Zhidu *et al. Stem Cell Research & Therapy* (2024) 15:266
https://doi.org/10.1186/s13287-024-03885-z

Stem Cell Research & Therapy

REVIEW

Open Access

# Translational potential of mesenchymal stem cells in regenerative therapies for human diseases: challenges and opportunities

Song Zhidu[1], Tao Ying[2], Jiang Rui[3] and Zhang Chao[1*]

**Abstract**

Advances in stem cell technology offer new possibilities for patients with untreated diseases and disorders. Stem cell-based therapy, which includes multipotent mesenchymal stem cells (MSCs), has recently become important in regenerative therapies. MSCs are multipotent progenitor cells that possess the ability to undergo in vitro self-renewal and differentiate into various mesenchymal lineages. MSCs have demonstrated promise in several areas, such as tissue regeneration, immunological modulation, anti-inflammatory qualities, and wound healing. Additionally, the development of specific guidelines and quality control methods that ultimately result in the therapeutic application of MSCs has been made easier by recent advancements in the study of MSC biology. This review discusses the latest clinical uses of MSCs obtained from the umbilical cord (UC), bone marrow (BM), or adipose tissue (AT) in treating various human diseases such as pulmonary dysfunctions, neurological disorders, endocrine/metabolic diseases, skin burns, cardiovascular conditions, and reproductive disorders. Additionally, this review offers comprehensive information regarding the clinical application of targeted therapies utilizing MSCs. It also presents and examines the concept of MSC tissue origin and its potential impact on the function of MSCs in downstream applications. The ultimate aim of this research is to facilitate translational research into clinical applications in regenerative therapies.

**Keywords** Mesenchymal stem cells (MSCs): regenerative therapies, Neurological disorders, Cardiovascular diseases, Respiratory diseases, Reproductive disorders, endocrine-related diseases, Skin burns

## Introduction

Stem cell therapy is an innovative method of treatment that uses the distinctive characteristics of stem cells, such as differentiation and self-renewal, to repair damaged tissues and cells in the human body or substitute these cells with healthy, new, and completely functional cells by providing exogenous cells into the patient [1]. The sources of stem cells used in cell-based therapies are either (1) autologous (also known as self-to-self therapies) or (2) allogeneic (which uses cells from a healthy donor) [2]. In the last 30 years, the use of mesenchymal stem cells (MSCs) has gained significant attention. due to their fascinating cellular biology, wide-ranging therapeutic

*Correspondence:
Zhang Chao
zhangchao1984@jlu.edu.cn
[1]Department of Ophthalmology, the Second Hospital of Jilin University, No. 218, Ziqiang Street, Nanguan District, Changchun City, Jilin Province, China
[2]Department of Anesthesiology, China-Japan Union Hospital of Jilin University, Changchun, China
[3]Department of Orthopedics, China-Japan Union Hospital of Jilin University, Changchun, China

possibilities, and role as a foundational component in the emerging field of regenerative therapies [3]. Depending on where they were isolated, MSCs can exhibit a broad range of cytokine profiles and surface markers [4]. However, MSCs are generally characterized by CD90, CD105, and CD73 expression and by the absence of CD19, CD79α, CD34, CD45, CD14 or CD11b, and HLA-DR [5, 6]. They possess the potential to move to damaged tissue through chemo-attraction, making them advantageous for a broad range of therapeutic uses [7, 8]. Furthermore, MSCs can secrete a range of bioactive substances, such as chemokines, proteins, microRNAs (miRNAs), growth factors, and cytokines, indicating their potential applications [9].

Friedenstein initially established a culture of bone-forming cells using guinea pigs, while Owen renewed this investigation by extending this research to rats [10, 11]. Human bone marrow MSCs (BM-MSCs) were isolated and cultured for the first time in 1992; patient infusion of BM-MSCs commenced in 1993, according to a 1995 report [12, 13]. Infusion techniques in the last 25 years have shown a high level of safety, resulting in more than 950 registered clinical trials using MSCs submitted to the FDA [3]. MSCs proliferate easily in vitro, possess unique differentiation capabilities not observed in other cell types, and secrete an abundance of beneficial cytokines and growth factors. The capacity of MSCs to be isolated from different tissues and then reimplanted at different sites raises the question of whether natural MSCs exist in vivo and are capable of repairing endogenous tissues. This process is difficult and has made tremendous advancements, but it is not yet completed.

MSCs possess diverse characteristics that make them ideal for cell-based regenerative therapy. They exhibit stemness potency, can be easily isolated from various sources, and can be rapidly developed on a large scale for clinical applications. Additionally, they present fewer ethical concerns in comparison to embryonic stem cells (ESCs) and a decreased chance of teratoma development than induced pluripotent stem cells (iPSCs). This review presents a comprehensive overview of regenerative therapies utilizing MSCs and highlights their remarkable clinical applications. Moreover, we elaborated on the potential of MSCs for "targeted therapy" by elucidating their distinct tissue origins and downstream applications, as well as providing a comprehensive analysis of their underlying mechanisms of action. We finally address the reasons that MSCs' tissue origin may greatly enhance their subsequent applications, thereby enhancing the effectiveness and safety of stem cell-based therapy.

## Cell biology of MSCs

Vertebrate stem cells are distinguished by their ability to divide asymmetrically or symmetrically to become mobile, differentiate into many lineages, and organize into multifunctional groups. A supportive and instructive environment is necessary for stem cells to differentiate into functionally organized cells. As a result, the phenotypic reprogramming of stem cells is determined by the cellular environment, as well as the temporal application and persistence of instructional agents. Pittenger et al. detected this characteristic in MSCs through their differentiation into chondrogenic, adipogenic, or osteogenic cells within 1 to 3 weeks [14]. Furthermore, Terzic et al. demonstrated the multilineage potential of MSCs through the progressive acquisition of cardiomyocyte characteristics by the sequential modification of culture conditions for 3–4 weeks [15]. Although the exact timing of events may fluctuate slightly for each cell, these combined results of MSC population differentiation reflect characteristics at the single-cell level. It is well-known that stem cell populations lack uniformity; instead, cells within them often display attributes that are characteristic of individual cells, regardless of their clonal origin [16, 17]. During development, stem/progenitor cells frequently exhibit this temporal stochasticity [18]. Stochastic processes and events involving progenitor/stem cells are probably the most difficult to explain or approach experimentally, even though comparable phenomena can be observed in vitro [19].

MSCs are characterized by the ability to differentiate in response to stimuli and the in vitro expression of a particular subset of cell surface proteins [20]. The significant expression changes that occur as a result of culture expansion, stimulus-directed differentiation, hypoxia preconditioning, biologic exposure, trans-differentiation, and coculture with other cell types can offer valuable information about the biological characteristics of MSCs, their anticipated physiological roles, involvement in disease pathophysiology, and potential therapeutic mechanisms. Gaining insight into MSC gene expression data has the potential to enhance the operational definition of MSCs, elucidate their intrinsic physiological function, and provide guidance on how clinical manufacturing protocols and culture conditions can most accurately characterize their function and composition before administering them to patients.

BM-MSC identification was the initial objective of MSC gene expression research. Through serial analysis of gene expression (SAGE), the transcriptomes of human and mouse BM-MSCs were compiled, revealing their stem/progenitor characteristics as well as paracrine functions associated with skeletal homeostasis and hematopoiesis support [21]. The gene expression data provide extensive support for the clinical applications of MSC

populations, which are known to possess angiogenic, skeletogenic, immunomodulatory, and anti-inflammatory properties. MSCs obtained from various tissues/organs share a closer relationship compared to other mesodermal lineages and exhibit a phenotypic signature resembling perivascular cells [22, 23]. The impact of culture conditions on MSC gene expression and the potential for manipulation are crucial factors for their therapeutic application. Understanding of the cellular responses of MSCs to stimuli that induce differentiation has been enhanced by RNA-seq research. As an illustration, a study found significant alterations in the MSC transcriptome after differentiation into the adipogenic rather than the osteogenic lineage. Furthermore, ChIP-Seq analyses revealed that osteoblasts derived from MSCs had an epigenome more similar to naïve cultivated MSCs than adipocytes [24]. The MSC genome has significant overlap in binding sites for master transcriptional regulators like RUNX2 and C/EBPβ. These sites are reduced in size through epigenetic changes during differentiation. The promoter regions display high plasticity, allowing MSCs to change from adipocytes to osteoblasts and vice versa [25]. These transcriptional pathways might influence the fate of MSC differentiation in vivo. It has been demonstrated recently that the osteogenic and adipogenic lineages are regulated by the Wnt intracellular signaling protein (CCN4 or WISP-1) [26]. The initial application of in vitro lineage priming to establish the molecular foundation for MSC multipotency was expanded by these results, which may lead to the development of more effective therapies.

