Am J Stem Cells 2025;14(2):53-72
www.AJSC.us /ISSN:2160-4150/AJSC0164690

Review Article

Mesenchymal stem cells in injury repair of vital organs: from mechanism to clinical application

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Received March 21, 2025; Accepted May 31, 2025; Epub June 15, 2025; Published June 30, 2025

Abstract: Mesenchymal stem cells (MSCs) are a type of pluripotent stem cells originating from the mesoderm, known for their capability to differentiate into various specific tissue cell types and fulfill corresponding physiological roles. Furthermore, MSCs are essential in modulating the tissue microenvironment through the release of soluble factors that can modify the local inflammatory conditions of injured tissues. As a result, MSCs show considerable promise for therapeutic use in a range of traumatic scenarios, including but not limited to liver damage, myocardial infarction, neurological conditions, lung trauma, kidney injuries, and disorders affecting the female reproductive system. They play a key role in alleviating cell apoptosis, sustaining cell survival, encouraging proliferation, enhancing the inflammatory milieu, minimizing tissue fibrosis, and supporting vascular regeneration. These mechanisms are crucial for controlling excessive and persistent inflammatory reactions that arise after organ injury, which may lead to cell death and hindered blood circulation, ultimately causing fibrosis and weakened organ functionality. Additionally, MSCs are gradually being incorporated into clinical settings, where careful considerations regarding methods of administration, dosing, safety, and effectiveness are vital for achieving optimal clinical results. This review provides an overview of the mechanisms by which mesenchymal stem cells aid in the repair of major bodily organs. We also examine their current status, obstacles, and pertinent issues concerning clinical applications.

Keywords: Cell therapy, mesenchymal stem cells, injury repair, immunomodulation

Introduction

The restoration of crucial organs after damage constitutes a fundamental pathological process observed in numerous diseases, Cellular injury represents the initial event leading to organ damage, characterized by phenomena such as cell swelling, membrane rupture [1], and mitochondrial dysfunction. These alterations subsequently trigger various forms of cell death, including necrosis, apoptosis, and autophagy. To facilitate the clearance of damaged tissues and cellular debris, the inflammatory response is typically activated within hours to days post-injury. Neutrophils play a crucial role in removing foreign materials through phagocytosis, while macrophages regulate the inflammatory response by secreting cytokines. After inflammation subsides, tissues begin the repair phase, which involves cell regeneration and increased cell proliferation, in addition to the activation and specialization of stem cells. In this phase, fibroblasts multiply and produce collagen; nonetheless, an overabundance of collagen can lead to fibrosis, ultimately resulting in scar tissue formation. Angiogenesis is essential for tissue repair, especially in cases of blood vessel rupture and ischemia, where endothelial cell migration and proliferation contribute to the establishment of new vascular networks, with vascular endothelial growth factor being a crucial factor in this mechanism [2-4].

However, it is met with several obstacles. The ability of cells to regenerate at injury sites is restricted, and the inflammatory responses that arise post-injury can hinder the repair process, possibly leading to fibrosis. Furthermore, even if damage is addressed, full recovery of organ function might not occur. Present pharmacological interventions mainly concentrate on symptom management and slowing the pro-

https://doi.org/10.62347/YGXA7976

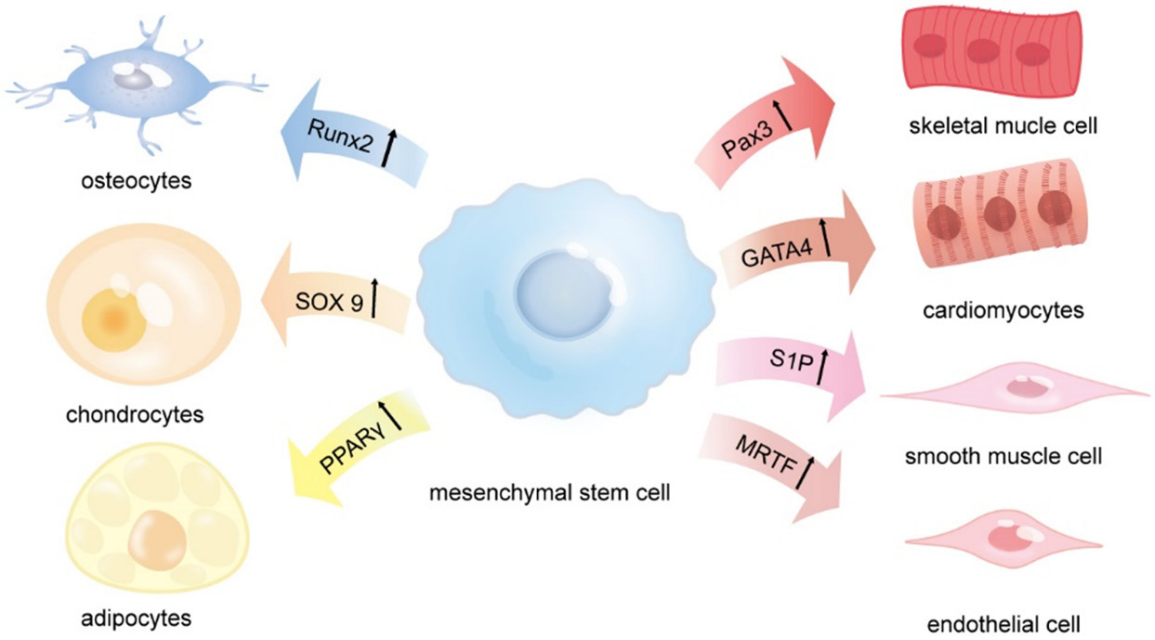

Figure 1. Transcription factors regulation in mscs differentiation. The differentiation capabilities of MSCs are diverse, allowing them to develop into various cell types, including osteocytes, chondrocytes, adipocytes, skeletal muscle cells, cardiomyocytes, smooth muscle cells, and endothelial cells. Key transcription factors involved in these differentiation processes include Runx2, Sox9, PPARγ, Pax3, GATA4, S1P, and MRTF, each playing distinct roles in the regulation of lineage commitment.

gression of the disease, which complicates the complete recovery of injured tissues. In instances of severe trauma, surgical intervention or organ transplantation often represent the sole viable solutions; notwithstanding, issues such as a shortage of donors and the possibility of immune rejection limit their broader use. In recent developments, mesenchymal stem cells (MSCs) have shown considerable promise in repairing organ damage. These cells have the capability to move to injured areas, differentiate into appropriate cell types, and either replace or mend dead and damaged cells. Moreover, MSCs are characterized by low immunogenicity, enabling them to diminish abnormal immune responses and lessen the risk of immune rejection. The growth factors, anti-inflammatory cytokines, and antioxidant substances released by MSCs can facilitate tissue repair and regeneration. The ways in which MSCs and the exosomes derived from them aid in the restoration of organ damage have become a prominent area of research. This review concentrates on the roles of MSCs and their exosomes in the healing of vital organs that have been damaged. We also provide a summary of findings from ongoing clinical trials involving MSCs, alongside the challenges and issues faced in this field.

Characteristics of MSCs

MSCs originate from various sources, with significant focus on bone marrow, adipose tissue, umbilical cord, peripheral blood, dental pulp, and menstrual blood, among others. In accordance with the criteria set forth in 2006, MSCs are required to adhere to plastic under standard culture conditions, express specific surface antigens including CD105, CD73, and CD90, and not express hematopoietic markers like CD45, CD34, CD14, or CD11b, CD79a or CD19, as well as class II HLA molecules. Additionally, MSCs should demonstrate the ability to differentiate into osteoblasts, adipocytes, and chondrocytes [5].

