



Study on MSCs transplantation in respiratory diseases

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ABSTRACT

Respiratory diseases threat to human life safety seriously, at present there is no good treatment for a number of diseases such as acute lung injury, pulmonary hypertension. Cell replacement and gene therapy is the development trend of the future. Bone marrow mesenchymal stem cells as a widely used stem cells have unlimited potential applications in acute lung injury, pulmonary hypertension and asthma therapy. In this paper, a brief overview on the latest progress of stem cell therapy for these diseases.

Keywords: Bone marrow mesenchymal stem cells, acute lung injury, pulmonary hypertension, asthma

INTRODUCTION

Respiratory diseases such as acute lung injury, pulmonary hypertension, asthma are threatening human health, although some ways improved the survival of the state, but to find a better way is urgent. Cell replacement and gene therapy came into being, as the stem cells can differentiate into lung epithelial cells, as a target or source for organ regeneration and repair of gene therapy, alternative lesions of the lung tissue, reduce lung fibrosis, and then gradually repair diseased lungs organization, mitigation and suppression pathological processes, improve lung function. This ideal treatment strategy has gradually shown great prospects for development and therapeutic potential. Currently, stem cells for respiratory diseases are mainly derived from bone marrow stem cells.

WHAT IS MSC

There are three kinds of stem cells in the bone marrow, including hematopoietic stem cells (haematopoietic stem cells, HSC) , bone marrow mesenchymal stem cells (mesenchymal stem cell, MSC) and endothelial progenitor cells (endothelial progenitor cells, EPC). MSC is a type of pluripotent stem cells of non-hematopoietic cells, with the ability to a variety of tissue cells [1]. MSC transplantation have a lot of advantages as well as can be easily obtained, no immune rejection and no ethical restrictions; MSC is easy to amplify in vitro quickly, can meet the needs of cells for treatment in short time; also can secrete a variety of cytokines and promote cell repair; Meanwhile, MSC is a good carrier for exogenous gene transfection and expression. Therefore, MSC transplantation is used for treating various diseases.

MSC and ALI

ALI (acute lung injury, ALI) is due to pulmonary or extrapulmonary injury factors directly or indirectly damage the alveolar epithelium and pulmonary vascular endothelial cells, resulting in pulmonary capillary permeability, a large infiltration of neutrophils, causing inflammation uncontrolled inflammatory mediator release injury. The most severe manifestations display acute respiratory distress syndrome (acute respiratory distress syndrome, ARDS). In the cause of death of ALI/ARDS, it is difficult to control pulmonary fibrosis, about 40% to 70%. Studies showed that fibrous tissue hyperplasia appeared at the early lesions of ALI/ARDS [2]. As the high mortality of ALI / ARDS, it has been a thorny issue of respiratory diseases. Although a great progress on the pathogenesis ALI/ARDS, how to improve symptoms, how to control mortality, etc, but there is no good way in the effective treatment of lung injury after injury and anti-fiber .So to find newer and more effective treatment is on going.

During the culture of a cell subsets of MSC-multipotent adult progenitor cells (multipotent adult progenitor cell, MAPC) [3], they found that vascular endothelial growth factor MAPC can differentiated to CD34⁺-VE-cadherin⁺-Flkl⁺ EPC, and then differentiate into EC. This EPC has the function of mature endothelial cell, can be formed vascular structures on the artificial basement membrane. MAPC should differentiate into EPC and then EPC, this discovery provides a reliable basis for of MSC to endothelial cells. So, MSC is also involved in the repair of lung injury due to its differentiate into alveolar epithelial cells.

A study demonstrated that murine MSCs home to lung in response to injury, adopt an epithelium-like phenotype, and reduce inflammation and collagen deposition in lung tissue of mice challenged with bleomycin [4]. Herzog et al [5] took bone marrow transplant on radiation-induced lung injury mice, found bone marrow cells participated in tissue repair at the damage of local, and can differentiated into lung epithelial cells directly, but also the degree repair of lung injury and bone marrow stem cells were in a dose-dependent manner. Kotton et al [6] gave bleomycin-induced lung injury rats lacZ-labeled bone marrow cells intravenously, and found that these bone marrow cells were arranged along the alveolar surface, the position of its shape and AECl, matching the size and direction of the expression of specific AECl morphological characteristics and molecular phenotype. In vitro experiments showed that under different conditions, MSC can differentiated to the EC [3], alveolar epithelial cells [7]. More studies in vivo have demonstrated that MSC cells transplanted in lung injury mice can differentiate into epithelial cells; significantly reduced tumor necrosis factor α , transforming growth factor β 1 and interleukin-6 levels, reducing inflammatory cytokines, inhibiting inflammation reaction, reducing collagen deposition, pulmonary fibrosis and growth factors to stimulate the growth of repair; inhibiting apoptosis of alveolar wall cells, causing Cdm33 or Cyb expression associated with apoptosis [4,8-10]. As granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor have the ability to promote endogenous stem cell mobilization and lung damage as a signal in the circulation to stimulate the bone marrow to release more MSCs, so the MSC transplantation may improve granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor levels in the circulation [9].