Aside from stimuli that induce differentiation, various treatments have been found to modify the biological function of MSCs by changing gene expression. Rodent MSCs, for instance, have been shown to have improved proliferation and osteogenic capability under low oxygen (5%) environments, which is similar to the conditions found in the BM niche [27]. The proangiogenic activity of MSCs was found to be enhanced after transient exposure to hypoxic settings (<2% oxygen saturation) in vitro [28] and in vivo [29] and positively affects survival and growth [30]. According to profiling studies, hypoxic preconditioning significantly alters the expression of a small fraction of genes linked to MSC glycolysis, cell growth, and survival, as well as vasculogenesis/angiogenesis. Notably, the majority of these genes exhibit upregulation [31]. To gain additional insight into the immunomodulatory and anti-inflammatory characteristics of MSCs, a comparable method is being applied to examine their response to inflammatory stimuli. For instance, in vitro stimulation of human mesenchymal stem cells (MSCs) with lipopolysaccharides, a ligand for TRL4, resulted in the upregulation of transcripts associated with inflammatory responses and chemotaxis. These responses were primarily regulated by interferon regulatory factor (IRF1) and nuclear factor kappa B (NF-κB). [32]. Exposure to interferon (IFN)-gamma activates the immunosuppressive function of MSCs by increasing the production of indoleamine 2,3-dioxygenase (IDO1), an enzyme that reduces inflammation by consuming tryptophan in the kynurenin pathway. Additionally, stimulation by TNF enhances the expression of TSG-6, an anti-inflammatory protein [33, 34]. Notably, it was established that while IFN-gamma and TNF-stimulated MSCs expressed distinct sets of pro-inflammatory factors, the combination of these proteins polarized MSCs uniformly toward a Th1 phenotype, characterized by the expression of the immunosuppressive factors IDO, IL-10, CD274/PD-L1, and IL-4 [35]. This result is particularly noteworthy because, at the population level, nonstimulated populations showed noticeably higher levels of inter-donor heterogeneity, based on data from hierarchical clustering of MSC donor gene expression [36]. Thus, this "cytokine priming" should be investigated in animal and human investigations, as treating MSCs with effective stimuli normalizes the population and may substantially eliminate interdonor differences in MSC function. It is imperative to emphasize that exposure to inflammatory stimuli, including IFN-gamma and TNF, not only improves paracrine signaling but also induces other noteworthy effects on MSCs. IFN-gamma, for instance, significantly impairs the growth and survival of MSCs by upregulating the expression of genes linked to cellular apoptosis and programmed cell death [37]. The IFN-gamma treatment-induced gene expression responses of MSCs are additionally accompanied by changes in their overall morphology [38]. Induced into the osteogenic lineage, MSCs have been observed to possess an increase in the expression of IFN-gamma inducible genes, accompanied by a decrease in angiogenic activity [39].

## MSCs origin and therapeutic potential

MSCs have been isolated from various tissue types. However, they can all be categorized into two major sources: perinatal and adult (Fig. 1). Adult sources of MSCs refer to tissues that can be collected from an individual, including peripheral blood, dental pulp, BM, AT, hair, lungs, or the heart [40]. Adult MSCs typically exist in specialized areas known as stem cell niches, which offer the cell-to-cell connections, growth factors, microenvironment, and external signals required to preserve stemness and differentiation potential [41]. The number of MSCs that may be extracted from various adult tissues varies greatly, depending on the tissue. Gradient centrifugation reveals that the proportion of MSCs within BM mononuclear cells varies between 0.001% and 0.01% [42]. AT comprises an estimated 5,000 MSCs per 1 g, which is a minimum of 500 times greater than the quantity of

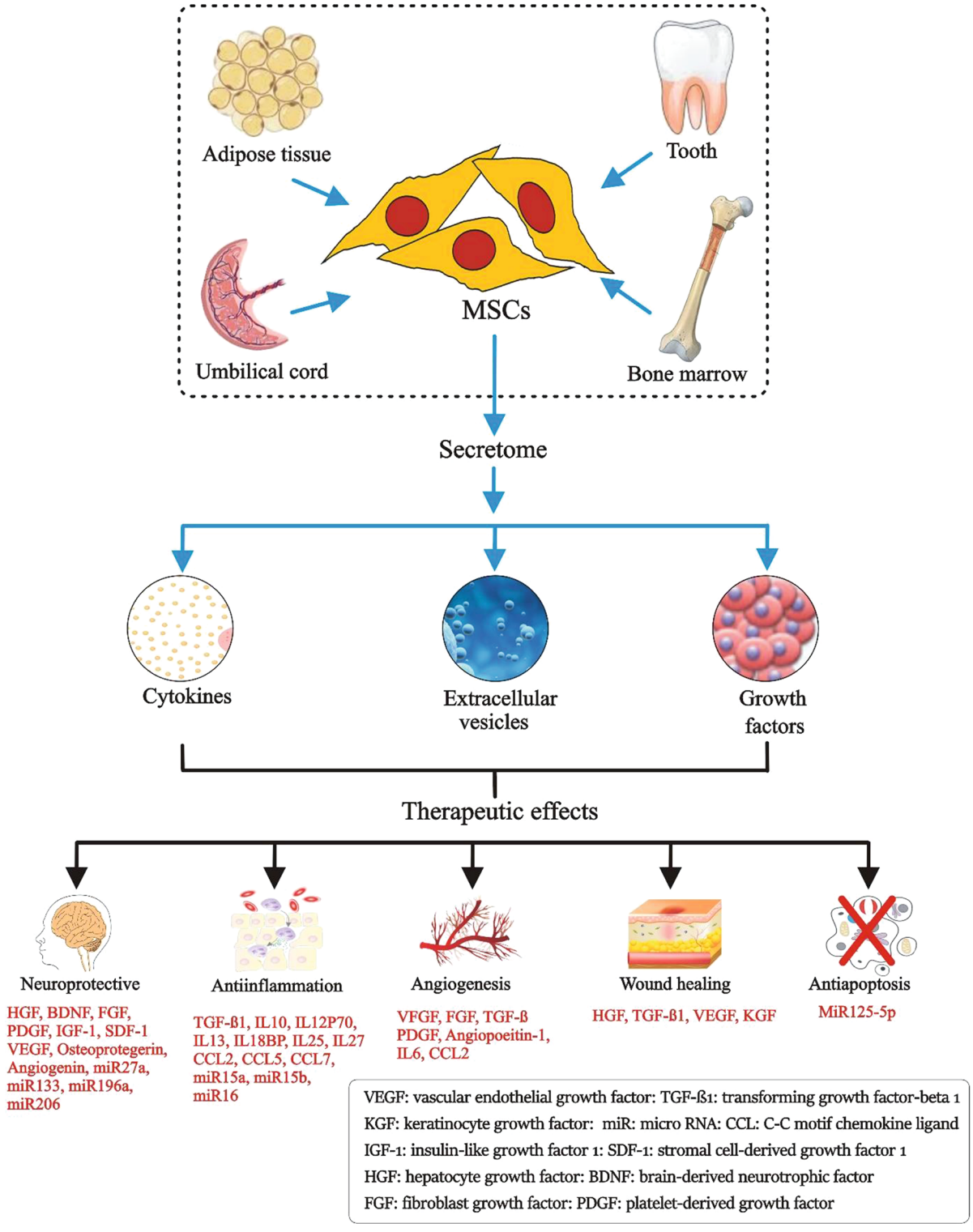


**Fig. 1** Sources, secretome composition, and therapeutic benefits of MSCs. MSCs can be obtained from several tissues, including the umbilical cord, BM, teeth, and AT. Prominent therapeutic applications of MSCs include neuroprotection, wound healing acceleration, angiogenesis induction, inflammation suppression, and prevention of cell apoptosis. This figure is modified by the corresponding author with permission from reference [44]

MSCs found in BM. Placental structures, including the amnion, amniotic fluid, and chorion membrane, as well as UC-derived components including UC, UC blood, and Wharton's jelly, constitute perinatal sources of MSCs [43]. MSCs isolated from BM, AT, and UC meet all essential requirements outlined by the International Society for Cellular Therapy (ISCT), such as specific morphology (adherence to plastic and spindle shape), expression of MSC surface markers (at least 95% positive for CD105, CD90, and CD73; less than 2% negative for CD45, CD34, CD19, CD13, CD11, and HLA-DR), and capability to differentiate into osteocytes, chondrocytes, and adipocytes [41].

MSCs obtained from adult or perinatal origins share basic properties and morphological similarities, research has shown that these cells are distinct from one another. According to the study, AT-MSCs exhibit low levels of Stro-1 and high levels of CD49d, with CD49d being more highly expressed in AT-MSCs than BM-MSCs [45]. BM-MSCs exhibit elevated CD133 expression, which is linked to metabolic processes, stem cell development, and regeneration. UC-MSCs have higher rates of attachment and proliferation than AT- and BM-MSCs due to the expression of CD146 [46]. Whereas AT-MSCs have a higher capacity for adipogenic differentiation, BM-MSCs are more likely to differentiate into osteogenic tissue [47]. Although UC-MSCs are capable of differentiating into osteocytes, adipocytes, and chondrocytes, their capacity for osteogenic differentiation is more pronounced in comparison to BM-MSCs [48]. However, the precise mechanism by which MSCs from various sources induce an immune response remains inadequately understood, necessitating extensive preclinical and clinical trial research.

Comprehending the distribution of MSCs after administration is essential for enhancing our understanding of their therapeutic mechanisms and ensuring their application in clinical trials. Preclinical data with different labeling strategies demonstrate that MSCs do not experience undesired homing, which could produce unfavorable outcomes. Human BMMSCs and AT-MSCs, when administered intravenously in a mouse model, were quickly captured in the lungs and recirculated throughout the body [49]. Human cells infused intravenously, on the other hand, exhibited prolonged persistence in numerous tissues after administration [50]. When MSCs were injected locally, they showed a preference for homing to specific tissues, with most of the injected cells being located in the renal cortex [51]. Research indicates that MSCs attract to and move toward the damaged area, as observed in the therapy for type 2 diabetes and intervertebral disc degeneration [52, 53]. Since MSCs are resident in the splenic or pancreaticoduodenal arteries, local distribution of MSCs by the intraarterial route is more efficient compared to IV.

MSCs have demonstrated efficacy in treating several diseases such as nervous system and brain problems, lung diseases, wound healing, and cardiovascular conditions, supported by extensive preclinical research and advances in clinical trial strategies [54, 55]. Extensive reviews and thorough studies have consistently shown that MSC-based therapy has high safety profiles and favorable results in various studied conditions [56]. Furthermore, the information that is currently available has identified several possible processes that might account for the advantageous impacts of MSCs, such as their capacity for differentiation, homing efficiency, trophic factor production (such as chemokines, cytokines, and growth factors), and immunomodulatory properties. However, because MSCs appear to have positive benefits independent of their source, it is still unclear which types of MSCs should be employed for particular diseases [57].

