Mesenchymal stem cells are being used in multiple diseases —Treatment prospects in COPD

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Mesenchymal stem cells (MSCs) are adult stem cells with low immunogenicity and strong immune regulation ability. In addition to commonly obtained from bone marrow, umbilical cord, cord blood, and placenta, it can also be extracted from a large number of other tissues. Under different induction conditions, MSCs can differentiate into a variety of tissue cells, and have hematopoietic support, immune regulation, tissue repair and other functions. In addition, MSCs also have immunomodulatory, anti-inflammatory and tissue repair effects, which can reduce graft-versus-host disease and other transplant-related complications.

Based on the unique immunomodulatory properties, MSCs have broad clinical application prospects. Especially for the treatment of inflammatory diseases, the treatment of multiple system diseases has been involved. Regarding the treatment of COVID-19, a number of clinical trials are also underway.

The immunomodulatory effect of MSCs depends on immunomodulatory mediators. Under the stimulation of pro-inflammatory factors, MSCs secrete immune-modulatory mediators to inhibit the activity and proliferation of T cells. For example, transforming growth factor β (TGF-β), interleukin-6 (IL-6), prostaglandin E2 (PGE2) and exosomes can inhibit the pro-inflammatory immune cell proliferation and immune function, and promote the increase of anti-inflammatory immune cells [1].

More than 65 million people worldwide are diagnosed with chronic obstructive pulmonary disease (COPD), an incurable lung disease that causes 3 million deaths each year. Statistics from the World Health Organization found that COPD will become the third leading cause of death in 2020. There are currently no approved therapeutic interventions to address the irreversible loss of lung function and incompletely reversible expiratory airflow limitation associated with COPD.

Changes in the function of lung infiltrating immune cells, oxidative stress, and imbalance in the activity of proteases and their inhibitors are the main causes of pathological changes in COPD patients [2]. Because MSCs have the ability to suppress harmful immune responses, maintain oxidative balance, and regulate the activity of matrix degrading enzymes, MSCs are considered as a potential method for COPD cell-based therapy.

The current MSCs therapy for COPD found that umbilical cord-derived mesenchymal stem cells (UC-MSCs) showed stronger immune regulation ability than bone marrow mesenchymal stem cells (BM-MSCs) in vitro [3]. MSCs transplantation can significantly reduce alveolar damage and the number of alveoli, and reduce the impact of emphysema. In the COPD animal model treated with MSCs, with the reduction of inflammatory cells in the alveolar septum, peribronchial and perivascular interstitial cells, lung function was statistically significantly improved [4].

Among lung infiltrating immune cells, the main cell target of MSCs in COPD animals is macrophages. MSCs secrete IL-10, TGF-β and HGF in a paracrine manner to inhibit the expression of cyclooxygenase-2 (COX-2) and the production of PGE2 in alveolar macrophages [5]. In inflammatory M1 macrophages, MSCs-mediated down-regulation of the COX2/PGE 2 pathway can occur through p38, mitogen-activated protein kinases (MAPKs) and extracellular signal-regulated kinases (ERK). Finally, the M1 macrophages are polarized towards the M2 anti-inflammatory phenotype. MSCs significantly improve the lung structure of COPD patients by reducing the production of macrophages, matrix metalloproteinases (MMP)-2, MMP-9 and MMP-12 mediate the degradation of elastin connective tissue fibers in the lung parenchyma and cause tissue remodeling [6-8].

However, there is currently no room for optimism in related clinical trials. Clinical trials based on MSCs for the treatment of COPD showed that although the serum C-reactive protein level in the COPD treatment group decreased significantly, there were no significant differences between the COPD treatment group and the untreated group in lung function tests and quality of life indicators. Although there are data indicating that the pathological degeneration process is generally slowed down, the natural history of emphysema has changed [9]. In an experimental elastase-induced emphysema model, compared with a single dose of MSCs [10], two doses of MSCs enhanced anti-inflammatory control and lung repair.

Although the prospects for the treatment of MSCs are very optimistic, clinical trials are also being carried out to record and evaluate data for a variety of diseases. However, based on the high prevalence and high mortality of COPD, MSCs therapy is relatively rare. Although a number of clinical trials have shown that the prospects are not optimistic, there has been a great improvement in the assessment of the quality of life of COPD patients. At present, what needs to be explored is not only the choice of

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treatment methods, but more importantly, targeted trials and analysis. The occurrence and development of COPD involves changes in a variety of cells and inflammatory factors, and precision medicine must be considered.

ACKNOWLEDGMENT

The authors did not receive any funding for this study.

Competing interests: The authors declare that they have no conflict of interest.

Citation: Ma YM, Ma MZ. Mesenchymal stem cells are being used in multiple diseases—Treatment prospects in COPD. Microenvironment & Microecology Research. 2021;3(3):13. doi: 10.53388/MMR20210922001.

Executive editor: Jin-Feng Liu.

Submitted: 22 September 2021, **Accepted:** 24 September 2021, **Online:** 24 September 2021

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