Regulation of MSC differentiation

In the area of tissue repair following injury, mechanisms that involve MSCs demonstrate the ability to differentiate into distinct cell lineages, thus effectively remedying tissue deficiencies. Research indicates that this differentiation process is chiefly regulated by transcription factors (**Figure 1**). For example, Runx2 acts as a crucial regulator in osteogenic differentiation while concurrently inhibiting chondrogenic and adipogenic pathways [6]. Mast4

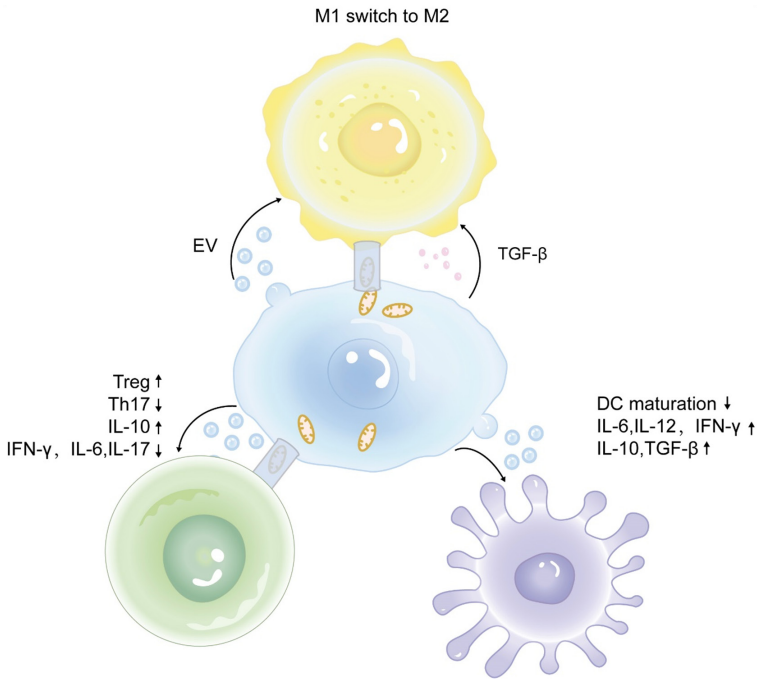

Figure 2. The immunoregulatory functions of MSCs. MSCs induce the polarization of macrophages from the M1 to the M2 phenotype through the secretion of cytokines and exosomes. MSCs can inhibit the maturation of DCs, promote the differentiation of T cells toward Tregs while inhibiting their differentiation into Th17 cells. Additionally, MSCs reduce the secretion of pro-inflammatory factors, and attenuate the increase of inflammatory mediators, thereby suppressing the overall inflammatory response. Furthermore, MSCs influence immune cells through mitochondrial transfer.

enhances the activity of β-catenin and Runx2 via WNT signaling, thereby fostering osteogenesis [7]. PPARγ plays a vital role in the adipogenic differentiation of MSCs, with its absence hindering the development of adipocytes [8]. Sox9 is essential for the chondrogenic differentiation of MSCs [9]. The regulation of myogenic differentiation involves PAX3, MyoD, myf-5, and myogenin, with Pax3 and Pax7 being the main regulators [10]. GATA4 promotes myocardial transdifferentiation by increasing the expression of IGFBP-4 [11]. Furthermore, MSCs are capable of differentiating into smooth muscle and endothelial cells, influenced by MRTF and factors associated with sphingosine-1-phosphate [12].

Immunomodulation of MSCs

Apart from their ability to undergo directed differentiation, MSCs also demonstrate considerable immunoregulatory functions through complex intercellular interactions and the release of diverse bioactive molecules (**Figure 2**). These cells engage with immune components, including macrophages, regulatory T cells (Tregs), and dendritic cells (DCs), in order to influence immune reactions. MSCs assist in transitioning macrophages from the proinflammatory M1 subtype to the anti-inflammatory M2 subtype via mechanisms involving the CD200-CD200R interaction and the release of TGF-β, which stimulates the Akt/FoxO1 signaling pathway [13, 14]. Moreover, extracellular vesicles derived from MSCs that contain microRNAs such as miR-27b-3p, miR-100-5p, miR-148a, and miR-182 enhance M2 polarization [15, 16]. MSCs also affect the function of DCs by suppressing their maturation and migration, while their exosomes diminish proinflammatory cytokine levels like IL-6 and IL-12p70, concurrently elevating TGF-β concentrations [17, 18]. Treatment with MSC-derived extracellular vesicles leads to reduced levels of IFN-γ and heightened amounts of TGF-β and IL-10 in DCs, thus shaping the T cell population by fostering Tregs and diminishing Th17 cells [19]. In addition, MSCs suppress pro-inflammatory cytokines, including IL-17 and IL-6 in CD4+ T cells, and boost IL-10 production, with their exosomes promoting Treg expression through IL-10, IL-33, and IL-34, which aids in the resolution of inflammation [20].

Mitochondrial transfer of MSCs

Moreover, MSCs play a crucial role in modulating immune responses and facilitating tissue repair via the transfer of mitochondria. When mitochondria are transferred to CD4+ T cells, they enhance the expression of activation and differentiation-related genes such as FOXP3, IL2RA, CTLA4, and TGFβ1. This process leads to an increase in the population of inhibitory CD25+FoxP3+ cells, resulting in better survival outcomes in models of graft-versus-host disease, while simultaneously diminishing the infil-

tration of CD8+ T cells and those expressing IFN-γ [21]. Significant mitochondrial transference from MSCs to macrophages is also observed, supported by the presence of nanotunneling tube-like structures. This acquisition improves the phagocytic capacity of the recipient macrophages [22]. Various research efforts have investigated the therapeutic potential of mitochondria derived from MSCs. For instance, one study demonstrated that injecting isolated mitochondria into mouse models of myocardial infarction led to a positive correlation between their localization in endothelial tissues and increased vascular density at injury sites, alongside enhancements in cardiac remodeling and the inhibition of apoptosis processes [23]. Additionally, MSC-derived exosomes (MSC-exosomes) possess the capability to guide differentiation and regulate immune responses, and they can repair damaged cells via mitochondrial transfer, indicating their promising applications in the treatment of injury repair diseases.

The mechanism of MSCs in injury repair

Due to the important function of MSCs in the repair of injuries, there has been significant interest in their potential for treating associated disorders. A multitude of scientific investigations are currently examining the specific mechanisms through which MSCs operate in various organ injuries. At the same time, numerous clinical trials are being conducted to assess the effectiveness of MSCs in promoting injury repair. This paper provides a review of the pertinent literature from the last five years, systematically outlining the mechanisms of MSCs in various organ injuries and addressing the obstacles encountered in clinical trials. We expect that these research efforts and experiments will lead to significant progress in the use of MSCs therapy for diseases related to organ damage.

Liver damage repair

MSCs are gaining recognition for their potential therapeutic applications in cases of liver damage. They play a role in liver regeneration by differentiating directly into hepatocytes, modulating inflammatory responses, and regulating immune functions. Furthermore, they block the activation of hepatic stellate cells, which leads to decreased collagen accumulation and enhances liver fibrosis. Additionally, MSCs help to avert degeneration and necrosis of hepatocytes, thereby sustaining cellular health and balance.

