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Mesenchymal stromal/stem cells: breaking the deadlock in the treatment of multiple organ dysfunction syndrome

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Multiple organ dysfunction syndrome (MODS) is a clinical syndrome characterized by the dysfunction of two or more systems or organs. This internal environment disorder occurs simultaneously 24 h after severe trauma, shock, or infection. MODS has a high fatality rate ranging from 20% to 100%.[1] In the development of MODS following severe trauma or infection, multiple organ system fail sequentially, involving the lungs, kidneys, liver, cardiovascular, central nervous system, gastrointestinal, immune, and the blood coagulation system. MODS has complex pathogenic factors, and there are four main pathogenesis hypotheses: (1) uncontrolled inflammation hypothesis, (2) ischemia–reperfusion injury, (3) the gastrointestinal hypothesis, and (4) the biphasic pre-excitation theory. Although the current clinical treatment methods of MODS, such as inflammatory factor antibodies, highly effective anti-coagulants, renal function replacement therapy, and other treatment methods, have been improved continuously, their effectiveness in MODS treatment is not ideal. Therefore, clinical MODS treatment is faced with great challenges [Figure 1].

Every organ in the body is made up of stem cell-derived cells. Theoretically, the stem cells and their derivatives can repair any tissue in the body that has been lost or damaged by disease or injury.[2] Mesenchymal stromal/stem cells (MSCs) have the potential for self-renewal and multi-lineage differentiation. They are favored for their strong paracrine ability, two-way immune regulatory ability, and tissue repair potential.[3] In MODS, the protective effect of beneficial local inflammation is transformed into harmful systemic inflammatory damage, and studies have shown that MSC has positive effects on the immune system, coagulation, and other systems. MSC therapy is thought to be an ideal remedy for such multifactorial complex systemic inflammatory disease.[4] Furthermore, MSCs and their derivatives have been shown to be effective in treating organ injury and dysfunction caused by trauma, infection, and other causes. Therefore, we reviewed the efficacy and mechanism of MSCs and their derivatives in treating different organ dysfunction to investigate MSCs' prospects in treating MODS.

MSCs and their derivatives therapy can secrete immunomodulatory factors, growth factors, and chemokines, promoting stem cell colonization in damaged tissue and tissue repair and inhibiting the body's inflammatory response. As a subtype of $CD4^+$ T cells, helper T cell 17 (Th17)/regulatory T cell (Treg) can regulate pulmonary inflammation and alleviate lung injury by regulating the imbalance of Th17/Treg in the lungs of acute respiratory distress syndrome mice after transforming growth factor β-1 overexpression in MSCs.[5] The expression of pro-inflammatory cytokines in knee synovial fluid decreased after treatment with bone marrow (BM)-derived MSCs-exosomes (MSC-Exos) in a rat osteoarthritis model, while the release of anti-inflammatory cytokines increased, inflammatory M1 macrophage production decreased, and anti-inflammatory M2 macrophage production increased; cartilage injury was alleviated, and osteophyte formation and synovial macrophage infiltration decreased, thereby relieving osteoarthritis.[6]

Lung tissue injury is repaired by MSCs through different mechanisms, and respiratory function is improved. Researchers discovered that the expression of miR-193b-5p target gene tight junction protein antibody

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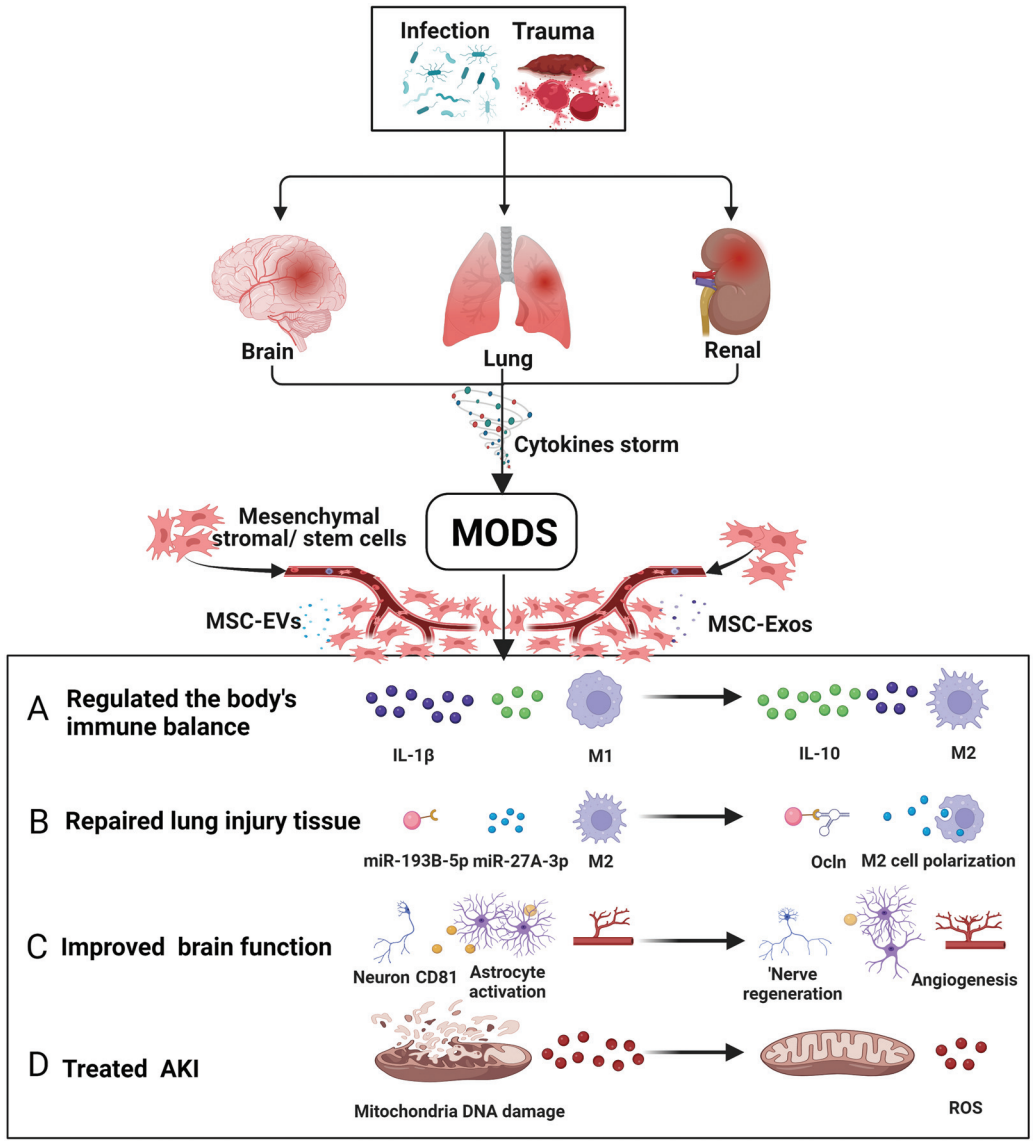