## Current and emerging clinical applications of MSCs in Human diseases

### Neurological diseases

Neurological impairments are typically considered irreversible as a result of restricted central nervous system (CNS) regeneration. The range of therapeutic alternatives for neurological disorders is limited in comparison to that of other conditions. Newly formed neurons in the hippocampus of adult humans and the migration of brain stem cells in animal models have both provided evidence to challenge the theory that brain cells are incapable of regeneration [58]. The preceding findings have generated anticipation regarding the potential of exogenous stem cell sources to restore or enhance the stem cell population in the brain, particularly in the context of neuronal diseases. Furthermore, conventional therapies for neurodegenerative disorders including autism, stroke, cerebral palsy, and spinal cord injury (SCI) are impeded by the brain and spinal cord's compromised regenerative capacity. In light of the inability of existing therapies to impede the advancement of these conditions, investigations have been conducted globally to analyze cell-based therapies, including the utilization of MSCs, as a potential treatment for neurodegenerative diseases. For stem cell treatment to effectively treat brain diseases, therapeutic cells must go to the damaged areas of the brain to replace, repair, or at least stop the degenerative effects of neuronal damage [59]. The ultimate goal of cell-based therapy is to transport the cells to the target site, activate the tissue repair mechanisms, and control immune responses via either paracrine effects or cell-to-cell contact [60]. MSCs are commonly utilized in many clinical trials focusing on a range of neurological disorders such as multiple sclerosis [61], stroke [62], SCI [63], cerebral

palsy [64], hypoxic-ischemic encephalopathy [65], autism [66], Alzheimer's disease (AD), Parkinson's disease, and ataxia [67]. Approximately two-thirds of these trials utilized MSCs primarily to treat multiple sclerosis, stroke, or SCI.

The most common form of cerebral disease is ischemic stroke [68]. MSCs exhibit the most promising potential for stroke therapy when compared to other forms of stem cells. Due to their immunomodulatory potential, neuroprotective, and neurogenic attributes, MSCs have been the subject of extensive research as a potential treatment for acute, subacute, and chronic stroke in numerous animal models [69]. In acute stroke, the inflammatory response is upregulated, destroying hypoxic tissue in the site of injury and the initiation of cytokine cascades that cause the enlargement of the damaged region, in addition to neuronal death. MSCs inhibit inflammation via the transport of the neuroprotective factor and their immunomodulatory capacity [70].

Furthermore, ischemic–reperfusion injury was prevented in damaged cerebral microvasculature by engrafting MSCs. One important factor contributing to the positive impact could be the mitochondrial transfer between external MSCs and impaired endothelial cells [71]. In addition to stabilizing the blood-brain barrier, MSCs may have therapeutic potential for functional enhancement following a stroke. Infusion of MSCs into various stroke models decreased the permeability of damaged neural tissue across the BBB [72]. According to the experimental findings, spinal cord injury (SCI) mice and rats treated with MSCs exhibited enhanced neural repair, neuroprotection, and neurogenesis-promoting trophic factors in the injured brain [73, 74]. It has been demonstrated that genetically modified MSCs increase hippocampal neurogenesis and improve cell homing to the site of injury in mice with TBI. The migratory capability of MSC-CXC-R4 in mice with TBI is also enhanced [75, 76]. One effective method is to increase the expression of anti-inflammatory substances like IL-4 or IL-10. These substances protect neural cells against inflammation and encourage microglia to display M2 markers [77].

MSC transplantation offers novel therapeutic prospects for AD. MSCs have demonstrated the ability to reduce A$\beta$ deposits and aberrant protein degradation, enhance acetylcholine levels, and promote neuronal survival in preclinical studies, ultimately enhancing spatial learning memory in animal models of AD [78, 79]. Furthermore, MSC transplantation in rodents with AD improves synaptic stability and stimulates hippocampal neurogenesis [80]. Significantly, MSC infusion controls neuroinflammation in the brains of AD patients by modulating the activation of microglia and astrocytes. A preclinical study has shown promising results in improving symptoms of AD, indicating great potential for using MSC therapy in individuals with AD [81]. Using the stereotactic cerebral infusion of MSCs in AD patients showed that the procedure was safe, practical, and devoid of major side effects [82]. Research has also demonstrated that MSC transplantation may improve motor dysfunctions associated with Parkinson's disease (PD) [83]. Behavioral experiments revealed that systemic infusion of human MSCs into rats with PD disorders decreased uncoordinated limb movement. A wide range of factors, including those secreted by exogenous MSCs, exhibit immunomodulatory characteristics, impede apoptosis, enhance neuronal survival, and distinguish between PD mice and rats [84, 85]. The amount of tyrosine hydroxylase (TH) and the number of DA neurons in the injured region were measured after MSC transplantation to the brains of PD mice.

Furthermore, the primary objective of therapies for Amyotrophic Lateral Sclerosis (ALS) disorders is to reduce inflammation; thus, cell-based therapies employing ALS with immunomodulatory properties hold promise for the treatment of ALS [86]. According to preclinical research, MSC transplantation modulates the immune response associated with MS disease. Transplanted MSCs diminish microglial activation and enhance neuroprotection by maintaining a favorable microenvironment through the release of several anti-inflammatory cytokines and neurotrophic factors [87]. In MS animal models, it has been shown that MSC infusion promotes oligodendrogenesis, enhances remyelination, and increases nerve conduction velocity [88]. A few patients with progressive MS who received autologous MSC infusions experienced a marginal improvement in their neurological disability. By inhibiting dendritic cells and T1 lymphocytes, inducing microglia with a phenotype transition from M1 to M2, and increasing the levels of anti-inflammatory cytokines in MS patients following MSC infusion, the immunomodulatory effect of MSCs was validated [89].

Another phase 2 trial, conducted by Connick et al., assessed the safety and feasibility of autologous BM-MSCs in secondary progressive MS, showing promising results in terms of safety and some improvement in visual function [90]. Moreover, in a randomized, double-blind phase 2 trial (MESEMS) conducted across several centers in Europe, the use of autologous MSCs derived from bone marrow was evaluated. The study found that MSC treatment was associated with a reduction in the number of new gadolinium-enhancing lesions on MRI and suggested possible clinical benefits [91]. A more recent study by Uccelli et al. evaluated the long-term safety and efficacy of MSC treatment in MS patients. The results indicated that MSCs could provide sustained immunomodulatory effects and improve clinical outcomes over an extended period [92].

These studies collectively underscore the potential of MSCs as a therapeutic option for MS, highlighting their safety profile and potential to modulate the disease course. However, it is crucial to note that further research, particularly larger and more comprehensive phase 3 trials, is needed to establish the definitive clinical efficacy and to standardize protocols for MSC therapy in MS.

Several clinical trials have utilized autologous BM-MSCs to treat neurological disorders, with some demonstrating enhanced outcomes and safety [93]. One study from 2005 indicated that stroke patients treated with MSCs had a higher Barthel index (BI). Autologous BM-MSCs increased in vitro and enhanced the patient's modified Rankin Scale (mRS), according to a follow-up investigation [94, 95]. In a current randomized controlled trial, autologous BM-MSCs administered with autologous serum were found to be safe; however, no enhancements in modified Rankin Scale scores were observed [62].

A 5-year follow-up study revealed that motor function scores significantly improved in the MSC group [96]. Patients diagnosed with chronic stroke have demonstrated a notable enhancement in both the BI score and the National Institutes of Health Stroke Scale (NIHSS) following a single intravenous administration of allogeneic BM-MSCs [97]. BM-MSCs are limited by the invasive nature of BM aspiration, which may lead to problems in elderly and pediatric patients [98]. UC-MSCs are being investigated as a substitute for treating neurological conditions in about 1550 individuals globally [99]. A recent study demonstrated that administering UC-MSCs enhanced gross motor function and cognitive abilities in cerebral palsy patients. The effects peaked at 6 months post-administration and persisted for 12 months after the initial transplantation [100].

#### Cardiovascular diseases

Cardiovascular diseases (CVDs) are a significant cause of the global disease burden because of their high rates of morbidity and mortality [101]. Infectious and noninfectious factors contribute to the development of CVDs. Infectious CVD encompasses conditions such as rheumatic heart disease, HIV-induced disease, and tuberculous pericarditis. Noninfectious CVD includes hypertension, stroke, peripheral artery disease, and myocardial infarction (MI). The prevalence of CVD due to noninfectious causes, particularly ischemic CVDs like MI, is expected to rise in the future [102]. Significant progress has been made in the past 20 years in the advancement of innovative cardiovascular research and regenerative medicine, particularly in stem cell technologies [103]. Owing to the potential for immaturity and teratoma formation, human embryonic stem cells and human induced pluripotent stem cells (hiPSCs) are not clinically applicable in the treatment of CVD, despite their therapeutic potential [104, 105]. Under the influence of paracrine effects, stem cells, including adult stem cells and progenitor cells, are capable of inducing myocardial repair after administration [106]. MSCs are crucial in treating CVD because of their unique characteristics such as their capacity to transform into cardiovascular cells, immunomodulatory abilities, anti-fibrotic properties, and capability to engage in neovasculogenesis [107]. The positive outcomes of MSC-based treatment in preclinical research on cardiac diseases improve understanding and support further investigation of its safety and effectiveness in clinical trials [108, 109].