Maintenance of cellular vitality: MSCs possess the ability to transform into hepatocytes, thus promoting liver regeneration. In experiments using mouse models, the infusion of MSCs has demonstrated a positive effect on the proliferation and survival of hepatocytes. Exosomes from human umbilical cord mesenchymal stem cells (hUMSCs), which contain miR-124, enhance liver regeneration post-hepatectomy in rats [24]. Both MSCs and their exosomes modulate the mRNA expression levels of Ptgs2, LOXs, and OTUB1, which subsequently restore SLC7A11 expression and inhibit ferroptosis [25]. Moreover, exosomes derived from MSCs (MSC-exos) downregulate COX2 via miR-214-3p, leading to the improvement of GSH metabolism, a reduction in oxidative stress, and the inhibition of ferroptosis [26]. Additionally, miR-124-3p found in hepatocyte exosomes targets Steap3, thereby reducing ferroptosis and alleviating liver injury [27].

Modulation of the inflammatory microenvironment: The liver injury-related inflammatory response is primarily affected by the polarization of macrophages and the abnormal recruitment of neutrophils. Research has demonstrated that MSCs release various mediators such as PGE2, TNF-α, ST6, IL-6, and IDO, which aid in shifting macrophages from a pro-inflammatory phenotype to an anti-inflammatory one. This transition contributes to lower levels of pro-inflammatory cytokines and decreased infiltration of inflammatory cells in the liver [28]. In addition, miR-182-5p found in MSC-exosomes enhances M2 macrophage polarization and anti-inflammatory responses through the FOXO1/TLR4 signaling pathway [29]. Moreover, MSCs significantly mitigate the recruitment of neutrophils by downregulating CXCL2, CXCL6, and CXCR2 expressions [30]. They also facilitate the transfer of mitochondria to liver neutrophils through exosomes, which decreases the formation of neutrophil extracellular traps (NETs) in liver tissue, thus inhibiting neutrophilic inflammation and reducing the effects of liver ischemia-reperfusion injury [21]. Lastly, extracellular vesicles from human umbilical cord MSCs can prevent the onset of inflammatory responses in the liver by lowering CD154 expression in CD4+ T cells [31].

Antifibrotic effects: MSCs are crucial in liver damage repair by reducing liver fibrosis. In a mouse model experiencing liver injury caused by Schistosoma japonicum infection, treatment with exosomes from human umbilical cord mesenchymal stem cells (hUCMSC-EVs) led to a notable decrease in the levels of α-SMA, collagen type I, and collagen type III, resulting in the improvement of liver fibrosis [32]. Furthermore, human amniotic MSCs (hAMSC) secrete IGFBP3, DKK-3, and DKK-1, which inhibit the activation of hepatic stellate cells by interfering with the PI3K/Akt and canonical Wnt/β-catenin signaling pathways, aiding in the reduction of liver fibrosis [33].

Additionally, research indicates that MSCs enhance the expression of microRNA-148a-5p within hepatocytes. This microRNA targets Notch2 and influences the Notch signaling pathway, which ultimately mitigates the severity of liver fibrosis in murine models. This approach significantly lowers the expression of fibrosis markers such as α-SMA and Col1α1 [30]. Furthermore, exosomes rich in microRNA-27b-3p derived from umbilical cord MSCs have been shown to effectively downregulate LOXL2, thus delaying liver fibrosis induced by CCL4 [34]. Moreover, exosomes obtained from human adipose-derived MSCs (hADMSCs-Exo) have demonstrated an ability to diminish lipid buildup, restore impaired choline metabolism, and improve hepatocyte damage and fibrosis [35].

Heart damage repair

In common cardiac injuries like acute myocardial infarction, heart failure, and ischemic heart disease, MSCs demonstrate therapeutic capabilities by reducing pro-inflammatory immune cell infiltration in the damaged myocardium through anti-inflammatory processes. Additionally, they regulate the formation of scars and myocardial repair through anti-fibrotic effects, while fostering cardiac regeneration by mechanisms that promote angiogenesis and prevent apoptosis.

Immunomodulation: MSCs are known for their strong immunomodulatory capabilities, primarily due to the exosomes they release, which contain a diverse array of miRNAs. Specifically, miR-182 is recognized for its ability to modulate and suppress TLR4 expression in macrophages, thereby aiding the conversion from M1 to M2 macrophages through the activation of the PI3K/Akt signaling pathway, ultimately diminishing inflammatory infiltration in cardiomyocytes [36]. Furthermore, microRNA-125a-5p targets Klf13 to inhibit ERK1/2, which promotes the increased polarization of M2 macrophages [37]. In addition, employing a combined therapeutic strategy that includes MSCs alongside low-dose tacrolimus (FK506) in heart transplant patients has been demonstrated to significantly decrease the phosphorylation of TBK1 and IRF3, resulting in lower levels of IFN-γ production. This mechanism is crucial for preventing the infiltration of inflammatory cells into the graft, thereby enhancing graft survival [38].

Anti-fibrosis: Myocardial fibrosis signifies an unavoidable advancement in various clinical cardiovascular disorders, leading to severe stages marked by substantial remodeling of the heart. This pathological phenomenon is strongly linked to arrhythmias, cardiac dysfunction, and a heightened risk of sudden cardiac death. Administering atorvastatin (ATV) in conjunction with excessive MSC treatment has shown to curb the abnormal increase of pro-inflammatory cytokines, including TNF-α and IL-6, in the peri-infarct area. Such intervention not only diminishes the influx of inflammatory cells into the myocardium but also lowers the expression levels of Col1a1 and Col3a1 in cardiac fibroblasts, thereby aiding in the reduction of myocardial fibrosis and improving the cardiac repair capacity [39].

Promotion of angiogenesis: Angiogenesis plays a vital role in the repair of cardiac injuries. The miRNAs released by MSCs are essential in enhancing angiogenesis and safeguarding cardiomyocytes. Notably, miR-205 markedly elevates the expression of HIF-α and VEGF, which supports the proliferation of microvascular endothelial cells and stimulates angiogenesis, thereby helping to mitigate cardiac damage [40]. Properly modifying MSCs can enhance their therapeutic potential. For example, the increased expression of HIF-1α in MSC-derived exosomes significantly improves the tube-forming ability, migratory prowess, and proliferation of human umbilical vein endothelial cells (HUVECs). This improvement results in heightened mRNA levels of VEGF, Ang-1, and PDGF, leading to enhanced neovascularization and

decreased fibrosis within the infarcted area, ultimately aiding in the preservation of cardiac function in a rat model of myocardial infarction (MI) [41].

Maintains cell activity: The goals of repairing cardiac injury include maintaining cellular functionality, reducing apoptosis, and fostering cell growth. Research indicates that exosomal miR-129-5p sourced from MSCs can counteract apoptosis and oxidative stress in heart failure by targeting TRAF3, which in turn influences the NF-κB signaling pathway [36]. Furthermore, miR-25-3p directly suppresses PTEN and FASL, resulting in diminished cellular apoptosis, restoration of eNOS expression, reduction of inflammation, and increased survival rates of cardiomyocytes [42]. Exosomes derived from hUC-MSCs can obstruct DMT3 expression via miR-1a 23p, effectively preventing ferroptosis and mitigating myocardial injury [43]. On the other hand, MSC-exosomes with low levels of miR-153-3p markedly boost the activation of ANGPT1 and the VEGF/VEGFR2/PI3K/Akt/eNOS signaling pathways, which together lessen apoptosis in endothelial cells and cardiomyocytes, thus enhancing their survival and alleviating hypoxia-induced myocardial and microvascular damage [44].

