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Editorial

Advances in mesenchymal stem cell-mediated tissue repair of lung injury

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The repair of lung injury has always been a fundamental problem in the treatment of acute and chronic lung diseases, and more effective treatment approaches have been sought. Regenerative medicine, which gradually repairs impaired tissue and improves lung function, has been increasingly applied in the field of acute and chronic respiratory diseases.

Mesenchymal stem cells (MSCs) were initially discovered in the bone marrow and subsequently isolated from the umbilical cord, placenta, and amniotic fluid.[1] MSCs exhibit an adherent growth pattern and could differentiate into chondrocytes, osteocytes, and adipocytes upon induction under different culture conditions.[2] MSCs have been shown to migrate and home to the site of inflammatory injury after tracheal instillation or tail vein injection and then play an anti-inflammatory role and reduce tissue damage.[3] Many studies have been conducted on MSC-based treatment of acute lung injury (ALI). It was found that MSCs can reduce inflammatory reactions and improve pulmonary edema and capillary permeability, thus demonstrating a definite therapeutic effect in lung injury.[4] MSCs are characterized by paracrine immune regulation and multi-directional differentiation, which are considered promising assets for the development of treatment strategies in the field of lung injury repair.[5]

Homing and multidirectional differentiation

MSCs, a type of pluripotent stem cells, can differentiate into type I alveolar epithelial cells, type II alveolar epithelial cells, endothelial cells, fibroblasts, and other cells after transplantation into lungs.[6] Studies have shown that MSCs can migrate to an injured tissue, exhibit homing and differentiation, and play a protective role in lung injury.[7] It has been shown that MSCs can differentiate into alveolar epithelial cells under different induction conditions *in vitro*.[8] The injury-associated chemotactic factors generated by inflammation in chronic obstructive pulmonary disease (COPD) can stimulate and induce mesenchymal cells to migrate to the site of lung injury; differentiate into alveolar epithelial cells, lung mesenchymal cells, airway epithelial cells, and other structural cells; and participate in the repair of lung tissue injury.[9] In a rat model of ALI MSCs were injected into the tail vein. Further investigations revealed that a large number of MSCs were found in the area of lung injury, and the

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degree of MSC aggregation was correlated with the degree of lung injury after 24 h of injection.[3] In addition, the process of MSC differentiation into alveolar epithelial cells is related to the Wnt signaling pathway. Overexpression of β-catenin in MSCs induces activation of the Wnt signaling pathway and promotes the recovery of injured epithelial cells to achieve effective treatment and repair of ALI.[10] Herzog et al[11] had performed bone marrow stem cell transplantations in mice with radiation lung injury and found that the bone marrow-derived stem cells were involved in tissue repair in the injured area. In addition, they found that these cells could differentiate into lung epithelial cells. More significantly, a dose-dependent relationship was observed between the degree of repair of lung injury and stem cells. In animal models of pulmonary fibrosis induced by bleomycin, MSC injection through the tail vein could alleviate or even partially reverse the pathological state of pulmonary fibrosis. In a rat model of pulmonary hypertension successfully induced by monocyrine, MSCs were injected through the caudal vein, and they were found to colonize the lung interstitium and establish collateral circulation through the formation of new blood vessels. As a result, the injection of MSCs could effectively reduce the degree of pulmonary hypertension and pulmonary tissue lesions.[12]

Anti-inflammatory function

MSCs serve a very important anti-inflammatory function by secreting IL-10, IFN-γ, hepatocyte growth factor (HGF), and other anti-inflammatory factors to promote the repair of lung injury.[13] In an ALI model, MSCs reduced the expression of tumor necrosis factor alpha (TNF-α) in lung tissue, reduced inflammatory reactions, inhibited pulmonary edema, improved inflammation, and promoted lung tissue repair.[14] In a mouse model of bleomycin-induced ALI MSCs were found to secrete and produce an IL-1 receptor antagonist, which has been proven to inhibit TNF-α *in vivo* and *in vitro*.[15]