After transplantation, MSCs exhibit a zonal distribution in myocardial tissue comparable to that of cardiac myocytes. They transform into cardiomyocytes by increasing the expression of myocardial-specific marker proteins such as troponin T. Perivascular cells from human UC aggregate on cardiomyocyte feeder layers within one week, producing contracting cell clusters [110]. MSC migration and survival can be stimulated in vitro by basic fibroblast growth factor (bFGF), thereby preventing adverse remodeling and restoring cardiac function [111]. Another method for inducing cardiac differentiation is to separate and amplify high-purity MSCs within cardiomyocytes while simultaneously stimulating them with bFGF and hydrocortisone [112]. Genetically engineered MSCs can differentiate into cells resembling cardiomyocytes, and their main impact on treating CVD is largely reliant on their paracrine function [113]. MSCs modulate the immune system by inhibiting specific types of white blood cells, such as T lymphocytes and B lymphocytes, and reducing inflammation [114]. Following MI, monocytes move to the site of infarction and undergo differentiation into macrophages. These cells release growth factors, chemokines, and cytokines to eliminate apoptotic neutrophils and infarct myocardial cells (Fig. 2). The process of activating macrophages results in the production of various cell types with distinct immune functions. Specifically, M1 macrophages generate tumor necrosis factor, interferon, and interleukin-23, while M2 macrophages are activated and induced by Th2-related cytokines or glucocorticoids, which in turn promote angiogenesis and cell proliferation [115]. MSCs have been shown to reduce the amount of proinflammatory monocytes with moderately or increased Ly6C levels, as well as the severity of myocarditis [116]. In vitro, the inflammatory response is inhibited by the interaction between macrophages and MSCs, which increases the expression of the anti-inflammatory cytokine IL-10 and CD206 [117]. Additionally, MSCs regulate the immune system via paracrine mechanisms, including the downregulation of IL-1, TNF-α, and IL-6 expression

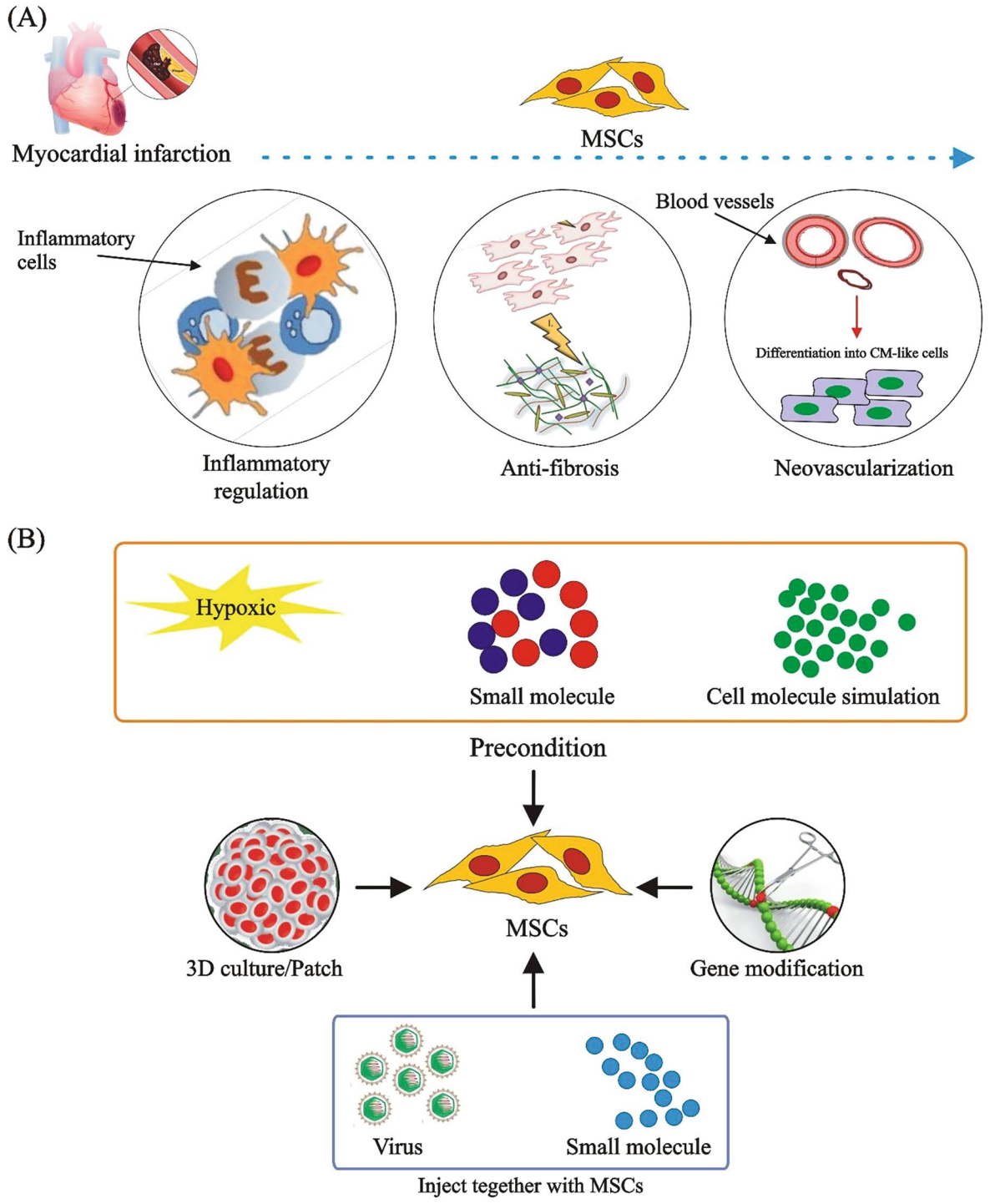


**Fig. 2** (**A**) MSCs treat CVD by regulating inflammation, preventing fibrosis, promoting neovascularization, and differentiating into cardiomyocyte-like cells. (**B**) Approaches to improve the therapeutic impact of MSCs in CVD. To improve the therapeutic effects of MSCs, techniques such as 3D culture, patches containing MSCs, preconditioning with hypoxia or chemicals, gene modification, and viral injections combined with small compounds or shRNA have been employed. This figure is modified from reference [107]

and the enhancement of cardiac function in mice with MI [118, 119].

In recent studies, preconditioning has shown significant promise in enhancing the therapeutic efficacy of treatments. Preconditioning refers to a process where cells are exposed to specific conditions or stimuli to improve their survival, integration, and function post-transplantation. This process is crucial for improving

outcomes in various regenerative therapies. Gene modifications have emerged as a powerful tool to enhance the therapeutic potential of multiple treatments [120]. By altering specific genes, researchers can improve cell function, increase resistance to apoptosis, and promote tissue regeneration. Recent advancements in CRISPR technology have further accelerated progress in this field [121].

Moreover, 3D patches have been developed to provide structural and functional support to damaged tissues. These patches are designed to mimic the extracellular matrix, offering a conducive environment for cell growth and integration. Studies have demonstrated the effectiveness of 3D patches in promoting tissue repair and regeneration [122, 123]. Co-injections with small molecules and viruses are being explored to enhance the delivery and efficacy of therapeutic agents. Small molecules can modulate cellular pathways to promote survival and function, while viral vectors can facilitate targeted gene delivery. This combination has shown potential in various preclinical models [124, 125] Fig. 2.

MSCs can modulate matrix metalloproteinase activity, suppress fibroblast activation, decrease extracellular matrix accumulation, and enhance myocardial function. The Hepatocyte Growth Factor (HGF), produced by MSCs, is a potent inhibitor of fibrosis and is the main factor responsible for its anti-fibrotic impact in vitro [126]. Additionally, MSCs fight fibrosis by blocking miR-155-mediated profibrotic signaling and releasing HGF when they come into direct contact with other cells [127]. The antifibrotic effects of gene-modified MSCs are more pronounced, as evidenced by the overexpression of miR133 in MI and IGF-1 in mice [128]. MSCs overexpressing miR133 decreased fibrosis in MI by suppressing Snail 1, a key controller of epithelial-to-mesenchymal transition (EMT), and promoting fibrosis in developmental and pathological conditions [129]. Native perivascular cells include MSC markers on their surface, which suggests that blood vessel walls contain a reservoir of progenitor cells. According to in vivo research, transplanted BMSCs can develop into endothelial cells, which increases microvascular density and enhances cardiac function in MI rat models [130]. Some researchers suggest that transplanted BMSCs facilitate angiogenesis and cardiac repair by releasing arteriogenesis factors and angiogenesis factors through indirect paracrine signaling [131]. To promote vascular repair and prevent the deterioration in heart function, BMSC transplantation combined with vascular endothelial growth factor (VEGF) treatment resulted in a considerable increase in vascular density and a decrease in collagen content [132]. MSCs also enhance angiogenesis through paracrine mechanisms, such as cardiac MSC-secreted exosomes enhancing cardiomyocyte proliferation and capillary density [133].

Chronic heart failure was initially investigated and treated with MSCs in the Cardiopoietic Stem Cell Therapy in Heart Failure (C-CURE) trial. The trial demonstrated enhancements in cardiovascular metrics, quality of life, functional status, and physical health [134]. In the CHART-1 trial, the treatment was unable to attain the desired primary outcomes [135]. The POSEIDON experiment showed that allogeneic BM-MSCs were more effective than other sources [136]. The MSC-HF trial and TRIDENT research both showed favorable results of BMMSCs in treating heart failure [137, 138]. UC-MSCs are promising allogeneic cells for treating CVD due to their ease of isolation, fast proliferation, and secretion of hepatocyte growth factors that play a role in cardiovascular regeneration and cardioprotection [139]. The RIMECARD trial, a pilot study involving 30 patients with heart failure, was the first reported trial to demonstrate the effectiveness of UC-MSCs. The results showed improvements in ejection fraction, left ventricular function, functional status, and quality of life in patients who received UC-MSCs [140]. Promising results from the HUC-HEART experiment in phases I and II indicated enhancements in LVEF and decreases in the size of the damaged myocardium area [141]. UC-MSCs with a collagen scaffold, however, did not significantly reduce the quantity of fibrotic scar tissue in patients with ischemic heart issues in a recently reported phase I randomized experiment [142]. The safety and feasibility of MSCs from AT, BM, and UC in treating CVD have been established. However, the relationship between the kinds of MSCs and their therapeutic effectiveness remains unclear due to varying outcomes in different clinical studies. Thus, the utilization of MSC-based therapy in CVD is still in its early phase, offering prospective advantages to patients. Large-scale, well-organized randomized clinical trials are therefore required to confirm the therapeutic potential of MSCs derived from various sources and to improve our understanding of cardiovascular regeneration after treatment.