Additionally, treatment involving adipose-derived stem cell-conditioned medium (ADSC CM) has been demonstrated to lower the expression of proteins associated with apoptosis, such as PUMA, p-p53, and BCL2, while significantly decreasing levels of ETS-1, fibronectin, and collagen type III. This approach effectively reduces cardiac cell apoptosis and fibrosis. Importantly, the release of miR-210 and miR-744 from MSCs exposed to hypoxic conditions sees a significant increase. The elevation of miR-210 correlates with reduced expression of AIFM3, p-AKT, and p-p53, thereby reinforcing protective effects on endothelial cells undergoing hypoxia/reoxygenation injury and enhancing the survival of cardiomyocytes alongside overall cardiac functionality during hypoxic states [45].

Lung injury repair

Lung damage is often seen in situations like pulmonary inflammation caused by acute infections and pulmonary fibrosis resulting from long-term injuries to the circulatory system. Mesenchymal stem cells (MSCs) have the ability to modulate different immune responses via direct interactions between cells and through paracrine signaling, thereby providing anti-inflammatory benefits and affecting the advancement of pulmonary fibrosis. Additionally, MSCs can encourage the formation of new blood vessels, support cellular functions, and decrease cell death, which ultimately helps maintain respiratory function and aids in tissue repair.

Promotion of epithelial cell regeneration and anti-fibrotic effects: By blocking the IL-6/STAT3 signaling pathway, mesenchymal stem cells (MSCs) can trigger the p63-JAG2 signaling cascade, which in turn fosters the proliferation of epithelial cells, hinders apoptosis, and diminishes the influx of inflammatory cells, collectively facilitating epithelial recovery [46]. Furthermore, MSCs can alleviate fibrosis by influencing the ratio between TIMPs and MMPs [47]. Exosomal microRNAs, particularly miR-182-5p and miR-23a-3p, released by MSCs, have demonstrated an ability to suppress NF-κB and Hedgehog signaling pathways, effectively reversing the advancement of lung injury and fibrosis induced by LPS [48]. In addition, extracellular vesicles derived from MSCs (MSC-EVs) can attenuate the ATM/p53/P21 signaling pathway through the transfer of miR-214-3p, leading to a reduction in radiation-induced DNA damage, a decrease in cellular senescence, and a lower release of pro-fibrotic cytokines [49].

Immune regulation: The development of lung injury is marked by a rise in both the quantity and protein concentration of inflammatory cells, mainly neutrophils, along with heightened levels of chemokines and cytokines such as CCL3, CCL4, CCL5, CXCL1, IFN-γ, TNF-α, and IL-6 in bronchoalveolar lavage fluid. MSCs are essential in modulating inflammatory immune responses, which helps to reduce lung injury. For instance, MSCs alleviate acute lung injury induced by LPS through the inhibition of the inflammatory activities of Ly6C CD8+ T cells [50]. A distinct group of MSCs known as dental follicular stem cells have the capability to address histopathological damage and improve lung permeability. This is accomplished by downregulating pro-inflammatory cytokines such as MCP-1, IL-6, and TNF-α while simulta-

neously enhancing the expression of the anti-inflammatory cytokine IL-10. Furthermore, these cells boost the levels of Arg-1, a marker associated with anti-inflammatory macrophages, inhibit the skewing of macrophages towards a pro-inflammatory phenotype, and encourage the shift of macrophages to an anti-inflammatory state by decreasing iNOS and CD86 levels, both of which are indicative of pro-inflammatory macrophage activation [51].

In addition, UC-MSCs can promote the expression of CD206, an anti-inflammatory marker, and mitigate the increase in TNF-α caused by LPS in alveolar macrophages (F4/80+). Importantly, UC-MSCs that undergo heat shock pre-treatment demonstrate improved immunomodulatory effects, especially in fostering M2 macrophage polarization. This pre-treatment has been found to reduce acute lung injury by lowering NLRP3 inflammasome activation in macrophages [52].

Promotion of angiogenesis: The enhancement of angiogenesis is crucial for the repair of respiratory damage. MSCs have been demonstrated to support angiogenesis. In reaction to inflammatory stimuli, these cells secrete several growth factors, such as VEGF, PDGF, FGF, and TGF-β. These growth factors activate the regenerative capabilities of resident stem cells, thus facilitating angiogenesis and the remodeling of the extracellular matrix (ECM). Importantly, VEGF is essential for MSC-mediated angiogenesis by activating endothelial cells, which promotes angiogenic activities, and assists in the maturation and proliferation of epithelial cells, while also contributing to the development of pulmonary tubules and cysts [53].

The disruption of the alveolar epithelial-capillary barrier is a defining characteristic of acute respiratory distress syndrome (ARDS), which may be associated with mitochondrial dysfunction. The delivery of mitochondria through MSC-EVs can help mitigate mitochondrial dysfunction in lung tissue demonstrated by precision-cut lung slices and re-establish LPS-inhibited mitochondrial respiration, thereby supporting the recovery of the alveolar-capillary barrier in cases of ARDS [54].

Reduction of apoptosis: MSCs play a crucial role in alleviating lung injury and enhancing survival outcomes in gram-negative bacterial pneumonia models. An innovative therapeutic approach hinges on MSCs' capacity to suppress miR-193b-5p in human primary pulmonary microvascular endothelial cells. This suppression mitigates the TNF-induced decrease in the expression of the occludin (Ocln) gene and its protein, which in turn maintains the integrity of the alveolar-capillary barrier and lowers the rate of apoptosis. As a result, this mechanism bolsters the body's defenses against lung inflammation and damage [55].

Kidney injury disease

MSCs display notable abilities to modulate immune responses and facilitate tissue regeneration, making them attractive candidates for therapeutic interventions in kidney disorders. These cells influence immune responses by releasing a range of anti-inflammatory substances, which in turn improve the immune environment within renal tissues. Additionally, MSCs have the capacity to either activate or suppress particular signaling pathways that help diminish collagen buildup in renal tissues, alleviate renal fibrosis, boost renal blood circulation through the process of angiogenesis, and support the growth and longevity of renal parenchymal cells.

Immunological regulation: The regulation of the immune system serves as an essential mechanism through which MSCs provide protection to kidney cells. MSCs have the capacity to hinder the transformation of CD4+ T cells into Th17 cells by influencing the mTOR-STAT3/5 signaling pathway, while also fostering the development of Tregs that promote effective anti-inflammatory responses [56].

Furthermore, the differentiation of macrophages between M1 and M2 phenotypes significantly contributes to reducing inflammation during kidney injury. In a murine model of acute kidney injury, the administration of MSC-exos promoted the shift from M1 to M2 macrophages, resulting in the release of anti-inflammatory mediators. This change enhanced the inflammatory microenvironment within kidney tubules and curtailed both apoptosis and fibrosis throughout the self-repair process [57]. Moreover, research has shown that infusing ADMSC-exos into renal veins led to an elevation in TSG-6, a decline in TNF-α levels, a decrease in the M1/M2 macrophage ratio, improved kid-

ney function, and reduced fibrosis. In vitro studies indicated that TNF-α stimulates the secretion of TSG-6 from MSCs, which subsequently lowers lactate dehydrogenase release from injured HK-2 cells, enhances the expression of M2 macrophage markers, and reduces the adhesion and migration of M1 macrophages [58].