Figure 1: MSCs therapy for MODS. After the organ is severely hitted by trauma and infection, it produces cytokine storm, and then develops into MODS. MSCs therapy regulates immune balance and repairs organ damage through paracrine. The picture is drawn by BioRender software (https://app.biorender.com). AKI: Acute kidney injury; CD81: Cluster of differentiation 81; DNA: Deoxyribonucleic acid; M1: M1 macrophage; M2: M2 macrophage; miR: Micro ribonucleic acid; MODS: Multiple organ dysfunction syndrome. MSC: Mesencymal stromal/stem cells; MSC-Exos:Mesencymal stromal/stem cells exocrine; MSC-EVs: Mesencymal stromal/stem cells extracellular vesicles; IL-1β: Interlukin 1β; IL-10: Interlukin 10; ROS: Reactive oxygen species.

(Ocln) increased in lung tissue after treatment of a septic mouse model with MSC.[7] The MSC-Exos-mediated miR-23a-3p and miR-182-5p can prevent lipopolysaccharide-induced lung injury in mice by silencing *Ikbkb* and *IKK β* and inhibiting nuclear factor kappa-B and hedgehog pathways.[8] miR-27A-3p is an important regulator of M2 macrophage polarization. MSCs and MSCs-extracellular vesicles (MSC-EVs) can transfer miR-27A-3p to alveolar macrophages, increasing the miR-27A-3p level in alveolar macrophages, promoting M2 cell polarization, and reducing acute lung injury (ALI).[9]

Most current research on improving MSCs function in the brain is focused on the neural circuit repair, neural plasticity, and astrocyte correlation. MSC-Exos can significantly improve sensorimotor and cognitive impairment, reduce hippocampal nerve cell loss, promote angiogenesis and nerve regeneration, and reduce neuroinflammation.[10] In the scratch injury model of human astrocytes (T98G cells), human adipose mesenchymal stem cells (CM-hMSCA) were found to regulate the expression of different proteins in AKT/pAKT and ERK1/2/pERK signal pathways, mediate the cellular localization of Ngb, decrease cytosolic calcium concentration, regulate mitochondrial dynamics and the respiratory chain, and decrease expression of astrocyte activation regulator cluster of differentiation 81 (CD81).[11]

MSCs and their derivatives may become an important treatment option for acute kidney injury (AKI). MSCs have been shown to regulate heat shock proteins 20 and phosphatidylinositol-3-kinase/Akt signal pathway in the treatment of AKI.[12] MSC-EVs act on the mitochondrial transcription factor A (TFAM) pathway in a mouse AKI

model, restoring the stability of TFAM protein and the TFAM-mtDNA complex in damaged renal tubular cells, reversing mitochondrial DNA deletion and mitochondrial oxidative phosphorylation (OXPHOS) deficiency, and reducing mitochondrial DNA damage and inflammation.[13] BM-derived MSC-EVs can increase microRNA-200a-3p expression in proximal renal tubular epithelial cells of mice with renal ischemia–reperfusion injury and activate Keap1-Nrf2 signal pathway, stimulate mitochondrial antioxidant defense and adenosine triphosphate production, reduce oxidative damage of proximal renal tubular epithelial cells, and achieve a therapeutic effect on AKI.[14]

The *in vivo* evolution of stem cells and the safety of stem cell therapy remain the focus of research. Although researchers have discovered that coagulopathy, thromboprophylaxis, and mode of delivery play an important role in the safety and efficacy of treatment,[15] the safety of MSCs transplantation under certain conditions remains unknown. Some researchers have investigated various cell therapy delivery platforms and biomaterials to increase survival rate and time, and improve treatment efficiency. Simultaneously, researchers also focused on its large-scale and standardized production. Overall, MSC and their derivatives' high proliferation characteristics, treatment timing, and cell microenvironment conditions need to be explored further [Figure 1].

This study focuses primarily on the stem cell mechanism in treating trauma and inflammation-induced MODS. MSCs and their derivatives are a good option for reducing MODS morbidity and mortality. Therefore, incorporating stem cell therapy into existing clinical treatment methods may become an effective breakthrough in reducing MODS mortality.

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Conflicts of interest

None.

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