#### Respiratory diseases

Over the past decade, there have been notable increases in the prevalence of respiratory diseases attributed to factors including air pollution, smoking habits, the aging of the population, and more recently, respiratory virus infections like coronavirus disease 2019 (COVID-19). These developments have placed considerable strains on healthcare systems and public health systems on a global scale [143]. In recent years, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), and bronchopulmonary dysplasia (BPD) have emerged as the three most prevalent inflammatory pulmonary diseases in infants and adults [144]. Airway remodeling, inflammatory cell infiltration, alveolar

structural integrity disruption, alveolar fluid clearance impairment, cytokine release, related cytokine storms, as well as the development of pulmonary fibrosis are typical pathological features associated with these conditions. Conventional therapies employ surfactants, mechanical ventilation, artificial respiratory support, antibiotics/anti-inflammatory medications, and surfactants to lessen symptoms and hinder the disease's progression. The impaired pulmonary epithelial cells and airway destruction, as well as other pathological respiratory system damages induced by the inflammatory response, remain largely unaffected by conventional drug interventions [144]. As a result of their ability to proliferate, differentiate in multiple directions, and exert immunoregulatory effects, stem cells, and MSCs in particular, have demonstrated tremendous therapeutic potential. Multiple systemic or endotracheal MSCs have demonstrated significant therapeutic effects against a variety of respiratory inflammation diseases, according to several preclinical investigations [145, 146].

Due to their inherent characteristics, MSCs can be utilized to treat common inflammatory diseases of the respiratory tract. For instance, immunological compatibility permits MSC transplantation to pass across histocompatibility obstacles, which infrequently results in an immune response [147]. Additionally, similar to endogenous MSCs, exogenously imported MSCs can migrate to impaired tissues via the SDF-1-CXCR4 axis. This migration is mediated by stromal cell-derived factor-1 (SDF-1), which is generated by the damaged lung tissue and binds to the MSC's C-X-C motif chemokine receptor 4 (CXCR4) [148]. Moreover, MSCs are capable of differentiating into type II alveolar epithelial (ATII)-like cells, secreting a variety of bioactive molecules with immunomodulatory properties that can promote tissue regeneration, and inhibiting immune cells via cellular interactions. Immunomodulatory substances can alter macrophages from M1 to M2 phenotype, hinder the migration of macrophages, neutrophils, and monocytes, impede the development of TH17 and TH1 cells, and encourage the generation of $T_{reg}$ cells [149]. The pulmonary vascular endothelial cells and alveolar epithelial cells can be protected from harm by growth factors [150]. The full extent of MSC differentiation capability has not been thoroughly examined. MSCs have been shown to differentiate into myofibroblasts and worsen pulmonary fibrosis in specific experimental settings. Therefore, it is crucial to identify suitable cultural conditions that guide MSC differentiation in the desired direction [151]. Furthermore, the secretome of MSCs is thought to be the primary mechanism by which MSCs can function in lung damage, as it plays a significant role in immunomodulation and tissue regeneration (Fig. 3). Cell-to-cell communication enables MSCs to modulate cell proliferation and the secretion of diverse immune cells additionally. TSG6 and PGE2, which are released by MSCs, can modify the inflammatory phenotype of macrophages [152]. Macrophages can ingest extracellular vesicles (EVs) released by MSCs containing active mitochondria that increase oxidative phosphorylation, hence improving their anti-inflammatory properties. In preclinical lung disease models, MSCs have also been shown to hinder neutrophil infiltration in a manner dependent on IDO [153, 154]. MSCs also can indirectly regulate adaptive immune cells

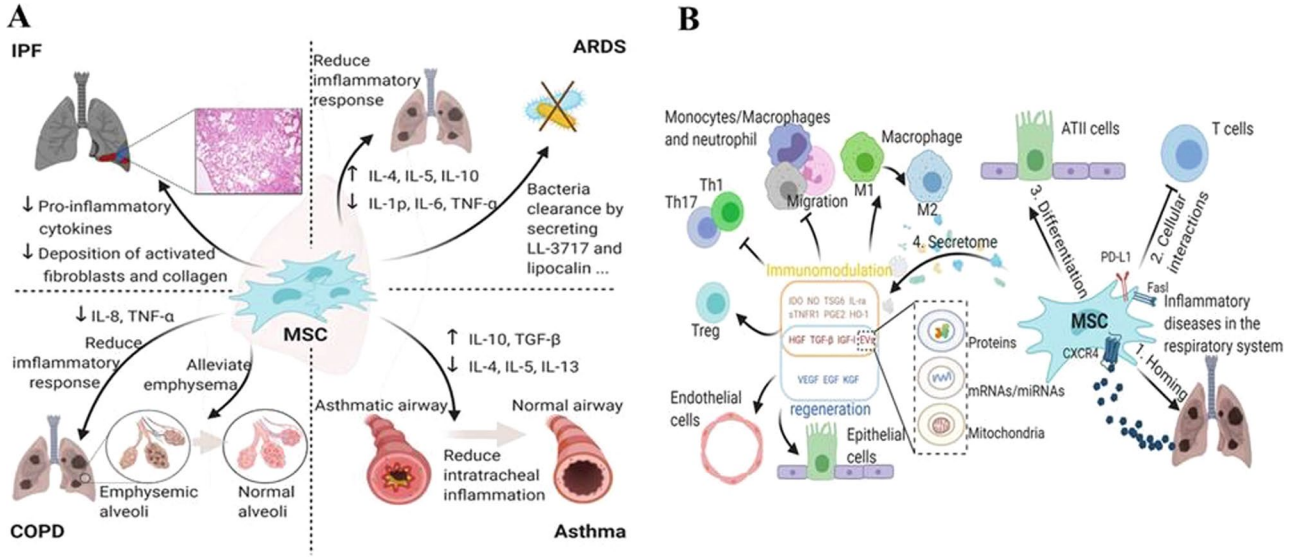


**Fig. 3** (**A**) The primary functions of MSCs in asthma, ARDS, idiopathic pulmonary fibrosis (IPF), and COPD. (**B**) Characteristics of MSCs in common respiratory inflammatory diseases. This figure is adapted and is freely accessible online from reference [163], Licensed under a Creative Commons Attribution 4.0 International License (CC BY 4.0)

by modulating innate immune cells [152]. For instance, MSCs can transform mature DCs into a suppressing immature phenotype and stimulate the development of IL-10-positive pDCs (plasmacytoid DCs), which inhibit effector T-cells and generate Treg cells [155]. MSCs are capable of directly inhibiting effector T-cells via the secretion of anti-inflammatory molecules, including IL-1ra, IDO, and PD-L1. Furthermore, MSCs activated by proinflammatory cytokines can generate ligands, such as CXCL9, CCL5, and CXCL11, for the CXC-chemokine receptor 3 (CXCR3) and the CC-chemokine receptor 5 (CCR5). In addition to secreting IDO/iNOS, which inhibits T cells in their vicinity, these chemokines also attract T cells to MSCs [152, 156]. In asthma, MSCs can attenuate airway hyperresponsiveness and reduce inflammation by modulating the activity of T cells and other immune cells [157].

Similarly, in ARDS, MSCs contribute to the repair of damaged alveolar epithelium and mitigate inflammation through the secretion of anti-inflammatory cytokines and growth factors [158]. In the case of IPF, MSCs help in reducing fibrosis by inhibiting fibroblast proliferation and differentiation, thus slowing down the progression of the disease [159]. For COPD, MSCs can enhance lung function and repair by reducing oxidative stress and inflammation, and by promoting the regeneration of damaged lung tissues [160].

The characteristics of MSCs in common respiratory inflammatory diseases further underscore their therapeutic potential. MSCs are characterized by their ability to migrate to the sites of inflammation and injury, where they exert their reparative functions. They can differentiate into various cell types, including epithelial cells, which is particularly beneficial for lung repair. MSCs also secrete a wide array of bioactive molecules, such as IL-10, TGF-β, and HGF, which play pivotal roles in modulating immune responses and promoting tissue regeneration [161]. Additionally, MSCs exhibit low immunogenicity, allowing for allogeneic transplantation without eliciting significant immune rejection [162]. This makes MSCs an attractive option for developing cell-based therapies for respiratory inflammatory diseases, offering hope for improved outcomes and quality of life for patients suffering from these chronic and often debilitating conditions (Fig. 3).

Extremely premature infants have lung development issues before alveolarization and pulmonary maturation, leading to BPD [164]. These newborns need specialized care for the initial three months, which includes interventions after birth. Continued infections impede the development of the lungs even further [165]. Several clinical trials involving the recruitment of 566 premature infants from around the globe have been proposed to utilize UC-MSCs for the treatment of BPD. Due to their accessibility, minimal antigenicity, rapid proliferation, regenerative capacity, and ethical implications, human UC tissue and its derivatives are exceedingly desirable cell sources for MSCs in treating BPD. Using MSCs derived from UC blood, Chang et al. prevented BPD in nine premature infants [166]. All individuals survived, with only three individuals developing BPD. The severity was significantly less in the infants than in the control group. Unrelated to the intervention, a follow-up analysis discovered one infection after discharge. All eight remaining patients survived with normal lung function, demonstrating the safety of the treatment. MSC treatment was safe in preterm infants, according to a phase II clinical research comprising 66 infants between the ages of 23 and 28 weeks. However, because of the limited sample size, statistical analysis could not support the trial's efficacy. Patients with severe BPD born between 23 and 24 weeks showed a significant improvement in severity compared to those born at 25–28 weeks [167]. Consequently, larger, controlled trials are required to verify the efficacy of MSCs derived from UC blood in the treatment of BPD.