Maintenance of cell viability: The death of renal tubular cells through apoptosis or necrosis during the processes of self-renewal and repair signifies a notable pathological change associated with renal diseases. It has been demonstrated that MSCs can reduce both tubular and endothelial injury in porcine models suffering from septic acute kidney injury by influencing the TLR4/NF-κB signaling pathway [59]. Furthermore, miR-34a found in MSC-exos significantly lessens TGF-β1-induced apoptosis in HK-2 cells [60]. This specific microRNA also effectively mitigates the senescence of primary renal tubular epithelial cells obtained from mice [61]. In addition, exosomal miR-30e-5p secreted by MSCs inhibits pyroptosis mediated by caspase-2 in proximal tubular cells through the targeting of ELAVL1 [62].

Antifibrotic effects: MSCs are crucial in restoring kidney function after an injury by effectively reducing renal fibrosis. In a chronic kidney disease model characterized by fibrosis, rats that received MSC transplants demonstrated restored collagen deposition, along with a marked reduction in the accumulation of macrophages and fibroblasts, and a decrease in TNF α expression in the kidneys [63].

Moreover, administering hUCMSC-exos to mice with diabetic renal fibrosis led to lower levels of albuminuria, less glomerular damage, and decreased fibrosis [64]. Additionally, the microRNA-34c-5p found in MSC-exos has been shown to significantly reduce the expression and activity of the core fucosylation enzyme FUT8, which in turn diminishes cell activation and renal interstitial fibrosis [65]. Furthermore, miRNA-34a, present in the exosomes derived from bone marrow MSCs, can inhibit EMT induced by TGF-β1 in renal tubular epithelial cells, leading to lowered levels of α-SMA and fibronectin, possibly by interfering with the Jagged-1/Notch-1 signaling pathways [64].

Nervous system injury

MSCs have shown considerable promise in facilitating the reconstruction of nerve function through various mechanisms. These include promoting neural differentiation, decreasing the infiltration of neuroinflammatory factors, enhancing the microenvironment through angiogenesis, and reducing damage by lowering apoptosis levels. Importantly, exosomes released by MSCs have the ability to pass through the blood-brain barrier, enabling safe delivery without requiring immunosuppression.

Promotion of neural differentiation: MiRNA-199a-3p and miRNA-145-5p, which are produced by hUC-MSCs, have the ability to enhance p-ERK and p-Akt levels through the targeting of the Cblb and Cbl genes. This action promotes the growth of neurites in NGF-stimulated PC12 cells while also diminishing secondary neuronal apoptosis [66]. In addition, collagen hydrogels infused with MSC aggregates have been shown to boost the release of endogenous trophic factors and ECM components, which aid in activating interactions between neuroactive ligands and receptors. This activation subsequently initiates the PI3K-Akt signaling pathway, a key player in the process of differentiating neural stem cells into neuronal lineages [67].

Anti-inflammatory effects: The administration of hADMSCs-EVs through intravenous means has demonstrated effectiveness in traversing the blood-brain barrier while displaying immunomodulatory properties. This therapeutic approach leads to a notable decrease in plasma concentrations of IFN-γ, TNF-α, IL-1β, and various other pro-inflammatory cytokines in murine models of multiple sclerosis (MS). MSC-exos are rich in specific microRNAs, including miR-467f and miR-466q, which impede the activation of the p38MAPK signaling pathway. This inhibition results in diminished production of inflammatory mediators, a reduction in the pro-inflammatory phenotype of microglia, and lower levels of neuroinflammatory markers within the spinal cord [68]. Furthermore, microRNA-22 sourced from exosomes prevents apoptosis in microglia, which in turn decreases the secretion of inflammatory factors and the expression of GSDMD [69]. MicroRNAs such as miR-17, miR-23a, and miR-125b, which are prevalent in

MSC-exos, downregulate the TLR4/NF-κB signaling pathway by targeting genes associated with TLR4/NF-κB receptor signaling as well as advanced glycation end products. This regulatory action inhibits the inflammatory cascade and encourages an increase in markers indicative of the M2 macrophage phenotype [70]. In addition, microRNA-125a obtained from BMSC-exos promotes the polarization of M2 macrophages in cases of spinal cord injury (SCI) by downregulating IRF2, leading to reduced inflammation and enhanced neuroprotection in SCI models [71]. Similarly, exosomal miRNA-124-3p has been shown to alleviate nerve injury in spinal cord ischemia-reperfusion scenarios by downregulating Ern1 and fostering M2 macrophage polarization [72].

Reduction of apoptosis: In the setting of ischemic perfusion injury, such as that occurring in ischemic stroke, there is an increase in levels of GOLPH3 protein, ROS, and intracellular calcium (Ca2+), coupled with a decrease in secretory pathway Ca2+-ATPase 1 (SPCA1). This sequence of actions results in heightened fragmentation of the Golgi apparatus (GA), leading to what is referred to as "GA stress", which ultimately triggers apoptosis. Addressing and inhibiting these stress-induced responses may promote the restoration of neural function. The protein PEDF derived from olfactory mucosal mesenchymal stem cells (OM-MSCs) has been demonstrated to enhance Akt phosphorylation in mouse neuroblastoma N2a cells experiencing oxygen-glucose deprivation and subsequent reperfusion injury, primarily through its engagement with the PEDF receptor. This engagement amplifies the Akt/mTOR signaling pathway, consequently diminishing GA stress responses, suppressing autophagy, and partially inhibiting apoptosis [73]. Moreover, MSC-derived exosomes (MSC-exo) have the ability to obstruct NF-κB signaling by downregulating PTEN. This adjustment leads to a decrease in inflammation and apoptosis within the spinal cord, thereby improving outcomes in models of SCI [74].

Induction of angiogenesis: MSC-exos were administered to a stroke animal model, leading to a notable increase in the count of newly generated bifocorticoid cells. The miRNA-126 found within these exosomes was shown to localize at injury sites in the spinal cord, where it suppressed the expression of SPRED1 and PIK3R2. This suppression facilitated angiogenesis and improved the migration of HUVECs, resulting in a reduction of lesion volume [75]. Additionally, MSC-exos are abundant in ECM metalloproteinase inducers, including MMP-9 and VEGF, all of which play a vital role in angiogenesis and support nerve injury repair [76].

Enhancing the treatment protocols for MSCs can further amplify their angiogenic capabilities. For instance, MSCs stimulated by human platelet-derived exosomes exhibited significant tube formation within 2 hours, and these activated MSCs effectively supported nerve tissue repair after spinal cord transection in rat models [77].

Intrauterine adhesion(IUA)

IUA poses a notable challenge for individuals suffering from a condition related to endometrial repair. The use of MSC transplantation has surfaced as a potential treatment option for mending endometrial damage and promoting fertility.

Studies have shown that BM-MSCs and their exosomes significantly boost the quantity of endometrial glands, considerably diminish the extent of endometrial fibrosis, and increase the expression of the epithelial marker CK-19, all while simultaneously lowering the level of the mesenchymal marker vimentin. Additionally, these interventions lead to a marked decrease in both mRNA levels and the phosphorylation of TGF-β and Smad2 [78]. The mechanisms at play may involve the suppression of epithelial-mesenchymal transition (EMT) facilitated by the Wnt/β-catenin signaling pathway [79]. Moreover, miR-145-5p found in exosomes derived from MSCs has been shown to counteract TGF-β1-induced fibrosis by targeting the ZEB2 axis, whereas miR-543 alleviates endometrial fibrosis linked to IUA by downregulating N-cadherin [80, 81].