Immunoregulation

MSCs can also affect the immune response in animal models of lung injury through paracrine signaling.[16] A study involving injection of fluorescently labeled MSCs into mice revealed that the labeled signal gradually disappeared from mice after 24 h, indicating that the survival time of MSCs *in vivo* is quite limited.[17] However, some studies have also shown that the immunomodulatory function of MSCs in animal models can last for several days. On one hand, the immunomodulatory function of MSCs may be related to the synergistic effects of other cells, whereas on the other hand, the immunomodulatory function of MSCs is exerted by the bioactive substances released by MSCs, which may be the key reason why MSCs affect the immune system. MSCs can also reduce the aggregation level of reactive oxygen species and hypoxia inducible factor-1α in tissues and reduce damage.[18] MSCs also maintain a certain level of HGF in lung tissue in a paracrine manner and induce lung injury and repair and maintain lung permeability. In addition, MSCs can reduce the release of pro-inflammatory factors, improve the anti-inflammatory effect, and reduce inflammatory injury. MSCs can be activated by lipopolysaccharide (LPS) or TNF-α to produce prostaglandin E2 (PGE-2), which causes the alveolar macrophage reprogramming to produce IL-10, thereby inhibiting the expression of MHC class II antigens, helper T cell proteins, and macrophage-related co-stimulatory molecules.[19] However, under certain conditions, MSCs can also promote the immune response of memory T cells. At low levels of inflammation, MSCs induce the expression of MHC II and thus exhibit an antigen-presenting role. MSCs attenuate LPS-induced ALI by upregulating the balance between Tregs and Th17 cells.[20] In addition, the expression of IFN-α in the microenvironment may also be key to the bidirectional immune regulation of MSCs.[21] Thus, MSCs participate in the regulation of the balance between pro-inflammatory and anti-inflammatory factors in ALI and induce a moderate immune response during the process of infection, consequently avoiding tissue damage induced by overreaction.[22,23] MSCs play an important role in the treatment of pulmonary fibrosis via paracrine cytokines.[9] It has been shown that in patients with pulmonary fibrosis, B cells aggregate with T cells in the lungs and persistently activate T cells, creating a self-sustaining inflammatory state. By regulating B cells, MSCs can break this vicious cycle and slow the progression of pulmonary inflammation.[24]

MSC-derived exosomes

Exosomes are extracellular lipid vesicles that contain special miRNAs, proteins, lipids, and other active substances and are the basis of cell–cell communication.[23] Studies have shown that the improvement in ALI by MSC- derived exosomes is related to keratinocyte growth factor.[25] MSCs pretreated with IL-1β demonstrated higher survival rate along with better remission effect in ALI caused by

sepsis in mice than in the control group of mice. Furthermore, it was found that miR-146a upregulated upon IL-1β stimulation of MSCs was transferred to the macrophages via exosomes. This phenomenon ultimately polarizes the macrophages to M2 phenotype, which reduces the degree of pulmonary edema and inflammatory cell infiltration. In addition, the transfection of MSCs with a miR-146a inhibitor could partially serve the role of IL-1β-pretreated MSC-derived exosomes.[26] However, the immunomodulatory effects of IL-1β-induced miR-146a were partially suppressed upon the inhibitor transfection. The results showed that MSC-derived exosomes reduce the expression of inflammatory factors such as IL-10, IL-6, and IL-1β in rats, and this effect was mainly attributed to the reduced exosome-associated phosphorylation of mitogen-activated protein kinase.[27] Further, a previous study from our group has revealed that MSC-derived exosomes transfer miR-23a-3p, and miR-182-5p reverses the progression of LPS-induced lung injury by inhibiting NF-κB and Hedgehog pathways.[28]

The mechanism underlying MSC-based invigorated treatment of acute and chronic respiratory diseases is not well defined. In addition, the therapeutic effect of MSCs differs depending on the degree, time, and treatment factors associated with lung injury. Advances in the field have led the research on stem cell therapy for lung injury in clinical trials. However, vigilance is required with regards to the safety of employing stem cells in disease treatment. At present, the long-term adverse effects of MSCs are unknown. Hence, the interaction between stem cells and lung injury requires extensive basic and clinical investigation.

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