COPD is a common lung condition characterized by ongoing symptoms and restricted airflow. The condition is a result of chronic bronchitis, deterioration of lung tissue, alterations in immune cell function, oxidative stress, and imbalances in protease activity [168]. The objective of MSC therapy for COPD is to stimulate the parenchymal cell and alveolar structure regeneration to restore lung function. Research indicates that MSCs can help relieve symptoms of emphysema and inflammation, enhance treatment outcomes in experimental COPD, decrease neutrophil infiltration and cell death, enhance elastic fiber content, and lower levels of keratinocyte-derived chemokines [169, 170]. Five clinical trials have utilized BM-MSCs as stem cells for treating COPD, however, the outcomes did not demonstrate notable therapeutic benefits [171–173]. After three years of administering BM-MSC, a phase I trial demonstrated a decrease in the progression of COPD pathology [171]. UC-MSCs have recently been identified as possible allogeneic stem cell options for treating COPD [174]. A preliminary clinical investigation established the potential efficacy and safety of UC-MSC allogeneic administration for COPD treatment [175]. Cell-based therapy was administered to 20 patients who had a documented history of smoking in one of the studies. Six months after treatment with UC-MSC, the number of pulmonary exacerbations and patient scores on COPD assessment tests decreased significantly. At three months following administration, the mean FEV1/FVC ratios, as well as the SGRQ scores and 6MWTDs, improved in the second experiment utilizing UC-MSCs [176]. The number of clinical trials employing UC-MSCs to treat COPD is consistently rising,

incorporating stronger designs and larger sample sizes. This accumulation of data provides strong support for the prospective applications of UC-MSCs. However, comprehensive evaluations of their efficacy are still in their early stages [177].

Acute respiratory distress syndrome (ARDS) is a serious respiratory disease that is defined by progressive lung failure as a result of lung tissue alterations brought on by both infectious and noninfectious agents. There are currently 13 registered clinical trials using MSC treatment for patients with ARDS. Despite their early stages and small sample sizes, all of them were able to effectively evaluate the safety of administering MSCs and the effectiveness of treatment in terms of clinical outcomes, such as hemodynamics, inflammation, and respiratory and systemic parameters. MSC injection has been shown in multiple recent clinical trials to alleviate ARDS symptoms in COVID-19 patients [178, 179]. However, this clinical research exhibits significant variation concerning inclusion and exclusion criteria, duration of follow-up, dose of MSC, source, mode of administration, and frequency of treatment, similar to the majority of experimental trials [180]. To target the pathogenic mechanism of SARS-CoV-2, MSCs have the potential to be utilized as a cell therapy to treat COVID-19. As previously indicated, the patient will experience tissue damage as a result of the immune system's overreaction to COVID-19. Additionally, MSC therapy can reverse the complicated cytokine storm by promoting endogenous tissue repair of injured tissues through its stem cell repair characteristics and lowering the amount of several inflammatory factors, including TNF-α [181, 182]. MSCs have the potential to restore the pulmonary microenvironment, impede pulmonary fibrosis progression, protect alveolar epithelial cells, and provide a remedy for both COVID-19 pneumonia and lung dysfunction [183]. Numerous case studies and clinical research have demonstrated that MSCs are safe and efficient in treating COVID-19 patients, particularly acute patients, by enhancing their clinical symptoms and immune system performance [184]. In a phase 2 trial, Shi Land and colleagues demonstrated the safety and effectiveness of using human UC-MSCs in treating severe COVID-19 patients [185].

While BM- and AT-MSCs have shown similar modes of action and therapeutic potential, UC-MSCs have become more prominent as viable options for the treatment of lung diseases because of their superior immune regulation, ease of production as "off-the-shelf" products, non-invasive isolation techniques, quick proliferation, and anti-inflammatory properties [175]. However, larger-scale phase III clinical trials using multiple MSC sources and therapy of pulmonary disease are necessary to provide further evidence for this hypothesis [186].

**Endocrine disorders**

The human body regulates its functions and maintains homeostasis through an intricate network of endocrine glands that produce and release various hormones. The endocrine system controls physiological processes such as heart rate, bone growth, reproductive function, and metabolism [187]. Dysregulation of the endocrine system is a critical factor in the pathogenesis of various metabolic disorders, including diabetes, growth disorder, thyroid disease, sexual dysfunction, and reproductive dysfunction [188]. Utilizing adult stem cells as a template for organ and tissue regeneration constitutes the fundamental principle of regenerative medicine. Endocrine signals include growth factors, hormones, and cytokines, as well as nervous system microenvironmental stimuli (quick reaction), which tightly govern the actions of these stem cells. Using a symphony of signals, this coordinated and harmonized system directly controls tissue homeostasis and post-injury repair. Disruption of these intricate networks causes an imbalance in tissue regeneration and homeostasis, which can result in the emergence of endocrine disorders in humans, including diabetes, Asherman syndrome, premature ovarian failure (POF), and sexual hormone deficiency [189].

Over the past few years, the most significant obstacles in endocrinology research have been obesity and diabetes (specifically type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM)). To address these issues, MSCs are being investigated as a novel therapeutic strategy [190]. T1DM is distinguished by the autoimmune disintegration of β-cells in the pancreas; conversely, T2DM is caused by the dysfunction of pancreatic insulin-producing cells and insulin resistance [191]. To stabilize the blood glucose levels of patients, regenerative medicine attempts to supply an exogenous cell source for the replacement of damaged or absent β-cells [192]. Three trials utilizing allogeneic AT-MSCs (NCT03920397), autologous BM-MSCs (NCT01068951), and allogeneic BM-MSCs (NCT0069066) have been completed among the numerous clinical trials utilizing MSCs to treat T1DM. Notably, UC-MSCs emerged as the preferred MSCs in the subsequent trials. Without any adverse events, all published studies have verified the safety of MSC treatments in the therapy of T1DM [193]. The initial trial utilizing autologous BM-MSCs demonstrated that patients in the MSC-administration group exhibited elevated C-peptide levels following a mixed-meal tolerance test (MMTT) compared to the control group [194]. Six months following therapy, autologous AT-MSCs and vitamin D administration were safe and resulted in improved HbA1C levels [195]. Wharton's jelly MSCs (WJ-MSCs) were the primary MSCs utilized in treating new-onset T1DM. Results demonstrated a notable enhancement in C-peptide and HbA1C levels at

three and six months after treatment compared to the control group [196]. Allogeneic WJ-MSCs, when combined with autologous BM-derived mononuclear cells, enhanced insulin production and decreased insulin needs in patients with T1DM [197]. Regarding T2DM, there are few trials utilizing MSCs for treatment, and their results indicate that MSCs are safe, as no severe side events were reported during these investigations [198]. MSC treatment was found to decrease HbA1C and fasting blood glucose levels while increasing C-peptide levels. However, these impacts were temporary, and several administrations were necessary to sustain the benefits of MSC. The autologous MSC method for treating diabetes patients is hindered because BM- and AT-MSCs obtained from diabetic patients exhibit decreased stemness and functional traits [199, 200]. Furthermore, there is a significant correlation between the durations of obesity and diabetes and the metabolic function of autologous BM-MSCs, in particular, mitochondrial DNA accumulation and respiration. These factors directly disrupt the operations of BM-MSCs and diminish the therapeutic efficacy of the approach [199]. With regards to AT-MSCs, the impairment of their therapeutic effects can be attributed to the detrimental impacts of T2DM, given the direct involvement of adipose tissue in lipid and glucose metabolism as well as appetite regulation [201]. Therefore, it is not recommended to use autologous AT-MSCs for treating metabolic diseases like T2DM (Fig. 4). Instead, employing MSCs from healthy donors in an allogeneic strategy is suggested as an option for stem cell therapy in treating diabetes patients.

### Infertility

Modern society is experiencing a growing issue of infertility, characterized by the failure to conceive after over 1 year of unprotected intercourse [202]. This issue has become a significant global health concern and social burden. In vitro fertilization technology and assisted