Beyond their immediate reparative properties, MSCs contribute to the reconstitution of the endometrium by modulating the immune response. Research shows that MSC treatment in rat models of intrauterine adhesions (IUA) leads to a notable decrease in pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-1β, and IL-6, while enhancing the levels of anti-inflam-

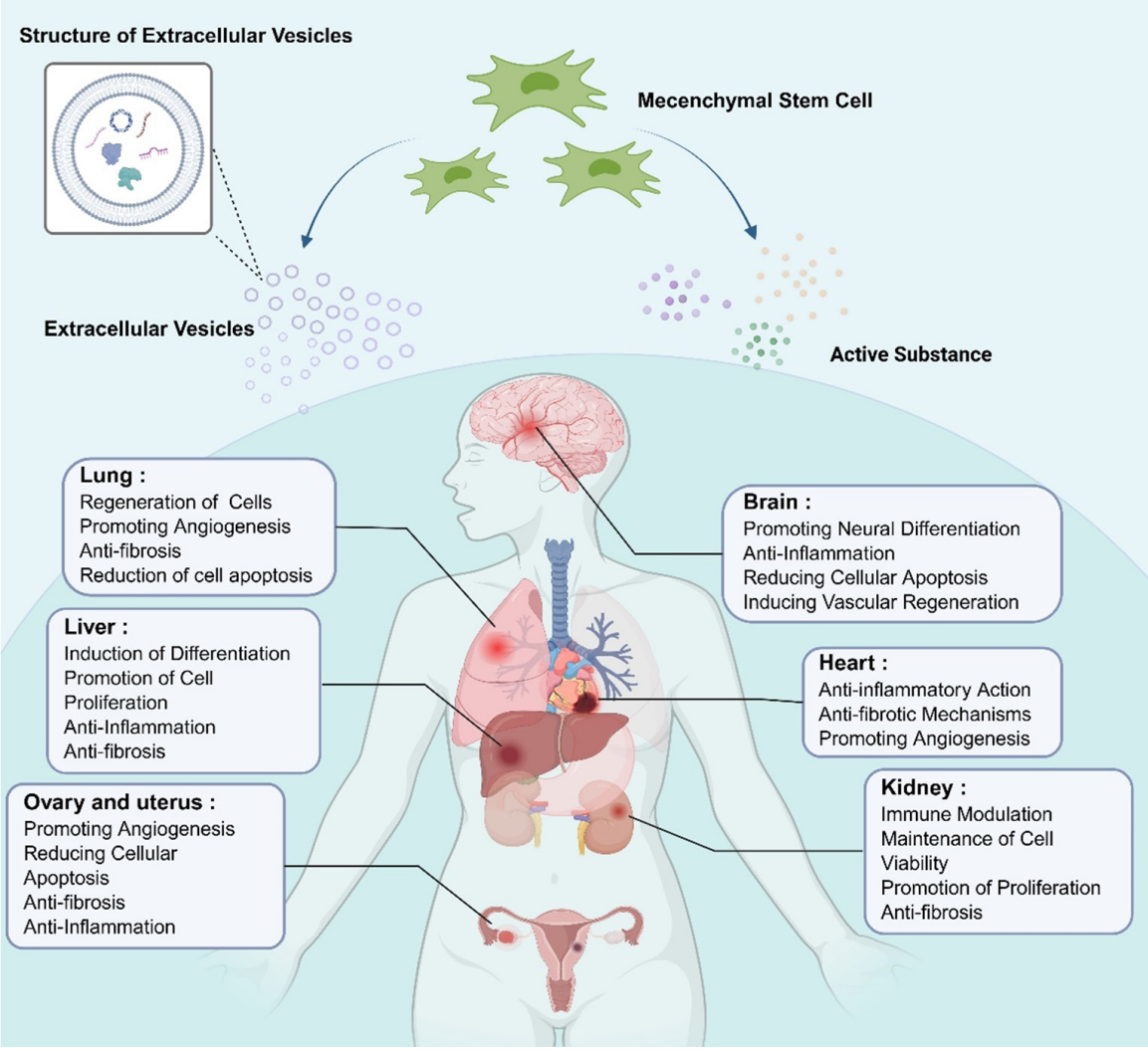

Figure 3. MSCs play a crucial role in the repair of tissue damage in vital organs. They secrete exosomes and associated active factors that specifically target major organs under pathological conditions. These secretions provide a variety of beneficial effects, including anti-inflammatory, anti-fibrotic, and anti-apoptotic actions. Furthermore, they contribute to the maintenance of cell viability, promote cell proliferation, and enhance angiogenesis.

matory cytokines like IL-4 and IL-10 [78, 79]. Additionally, MSCs may influence the equilibrium between Th17 cells and regulatory Tregs through NF-κB signaling, which can suppress the immune response in the compromised endometrium, encourage macrophage polarization towards the M2 phenotype, and ultimately reduce the inflammatory milieu in the uterus, thereby fostering endometrial regeneration [82-85].

Summary of MSCs' mechanism

MSCs have demonstrated significant potential in the regeneration and repair of various tissues and organs. Their therapeutic effects primarily arise from the paracrine mechanism, which involves the secretion of a range of cytokines and extracellular vesicles (EVs) that exert multiple biological effects, including the inhibition of fibrosis, alleviation of inflammation, reduction of apoptosis, and promotion of angiogenesis (see **Figure 3**). Notably, MSCs can produce a substantial quantity of exosomes enriched with small RNAs, which are crucial for tissue repair following injury (see **Table 1**). Understanding the paracrine actions of MSCs can pave the way for refining cell therapy approaches by boosting the secretory potential of MSCs via genetic modification or pharmaco-

Table 1. The role of miRNAs secreted by MSCs and their roles in disease repair

Source of Cells	RNA	Type of Disease	Functions in Repairing Injuries
BMSC	let-7a-5p	Rat cranial bone defect	Facilitate bone regeneratio [93]
BMSCs	let-7c-5p	Rat cranial bone defect	Facilitate bone regeneratio [93]
BMSCs	miR-328a-5p	Rat cranial bone defect	Facilitate bone regeneration [93]
BMSCs	miR-31a-5p	Rat cranial bone defect	Facilitate bone regeneration [93]
HUCB-MSC	miR-21	Rat cranial bone defect	Promote vascular formation [94]
BMSC	miR-210-3p	Rat cranial bone defect	Promote bone regeneration and vascular formation [95]
HUCMSCs	miR-196a-5p	Rat cranial bone defect	Promote bone regeneration [96]
BMSCs	miR-34c-5p	Diabetic nephropathy	Improve proximal renal tubular cell apoptosis, inhibit fibrosis [65]
BMSCs	miR-34a	apoptosis in renal tubular cells	Inhibit epithelial-mesenchymal transition and cell apoptosis [60]
BMSCs	miR-374a-5p	Renal interstitial fibrosis	Inhibit fibrosis [97]
BMSCs	miR-30e-5p	Diabetic nephropathy	Inhibit proximal tubular cell apoptosis [62]
BMSCs	miR-214-3p	Liver injury	Reduce oxidative stress, inhibit ferroptosis [26]
BMSCs	miR-124-3p	Liver ischemia-reperfusion injury	Inhibit ferroptosis [27]
HUCMSCs	miR-124	Liver resection	Promote hepatocyte proliferation [24]
BMSCs	miR-182-5p	Liver injury, pulmonary fibrosis	Anti-inflammatory, reverse epithelial-mesenchymal transition [29]
HUCMSCs	miR-27b-3p	Liver fibrosis	Anti-fibrotic [34]
BMSCs	miR-144-5p	Premature ovarian failure	Reduce granulosa cell apoptosis [98]
BMSCs	miR-664-5p	Premature ovarian failure	Inhibit granulosa cell apoptosis [99]
HUCMSCs	miR-543	Intrauterine adhesions	Anti-fibrotic [80]
HUCMSCs	miR-145-5p	Intrauterine adhesions	Improve endometrial fibrosis [81]
BMSCs	miR-182	Myocardial ischemia-reperfusion injury	Anti-inflammatory, promote M2 polarization [100]
BMSCs	miR-125a-5p	Myocardial ischemia-reperfusion injury	Improve apoptosis and inflammation, promote vascular formation [37]
ADSCs	miR-205	Acute myocardial infarction	Inhibit cardiomyocyte apoptosis, promote vascular formation [40]
BMSCs	miR-129-5p	Heart failure	Alleviate cell apoptosis [36]
BMSCs	miR-25-3p	Acute myocardial injury	Anti-inflammatory, anti-apoptotic [42]
BMSCs	miR-210	Acute myocardial infarction	Promote myocardial survival [45]
HUCB-MSCs	miR-23a-3p	Acute myocardial infarction	Inhibit ferroptosis, alleviate myocardial injury [43]
HUCMSCs	miR-199a-3p	Spinal cord injury	Reduce secondary neuronal apoptosis [66]
HUCMSCs	miR-145-5p	Spinal cord injury	Reduce secondary neuronal apoptosis [66]
BMSCs	miR-467f	Neuroinflammation	Inhibit microglial pro-inflammatory phenotype [68]
BMSCs	miR-466q	Neuroinflammation	Inhibit microglial pro-inflammatory phenotype [68]
BMSCs	miR-17	Diabetic peripheral neuropathy	Anti-inflammatory [70]
BMSCs	miR-23a	Diabetic peripheral neuropathy	Anti-inflammatory [70]
BMSCs	miR-125b	Diabetic peripheral neuropathy	Anti-inflammatory [70]
BMSCs	miR-126	Spinal cord injury	Promote vascular formation, inhibit cell apoptosis [75]
HUCMSCs	miR-100-5p	Autoimmune dacryoadenitis	Anti-inflammatory, promote M2 polarization [101]

