucus.

Besnard et al.,[20] demonstrated that activation of NLRP3 inflammasome is essential in alum-free models of allergic asthma that leads to the production of IL-1, a critical factor for the Th2 inflammatory allergic response induction. A study in 2013 presented that in the mice model of allergic asthma, BMDMC therapy through the intravenous and intratracheal resulted in similar benefits, and could decrease bronchoconstriction, eosinophil infiltration, alveolar collapse, collagen fiber content in the airway, and alveolar septa, myofibroblast hypertrophy and hyperplasia.[7] Another study in 2011 showed that BMDMC therapy in the mice model of allergic asthma could decrease airway and lung parenchyma remodeling.[8] BMDMCs, as a heterogeneous mix of progenitor and immune cells, were administered easily and safely and express several genes involved in inflammatory response and chemotaxis.[7] In asthma, the determination of which specific cell types were responsible for these features will require future experiments. This would translate in clinical practice into the delivery of immune cells that can be performed in asthmatic patients.

BMDMCs have an ability to modulate the synthesis of cytokines and growth factors without being present at the injury site and may potentiate airway epithelial cell repair. These cells could control IL-4, IL-13 and also TGF-β and vascular endothelial growth factor (VEGF) levels. On the other hand, BMDMCs are smaller compared to other cell types; and can pass easily through the pulmonary capillaries and remain in the lung tissue.[7,21] Identifying the presence of these cells in lung parenchyma showed that the cells were not attracted in healthy lungs but were attracted to damaged tissue and retained in damaged tissue.[7,22] IL-4, IL-5, and IL-13 as main allergo-inflammatory cytokines (type 2 cytokines) in allergic asthma were reduced by BMDMCs and IL-2-BMDMCs treatment. IL-2-BMDMCs could strongly reduce IL-13 level compared to

BMDMCs treatment. This result showed that co-treatment with IL-2 could notably control IL-13 and in continuous, IL-2-BMDMCs by reducing IL-13, can control mucus hypersecretion. Hence, it can harness airway obstruction by mucus. On the other hand, TGF-β and HP, as main remodeling factors, were decreased by treating with BMDMCs and IL-2-BMDMCs. IL-2-BMDMCs could strongly control TGF-β and HP compared to BMDMCs treatment. This result showed that co-treatment of BMDMCs with IL-2 could significantly prevent remodeling and as a result, it can prevent lung fibrosis for a long time.

IL-2 as a type I cytokine is produced by Th cells and by other immune system cells. Upon activation of the T cell receptor and CD28 (as a co-stimulatory molecule), multiple key transcription factors including activator protein(AP)-1, nuclear factor(NF)-κB, nuclear factor of activated T cells (NFAT), and constitutive factor Oct-1 are activated to regulate the IL-2 production. Following the activation of the receptor by IL-2, downstream signaling is initiated from Janus kinase (JAK)1 and/or JAK3 that phosphorylate signal transducer and activator of transcription (STAT)5 and subsequently regulate other targeted genes.[9,14,23] IL-2 plays dual roles in immune modulation, sustaining Treg for immune tolerance and supporting cytotoxic T and natural killer (NK) cells for immune activation. This evidence makes it plausible to design IL-2-based immunotherapies for autoimmunity and inflammatory diseases. Low-dose IL-2 therapy selectively promotes immunotolerance to treat inflammation and autoimmunity that predominantly activates Treg, unlike high-dose IL-2 induces strong toxicity in many cancer patients.[9,24-26] IL-2 induces interferon (IFN)-γ production and augments the expression of IL-12 receptor during Th1 differentiation. Additionally, IL-2-enhanced mTORC1 signaling can positively influence the differentiation of Th1.[9] Low-dose IL-2 therapy could efficiently promote Treg for immunosuppression. Treg expresses a high level of CD25, the high-affinity IL-2 receptor subunit, which makes it highly responsive to IL-2.[27-29] In this study, BMDMCs and IL-2-BMDMCs therapy could decrease LTB4 and LTC4 levels as important inflammatory factors and by controlling these factors, could harness inflammation in lungs around bronchi and vessels. There is no significant difference between BMDMCs and IL-2-BMDMCs groups in levels of LTB4 and LTC4 and this showed that co-treatment with IL-2 had no significant effect on the control of inflammation by LTB4 and LTC4. It was observed in this study that cell therapy via BMDMCs could control allergo-inflammatory factors of allergic asthma. Also, remodeling factors in lungs and the most of the factors were controlled strongly when cell therapy via BMDMCs was applied with co-treatment with IL-2. Therefore, cell therapy with BMDMCs had a strong and notable effect on the control of allergic asthma pathophysiology when co-cultured and used with IL-2.

In this study, we had some limitations: (1) effect of BMDMCs therapy in different times on the allergic factors and remodeling process were not studied; (2) we could not evaluate changes in gene expression via this treatment; (3) we were unable to compare effect of BMDMCs with other types of cells; (4) it is proposed that collagen deposition and other more remodeling factors will be measured in future studies.

Ethics Approval and Consent to Participate

Methods, protocols, and animal study were approved by the ethics committee of the animal house of ix.med.vet. dep, 2022 (No. IX.MED.VET.DEP.REC.2022.4600019.7).

Availability of Data and Materials

Data are available upon request from the corresponding author.

Conflicts of Interest

There are no conflicts of interest.

Authors' Contributions

JY, FY, RZ, XW, SSA contributed to laboratory examination, data analysis, writing, and scientific revision of the manuscript. All the authors viewed and confirmed the final manuscript before submission.

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