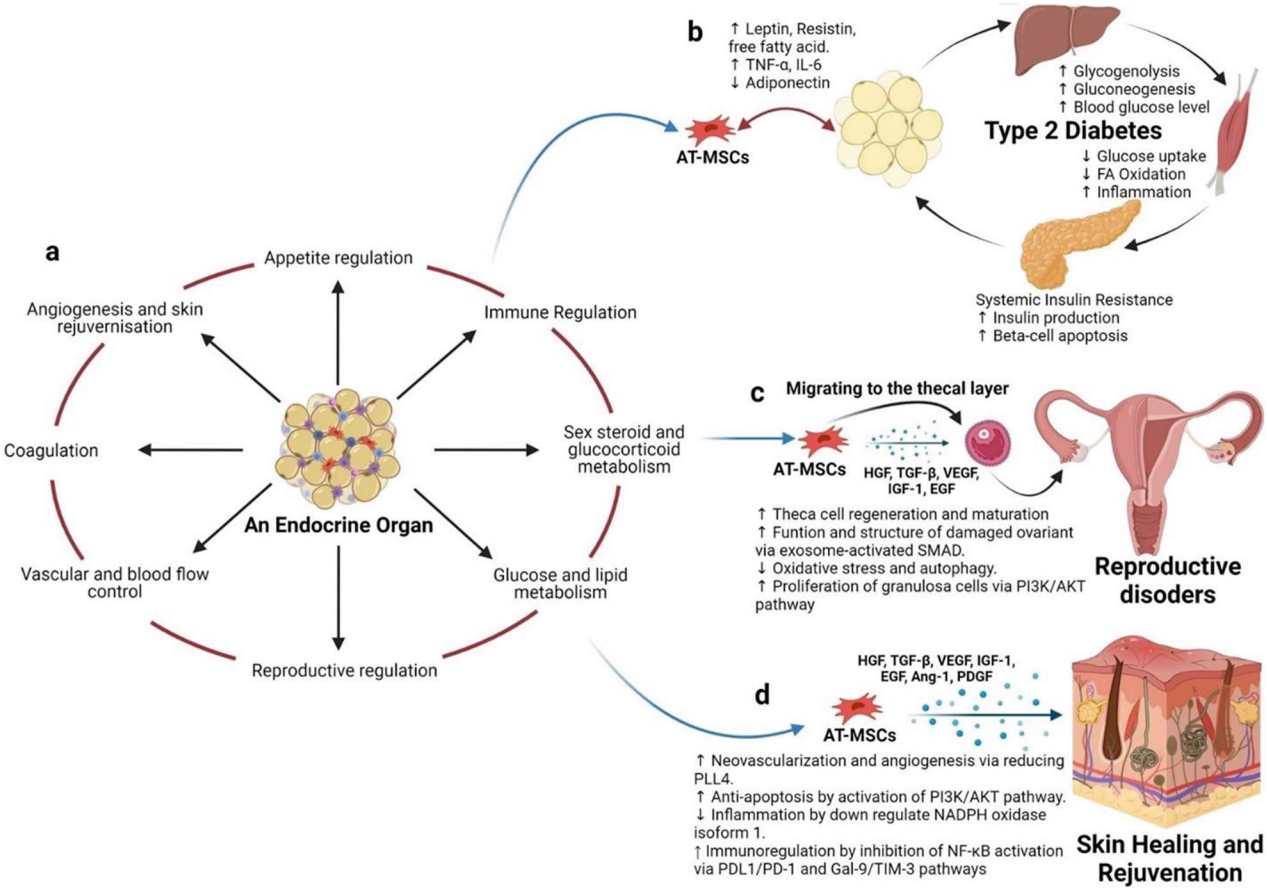


**Fig. 4** (**A**) AT, which supports and regulates numerous functions, is regarded as an endocrine organ. (**B**) T2DM affects AT's function in lipid and glucose metabolism as well as appetite regulation, rendering autologous AT-MSCs inappropriate for treating metabolic disorders. Healthy donor-derived allogeneic AT-MSCs may therefore represent a more viable alternative. (**C**) AT-MSCs are effective in treating reproductive disorders owing to their capacity to migrate and establish a microenvironment within the damaged ovary, enhance cell regeneration, and regulate growth hormones. (**D**) AT-MSCs promote skin healing and regeneration by supporting neovascularization, angiogenesis, anti-apoptosis, inflammation regulation, and immunoregulation. This figure is adapted and is freely accessible online from reference [40], Licensed under a Creative Commons Attribution 4.0 International License (CC BY 4.0)

reproductive techniques are highly effective methods for treating human infertility. However, their application is restricted due to limitations such as the inability to be used in patients with no sperm or those who cannot support pregnancy implantation, associated complications, time-consuming and costly procedures, and ethical concerns in some regions [203]. Infertility can be associated with several diseases such as POF, endometrial dysfunction, nonobstructive azoospermia, and Asherman syndrome. Stem cell-based therapies have recently shown promise in preclinical studies for reestablishing reproductive function. Recent investigations on MSCs offer promising prospects for individuals with reproductive and infertility diseases [204].

POF is defined as the loss of ovarian function in middle age (before 40 years old) and affects 1–2% of women during their reproductive years [205]. Patients with POF have oligo/amenorrhea for a minimum of four months and raised levels of follicle-stimulating hormone (FSH) above 25 IU/L on two occasions more than one month apart. POF has been attributed to a variety of factors, including idiopathic and iatrogenic situations, environmental conditions, genetic backgrounds, and autoimmune disorders. Hormone replacement therapy, psychosocial support, and fertility management can all be used to treat POF, although their efficacy is restricted [206]. In preclinical investigations employing chemotherapy-induced POF animal models, MSCs derived from BM, AT, and UC were utilized to treat POF, resulting in enhancements in ovarian function. The initial POF trial, which utilized BM-MSCs as the primary cell source, was a single case report detailing the successful treatment of a perimenopausal woman. The woman experienced enhanced follicular regeneration, and elevated AMH levels, leading to a successful pregnancy, and the birth of a healthy infant [207]. Examination of two women with POF utilizing autologous BM-MSCs showed a rise in initial estrogen levels and the size of the treated ovaries, as well as improvement in menopausal symptoms [208]. A laparoscopy and a BM aspiration were the two invasive clinical procedures used in this early study on participants. Two trials were carried out using a similar technique on Thirty patients (aged 18–40) and ten women with POF (aged 26–33) [209]. A subsequent study examined two distinct methods of cell administration, via the ovarian artery and laparoscopy, although the findings have not been disclosed yet [209]. An autologous stem cell ovarian transplantation (ASCOT) trial was initiated utilizing BM-derived stem cells in response to the favorable results observed in the mouse model. Notable advancements in ovarian function were documented through an ASCOT trial, which yielded three healthy infants, greater AFC and AMH levels in 81.3% of individuals, and six pregnancies [210]. A randomized experiment (NCT03535480) was carried out on 20 patients with POF under the age of 39 to provide more detailed information on the findings of the ASCOT trial [211]. There are currently no completed trials using UC- or AT-MSCs to treat POF patients, which makes it difficult to evaluate these MSCs in POF treatment. POF is an uncommon disorder that impacts 1% of women under 40 years old. Furthermore, advancements in assisted reproductive technology have provided patients with a variety of alternative strategies to facilitate the restoration of reproductive function [212].

#### Skin burns and wound healing

Burns rank as the fourth most prevalent injury globally, impacting around 11 million individuals and serving as a significant contributor to mortality with 180,000 deaths reported annually. Burns are typically categorized into varying degrees of burns (first, second, third, and fourth) according to the burn location, burn depth, percentage of surface area burned, and patient age [213]. The efficacy of treatment and the extent of burn severity are determinants of postburn recovery. In patients with extensive burns, the long-term consequences may include scar formation and disability, whereas the process of recovery can progress from weeks to months. Burn injury, in contrast to mechanical injury, is an invasive development of tissue injury at the site of the burn, including biological damage that causes prolonged severe inflammation by spontaneous apoptosis, reduced tissue perfusion, and oxidative stress as well as mechanical damage to the skin's surface [214]. Currently, stem cell therapy offers patients with burn injuries an alternate treatment option since it is not possible to fully reverse the devastating damage caused by severe burns. In addition to demonstrating the therapy's safety, the initial case report of BM-MSCs used to treat burns on 40% of the body (a 45-year-old patient) revealed partial improvements in wound site vascularization and a reduction in irregular cicatrices [215]. Autologous or allogeneic BM-MSCs were then sprayed over burn sites or added to a dermal matrix sheet to cover wounds in further treatments for patients with deep burns, second-and third-degree burns, and other types of burns. The outcomes of these case studies demonstrated MSC-based therapy's potential effectiveness, which reduced pain, increased blood flow, and sped up wound healing without increasing the risk of infection [216]. In 2017, a study using autologous BM-MSCs or UCMSCs shortened the length of hospital stay and increased the healing rate in 60 patients who had burned between 10 and 25% of their total body surface [217]. The invasive harvesting technique, which induces discomfort and potentially leads to complications in patients, is a limitation of BMMSCs when used to treat burns. Therefore, the preferred therapeutic approach is to utilize

allogeneic MSCs derived from healthy donors; AT- and UC-MSCs are two viable candidates for this purpose. To date, few clinical trials involving MSC therapy have been carried out. The design of this research presents several challenges, including the lack of blinding and a negative control group, limited sample sizes, and the application of standardized measuring tools for burn damage and wound healing. AT-MSCs are now being utilized in seven current phase I and II studies for the treatment of burns. Therefore, it is critical to note that after extensive research, ATMSCs exhibit certain benefits in comparison to BM-MSCs when derived from an allogeneic source; however, their efficacy in the treatment of burns is yet to be determined. The optimal MSCs for burn tissue regeneration are not identified. Our observation suggests that AT-MSCs are more advantageous because of their biological properties, which promote the production of secretion and keratinocyte profiles that significantly improve skin regeneration [218, 219] (Table 1).

## Current challenges for MSCs-based therapies

Transferring MSCs from the laboratory to clinical use has faced challenges due to inadequacies in quality control and discrepancies in several aspects such as stability, immunocompatibility, differentiation, heterogeneity, and migratory capacity observed in clinical trials [227]. The long-term survival of allogeneic cells following administration is the primary obstacle for MSC-based therapies, especially when it comes to the treatment of specific diseases. Although most MSCs are typically trapped in the lung and eliminated from the bloodstream, there have been raised concerns regarding the possible incidence of embolism events during infusion. These events are linked to innate immune responses triggered by MSCs [228]. The homing capacity of infused MSCs and the quantity of dead cells infused into patients are significant challenges in MSC-based therapy. The release of phosphatidylserine from dead MSCs exhibited an immunomodulatory effect identical to that of living MSCs, according to one study [229]. The cell-based product always contains dead cells, raising concerns about their impact on the patient's health.

**Table 1** Summary of clinical trials evaluating MSCs therapies

| Targeted Disease | Source of MSCs Used | Observed Therapeutic Effects | Ref. |
|---|---|---|---|
| Neurological Disorders | Bone Marrow, Adipose Tissue | Improved motor function, reduced inflammation, neuroprotection | [220] |
| Cardiovascular Diseases | Umbilical Cord, Bone Marrow | Enhanced cardiac function, angiogenesis, reduced scar tissue formation | [221] |
| Respiratory Dysfunctions | Adipose Tissue, Umbilical Cord | Improved lung function, anti-inflammatory effects, tissue repair | [222] |
| Metabolic/Endocrine Diseases | Adipose Tissue, Bone Marrow | Enhanced insulin sensitivity, regulation of metabolic markers, tissue regeneration | [223] |
| Reproductive Problems | Bone Marrow, Umbilical Cord | Increased ovarian function, improved fertility outcomes, hormone regulation | [224] |
| Skin Burns, Wound Healing | Adipose Tissue, Bone Marrow | Accelerated wound healing, reduced scar formation, enhanced tissue regeneration | [225] |
| Orthopedic Conditions | Bone Marrow, Adipose Tissue | Cartilage and bone regeneration reduced pain and inflammation | [226] |

Recent studies emphasize the critical need for standardized protocols and rigorous quality control measures in the field of MSC therapy. For instance, a study by Stronceket al. (2020) highlighted the variability in MSC potency assays across different laboratories and emphasized the importance of harmonizing these assays to ensure consistent therapeutic outcomes [230]. Furthermore, initiatives such as the International Society for Cellular Therapy (ISCT) have developed guidelines to standardize the characterization and manufacturing of MSCs, promoting uniformity in cell identity, purity, and functional properties [231]. Quality control in MSC-based therapies also involves rigorous screening for contaminants, genetic stability assessments, and validation of cell expansion protocols to maintain safety and efficacy. These efforts are crucial for advancing MSC therapies from preclinical research to robust clinical applications, ensuring patient safety and enhancing the credibility of MSC-based treatments across various therapeutic indications.