logical pretreatment, thus increasing their therapeutic effectiveness. A thorough comprehension of the mechanisms by which MSCs function in various tissue injuries can facilitate their advancement from research settings to clinical usage, offering innovative treatment alternatives for a range of challenging diseases, encompassing neurodegenerative and cardiovascular conditions.

Clinical application of MSCs

MSCs have demonstrated beneficial effects on the restoration of damage in essential organs and display immune tolerance, offering significant advantages for their use in clinical contexts [86]. However, it is crucial to consider several important factors when applying MSCs in clinical practice, including their source, dosage, administration techniques, safety, and therapeutic efficacy.

Source of MSCs in clinical trails

At present, MSCs utilized in clinical settings predominantly come from either allogeneic or autologous transplantation. In contrast to animal studies, where MSCs are subjected to treatments, inductions, and modifications aimed at improving their therapeutic potential, most clinical trials do not involve modifications to MSCs. Only a small number of clinical trials have utilized hypoxic preconditioning for MSCs. For example, during a Phase I trial focusing on myocardial infarction (NCT04056819), participants were administered hypoxia-preconditioned bone marrow-derived stem cells (BMSCs). Moreover, another trial aimed at radiation-induced lung injury (NCT06021067) involved the infusion of non-viable MSCs. There is a scarcity of studies on the clinical use of genetically modified MSCs due to concerns regarding safety. Although it is thought that genetic modifications can improve the efficacy of MSCs in meeting treatment objectives for various diseases, safety must always be the top priority, with careful consideration given to ensure any effects on the human body are beneficial and manageable.

Mode of administration

Currently, there are two main techniques for administering MSCs: arteriovenous infusion and localized injection. Arteriovenous infusion is mainly used for treating systemic diseases and significant organ injuries. For example, intravenous delivery of MSCs has been reported in the management of psoriasis due to immune system imbalance (NCT03265613). Phase I clinical studies utilizing MSCs for myocardial infarction have included both arterial and intravenous infusion methods (NCT04056819), while analogous strategies have been employed for ailments like liver cirrhosis (NCT01591200) and acute kidney injury (NCT04194671). In particular, renal aortic infusion was used to tackle acute kidney injury following heart surgery (NCT00733876), while intravenous infusion was applied in the treatment of COVID-19 pneumonia (NCT04713878) and lung injury due to radiation exposure (NCT06021067).

In contrast, localized injuries are more often treated through local injection methods. For instance, during clinical trials focused on osteoarthritis, intra-articular injections are the primary way that MSCs are delivered (NCT03990805; NCT0152264). In research on spinal cord injuries, intrathecal injections are predominantly used for therapeutic interventions (NCT02482194), or MSCs may be loaded onto NeuroRegen scaffolds for transplantation (NCT02688049). Moreover, local skin injections have been utilized in clinical studies addressing skin scar healing (NCT06135519; NCT05984628). In a study focused on IUA, hUC-MSCs were transplanted into the uterine cavity with the aid of collagen scaffolds (NCT02313415) [87], while autologous BM-MSCs were introduced into the spiral arterioles of the uterus (NCT02144987) [88]. Additionally, intramyocardial injections can be executed in instances of significant organ injuries, including cardiac injury (NCT01219452, NCT02460770). Furthermore, clinical trials targeting diabetic nephropathy have involved injecting UC-MSCs into the renal parenchyma (NCT03288571). Exosomes, which are effective mediators secreted by MSCs, provide improved options for drug delivery. In a clinical trial aimed at using MSC-exosomes to treat severe COVID-19, these exosomes were administered via aerosol inhalation (NCT04313647). Furthermore, a separate clinical trial with Taedermus vulgaris is applying an MSC-derived exosomal cream topically (NCT05523011). Clearly, these administration methods are more convenient and safer.

Dosage of MSCs

When MSCs are infused intravenously, the typical dosage ranges from 5 × 10^5 to 1 × 10^6 MSCs per kilogram (NCT03265613, NCT04194671, NCT04713878). In the treatment of chronic diseases, multiple infusions are generally administered at longer intervals, whereas in acute illnesses, infusions are conducted at shorter intervals. The dosage for local injections varies significantly, ranging from 1 × 10^6 to 1 × 10^8 MSCs (NCT05984628, NCT02481440). For the aerosol inhalation of MSC-exos to treat severe COVID-19, the recommended dosage is 2.0 × 10^8 nanovesicles inhaled once daily, while the exosome cream contains 100 μg of MSC exosomes per gram of ointment, applied three times daily. Currently, there is no clear clinical dosage guidance for the infusion of MSCs across different diseases.

Therapeutic effect and safety

The main goal of clinical trials is to determine the efficacy and safety of MSCs in treating various diseases. In a clinical trial investigating osteogenesis imperfecta in children (NCT02172885), five infusions of allogeneic MSCs at a dosage of 4 × 10^6 MSCs/kg per patient resulted in fewer fractures without any significant changes in trabecular thickness. Notably, two patients who exhibited reduced trabecular pore size tolerated the five repeated infusions well, with no alterations observed in immunoglobulin levels (IgG, IgM, and IgA), anti-HLA antibodies, antinuclear antibodies, or monocyte and lymphocyte subsets [89]. In a Phase III clinical trial focusing on knee arthritis, patients experienced significant pain relief and improved motor function following infusion with autologous AD-MSCs [90]. In another clinical trial assessing MSCs therapy for knee arthritis (NCT01809769), subjects received three injections comprising low-dose (1 × 10^7 cells), medium-dose (2 × 10^7 cells), and high-dose (5 × 10^7 cells) regimens over a follow-up period of 96 weeks. The investigators concluded that the high-dose group demonstrated the most pronounced effectiveness in treating knee arthritis without any reported adverse events.