MSC AND PAH

Pulmonary hypertension (pulmonary arterial hypertension, PAH) is a serious life-threatening disease, its cause is unknown, the pathological changes manifested in pulmonary artery intimal thickening, vascular remodeling, leading to severe shortage oxygen and pulmonary vascular resistance continues to rise, often die caused by refractory right heart failure [11]. For the clinical treatment of the disease currently, vasodilators were used mainly, but invalid for advanced diseases.

Studies have reported that PAH rats treated of rats using by MSCs, pulmonary arterial pressure reduced as an average of more than 30%, the maximum decrease of 50%. Survival was significantly improved, right ventricular hypertrophy index fell. Quantitative analysis of the structure of small pulmonary arteries showed that after treatment of MSCs vascular lesions significantly reduced or completely improved. After MSCs treatment, pulmonary vascular remodeling appeared to be reversed, pulmonary blood gas exchange improved and lung ultrastructure and right ventricular hypertrophy virtuous cycle of improved [12].

In our precious research found that glyceraldehyde-3-phosphate dehydrogenase plays a critical role in determining the superior functions of female bone marrow-derived mesenchymal stem cells in cell therapy against pulmonary arterial hypertension by regulating [Ca(2+)]_i signal-associated cellular behaviors [13].

MSC AND ASTHMA

Bronchial asthma is a chronic inflammatory airway disease, as glucocorticoid treatment the first choice, but a large number of long-term inhaled corticosteroids can cause serious side effects, and poor treatment of steroid-resistant asthma. Recent studies showed that, asthma is closely related to CD4⁺ CD25⁺ regulatory T cells allergic inflammation and own immune tolerance [14].

Mesenchymal stem cells have a pluripotent ability [15], but also have immunomodulatory effects in specific conditions [16,17]. Mesenchymal stem cells can increase CD4⁺ CD25⁺ regulatory T cells [18], inhibit mixed lymphocyte reaction or the proliferation of T lymphocytes stimulated by nitrogen PHA [19, 20]. Mesenchymal stem cells can inhibit the differentiation of dendritic cells to mature dendritic cells, interfere endocytic function, reduce the secretion of interleukin-12, making allogeneic T lymphocyte proliferation reduced [21]. Mesenchymal stem cells do not express major histocompatibility complex MHC-II molecules, Fas ligand and T cell costimulatory molecules B7-1, B7-2, CD40, CD40L, so cannot be identified host immune cells easily, and can evade the immune system immune rejection [22-24]. Asthma is also a kind of immune disorders related diseases, studies showed marrow mesenchymal stem cells transplanted at that early induction of asthma, CD4⁺ CD25⁺ regulatory T cell ratio in peripheral blood increased, the number of inflammatory cells in bronchoalveolar lavage fluid reduced, reducing

small bronchial asthma in mice, peripheral vascular mucosa and lung tissue inflammatory cell infiltration of airway inflammation in asthmatic mice significantly inhibited. Experiments confirmed that allogenic bone marrow mesenchymal stem cells transplanted in asthmatic mice can increase their peripheral CD4⁺ CD25⁺ regulatory cell ratio T, showed CD4⁺ CD25⁺ regulatory T cells increased by marrow mesenchymal stem cells may be one of the mechanisms. In addition, marrow mesenchymal stem cells suppressed airway inflammation in asthmatic mice by inhibiting the proliferation of T lymphocytes and antigen presentation [25]. Another study showed that exogenous MSC implantation in bronchial asthma mice induced by chicken ovalbumin, significantly reduced airway inflammation in asthmatic lung tissue through inhibition of Th2 allergic reactions [26].

CONCLUSION

Respiratory diseases threat to human health directly, to find more effective treatments is in quite imminent. With the clinical application of molecular genetic techniques, Stem cell transplantation will be an important treatment for respiratory diseases and other diseases in future.

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