In a clinical trial investigating chronic myocardial ischemia, treatment with autologous BM-MSCs resulted in significant improvements in left ventricular ejection fraction (LVEF), left ventricular end-systolic volume, the 6-minute walk test, and New York Heart Association (NYHA) functional class (NCT01076920) [91]. Another phase I clinical trial (NCT02672267) involving patients with myocardial infarction treated with MSCs demonstrated lower levels of NT-proBNP, higher LVEF, and reduced wall motion scores compared to baseline values. In a phase I trial, transplantation of UC-MSCs was associated with increased endometrial thickness, decreased IUA scores, and enhanced expression of ERα, vermentin, Ki67, and vWF, while showing decreased expression of ΔNP26. These findings suggest that endometrial proliferation, differentiation, and neovascularization are improved following treatment (NCT02313415) [87]. In another clinical study involving 16 women of childbearing age diagnosed with IUA or uterine atrophy who received infusions of autologous BM-MSCs into the spiral arterioles of the uterus post-treatment revealed that 11 patients exhibited improvements in uterine cavity conditions along with increased endometrial thickness and enhanced density of mature uterine vessels as well as prolonged duration and intensity of menstruation. Notably, three patients achieved natural conception while seven conceived through embryo transfer (NCT02144987) [88]. However, a study utilizing aerosol inhalation of MSC-exos for treating novel coronavirus pneumonia (NCT04276987) reported only a slight increase in serum lymphocyte counts among patients; nonetheless lung lesions regressed to varying degrees - most notably observed in four out of seven patients. The aerosolized human adipose-derived MSC exosomes were well tolerated by all participants without any adverse events or indications of clinical instability [92].

MSCs demonstrate considerable therapeutic potential in the repair of tissue damage related to a variety of diseases. Numerous clinical trials are presently underway, and additional results are expected in the near future. The safety profile of MSCs is largely well-established, with no adverse effects reported to date.

Conclusion and prospect

In conclusion, although the mechanisms by which mesenchymal stem cells (MSCs) pro-

mote tissue repair vary across different organs, they primarily facilitate the repair of damaged tissues through several key processes: directed differentiation, immune modulation, mitochondrial transfer, promotion of cell proliferation, reduction of cellular damage, enhancement of angiogenesis, and alleviation of tissue fibrosis. Furthermore, due to their low immunogenicity, MSCs are particularly well-suited for a wide range of clinical applications. In recent years, numerous clinical trials have substantiated their efficacy in treating injury repair diseases. The cellular components and secretions of MSCs exhibit significant potential across multiple fields. Targeted delivery mechanisms that utilize exosomes or engineered variants may enable precise treatments for specific underlying issues.

However, several technical obstacles must be addressed to facilitate the widespread clinical application of MSCs and their cellular components. Key challenges include obtaining a large and stable supply of MSCs and exosomes while ensuring their proper preservation; employing minimally invasive or non-invasive methods for precise in vivo targeted therapy involving MSCs or exosomes; and preventing the clearance of MSCs and exosomes by the body's internal environment. These challenges present considerable obstacles to the advancement of mesenchymal stem cell therapy.

Disclosure of conflict of interest

None.

Abbreviations

ARDS, acute respiratory distress syndrome; Ang-1, angiopoietin-1; ANGPT1, angiopoietin-1; AIFM3, apoptosis-inducing factor mitochondria-associated 3; ATM, ataxia telangiectasia mutated; Arg-1, arginase-1; ATII, Type II alveolar epithelial cells; BCL2, B-cell lymphoma; Bnip3, Bcl-2/adenovirus E1B 19-kDa interacting protein 3; Bax, Bcl-2-associated X protein; CK-19, cytokeratin-19; Col1a1, collagen type I alpha 1; Col3a1, collagen type III alpha 1; CXCR4, C-X-C chemokine receptor type 4; CHOP, C/EBP homologous protein; CCL4, carbon tetrachloride; DCs, dendritic cells; DMT3, death-associated protein 3; DKK-3, Dickkopf-related protein 3; ERα, estrogen receptor α; ERK1/2, extracellular signal-regulated kinase 1/2; Enos, endothelial nitric oxide synthase; EGF, epidermal growth factor; ELAVL1, ELAV-like RNA binding protein 1; ETS-1, endothelial transcription factor 1; Ern1, endoplasmic reticulum to nucleus signaling 1; eNOS, endothelial nitric oxide synthase; FGF, fibroblast growth factor; FGF2, fibroblast growth factor 2; FASL, Fas ligand; GSK-4β, insulin-like growth factor binding protein 4; GSH, glutathione; GPX1, glutathione peroxidase 1; GSDMD, gasdermin D; HGF, hepatocyte growth factor; HIF-1α, hypoxia-inducible factor 1-alpha; HUVECs, hypoxic-injured human umbilical vein endothelial cells; H2O2, hydrogen peroxide; IDO, indoleamine 2, 3-dioxygenase; IGFBP3, insulin-like growth factor binding protein 3; IGFBP-4, insulin-like growth factor binding protein 4; IFN-γ, interferon-gamma; IGF-1, insulin-like growth factor 1; ILK, integrin-linked kinase; IL-1β, interleukin-1 beta; IL-4, interleukin-4; IL-6, interleukin-6; IL-10, interleukin-10; IRF2, interferon regulatory factor 2; IRF3, interferon regulatory factor 3; iNOS, inducible nitric oxide synthase; Klf13, Kruppel-like factor 13; LPS, lipopolysaccharide; LOXs, lipoxygenases; LOXL2, lysyl oxidase-like 2; MAPK, mitogen-activated protein kinase; Mast4, microtubule-associated serine/threonine kinase family member 4; MCP-1, monocyte chemoattractant protein-1; MMPs, metalloproteinases; MMP3, matrix metalloproteinase-3; MRTF, myocardin-related transcription factor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NGF, nerve growth factor; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; PEDF, Pigment epithelium-derived factor; PGE2, prostaglandin E2; PIK3R2, phosphoinositide 3-kinase regulatory subunit 2; PI3K, phosphoinositide 3-kinase; PPARγ, peroxisome proliferator-activated receptor gamma; PUMA, p53-upregulated modulator of apoptosis; PTEN, phosphatase and tensin homolog; Ptgs2, prostaglandin-endoperoxidase 2; p-Akt, phosphorylated protein kinase B; p-Erk, phosphorylated extracellular signal-regulated kinase; p-p53, phosphorylated p53; Runx2, Runt-related transcription factor 2; SDF-1, stromal cell-derived factor-1; Sox9, SRY-related high mobility group-box gene 9; SPRED1, SPTY-associated EVH1 domain protein-containing 1; STAT3, signal transducer and activator of transcription 3; ST6, Stimulating Gene/Protein 6; TBK1, TANK-binding kinase 1; TGF-β, transforming growth factor-beta; TIMPs, metalloproteinases; TLR4, Toll-like receptor 4;

TNF-α, tumor necrosis factor-alpha; TRAF3, D-TNF receptor-associated factor 3; Tregs, regulatory T cells; TSG-6, necrosis factor-stimulated gene 6; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; Vwf, von Willebrand factor; ZEB2, zinc finger E-box binding homeobox 2; α-SMA, α-smooth muscle actin; 3'-UTRs, 3' untranslated regions.

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