MSCs present several significant processing, safety, and isolation difficulties. The source of the MSCs significantly influences the manifestation of their therapeutic characteristics. Factors such as the age, sex, health status, surgical history, etc. of cell donors are crucial for the effective isolation of MSCs. MSC characterization presents additional difficulties. It is important to confirm that MSCs are functional, pure, untransformed, and therapeutically active after they have been isolated and selected. Microbiological safety and additional cell culture safety protocols must be followed during the whole process from isolation to therapeutic application.

Despite the promising results observed in preclinical studies and initial clinical trials, MSC-based therapies face several limitations and challenges that warrant careful consideration. One of the primary challenges is the variability in MSC characteristics and potency due to donor age, health status, and tissue source, which can influence therapeutic outcomes. Standardization of MSC isolation, expansion protocols, and characterization methods remains a critical issue to ensure reproducibility and efficacy across different studies and clinical settings. Moreover, the biodistribution and fate of administered

MSCs post-injection are not fully understood, raising concerns about their long-term safety and potential adverse effects, such as ectopic tissue formation or immunogenicity. The immunomodulatory properties of MSCs, while beneficial in many cases, can also pose challenges in inflammatory microenvironments where their effects may be unpredictable or insufficient. Additionally, optimizing delivery methods to enhance MSC engraftment, survival, and targeted tissue localization remains a significant hurdle. Furthermore, the high costs associated with MSC isolation, expansion, and clinical-grade production hinder the widespread adoption and affordability of these therapies. Addressing these challenges through rigorous preclinical research, well-designed clinical trials, and advancements in biotechnological approaches will be crucial for realizing the full therapeutic potential of MSCs in regenerative medicine.

## Conclusion

MSCs have become more accessible for clinical applications in the treatment of diseases and regeneration of various tissues over the past few decades due to advancements in culture, isolation, and differentiation techniques. MSCs possess several crucial attributes that render them favored candidates for application in regenerative medicine: immunomodulatory capability, which is advantageous in improving diseases of the immune system; paracrine or autocrine functions that generate growth factors; and the vital capacity for various cell differentiation. Both allogeneic and autologous MSCs are effective sources of regenerative treatments in multiple clinical trials. From a molecular and cellular perspective, UC, AD, and BM-MSCs display distinct functional activities and therapeutic efficacy for a wide range of human diseases. The source of MSCs from different tissues significantly impacts their therapeutic capabilities, as all forms of MSCs have similar safety profiles and efficiency. In conclusion, BM-MSCs exhibit potential as therapeutic agents for neuronal disorders, AT-MSCs demonstrate suitability for endocrine disorders, infertility, and skin regeneration, while UC-MSCs may serve as viable alternatives for pulmonary diseases and ARDS. MSC-based therapeutic applications in CVD are still in an early stage, offering prospective advantages to patients. To increase the therapeutic effectiveness of MSCs, targeted therapies based on their origin are essential.

**Abbreviations**

| | |
|---|---|
| ASCOT | Autologous Stem Cell Ovarian Transplantation |
| FSH | Follicle-Stimulating Hormone |
| MMTT | Mixed-Meal Tolerance Test |
| T1DM | Type 1 Diabetes Mellitus |
| T2DM | Type 2 Diabetes Mellitus |
| POF | Premature Ovarian Failure |
| ARDS | Acute Respiratory Distress Syndrome |
| MSCs | Mesenchymal Stem Cells |
| UC | Umbilical Cord |
| BM | Bone Marrow |
| AT | Adipose Tissue |
| miRNAs | microRNAs |
| ESCs | Embryonic Stem Cells |
| iPSCs | induced Pluripotent Stem Cells |
| HSCs | Hematopoietic Stem Cells |
| IRF | Interferon Regulatory Factor |
| NF-κB | Nuclear Factor Kappa B |
| CNS | Central Nervous System |
| TBI | Traumatic Brain Injury |
| PD | Parkinson's Disease |
| BI | Barthel Index |
| CVDs | Cardiovascular Diseases |
| HGF | Hepatocyte Growth Factor |
| EMT | Epithelial-to-Mesenchymal Transition |
| VEGF | Vascular Endothelial Growth Factor |
| COPD | Chronic Obstructive Pulmonary Disease |
| ARDS | Acute Respiratory Distress Syndrome |
| BPD | Bronchopulmonary Dysplasia |
| EVs | Extracellular Vesicles |
| MS | Multiple Sclerosis |
| IPF | Idiopathic Pulmonary Fibrosis |
| CXCR3 | CXC-Chemokine Receptor 3 |
| CCR5 | CC-Chemokine Receptor 5 |
| SCI | Spinal Cord Injury |
| AD | Alzheimer's Disease |
| TH | Tyrosine Hydroxylase |

**Acknowledgements**
Not applicable.

**Author contributions**
Song Zhidu: Conceptualization, Writing – original draft, and Visualization. Tao Ying: Conceptualization and Writing – original draft. Jiang Rui: Investigation and Writing – review & editing. Zhang Chao: Writing – review & editing, visualization and supervision. All authors have read and agreed to the published version of the manuscript.

**Funding**
Not applicable.

**Data availability**
Not applicable.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Conflict of interest**
The authors declare no conflict of interest.

Received: 17 May 2024 / Accepted: 14 August 2024
Published online: 26 August 2024

**References**

1. Biehl JK, Russell B. Introduction to stem cell therapy. J Cardiovasc Nurs. 2009;24(2):98.
2. Srijaya TC, Ramasamy TS, Kasim NHA. Advancing stem cell therapy from bench to bedside: lessons from drug therapies. J Translational Med. 2014;12:1–17.
3. Pittenger MF, Discher DE, Péault BM, Phinney DG, Hare JM, Caplan AI. Mesenchymal stem cell perspective: cell biology to clinical progress. NPJ Regenerative Med. 2019;4(1):22.

4. Wu Y, Hoogduijn MJ, Baan CC, Korevaar SS, Rd K, Yan L et al. Adipose tissue-derived mesenchymal stem cells have a heterogenic cytokine secretion profile. Stem Cells International. 2017;2017.
5. Abbaszadeh H, Ghorbani F, Abbaspour-Aghdam S, Kamrani A, Valizadeh H, Nadiri M, et al. Chronic obstructive pulmonary disease and asthma: mesenchymal stem cells and their extracellular vesicles as potential therapeutic tools. Stem Cell Res Ther. 2022;13(1):1–15.
6. Mushahary D, Spittler A, Kasper C, Weber V, Charwat V. Isolation, cultivation, and characterization of human mesenchymal stem cells. Cytometry Part A. 2018;93(1):19–31.
7. Steens J, Klein D. Current strategies to generate human mesenchymal stem cells in vitro. Stem cells international. 2018;2018.
8. Beeravolu N, McKee C, Alamri A, Mikhael S, Brown C, Perez-Cruet M, et al. Isolation and characterization of mesenchymal stromal cells from human umbilical cord and fetal placenta. JoVE (Journal Visualized Experiments). 2017;122:e55224.
9. Aravindhan S, Ejam SS, Lafta MH, Markov A, Yumashev AV, Ahmadi M. Mesenchymal stem cells and cancer therapy: insights into targeting the tumour vasculature. Cancer Cell Int. 2021;21(1):1–15.
10. Friedenstein A, Chailakhjan R, Lalykina K. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Prolif. 1970;3(4):393–403.
11. Owen M, Friedenstein A, editors. Stromal stem cells: Marrow-derived osteogenic precursors. Ciba Foundation Symposium 136-Cell and Molecular Biology of Vertebrate Hard Tissues: Cell and Molecular Biology of Vertebrate Hard Tissues: Ciba Foundation Symposium 136; 2007: Wiley Online Library.
12. Haynesworth S, Goshima J, Goldberg V, Caplan A. Characterization of cells with osteogenic potential from human marrow. Bone. 1992;13(1):81–8.
13. Lazarus H, Haynesworth S, Gerson S, Rosenthal N, Caplan A. Ex vivo expansion and subsequent infusion of human bone marrow-derived stromal progenitor cells (mesenchymal progenitor cells): implications for therapeutic use. Bone Marrow Transplant. 1995;16(4):557–64.
14. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science. 1999;284(5411):143–7.
15. Behfar A, Yamada S, Crespo-Diaz R, Nesbitt JJ, Rowe LA, Perez-Terzic C, et al. Guided cardiopoiesis enhances therapeutic benefit of bone marrow human mesenchymal stem cells in chronic myocardial infarction. J Am Coll Cardiol. 2010;56(9):721–34.
16. Freeman BT, Jung JP, Ogle BM. Single-cell RNA-Seq of bone marrow-derived mesenchymal stem cells reveals unique profiles of lineage priming. PLoS ONE. 2015;10(9):e0136199.
17. Bhat S, Viswanathan P, Chandanala S, Prasanna SJ, Seetharam RN. Expansion and characterization of bone marrow derived human mesenchymal stromal cells in serum-free conditions. Sci Rep. 2021;11(1):3403.
18. Capp J-P, Laforge B. A darwinian and physical look at stem cell biology helps understanding the role of stochasticity in development. Front Cell Dev Biology. 2020;8:659.
19. Dunn CM, Kameishi S, Grainger DW, Okano T. Strategies to address mesenchymal stem/stromal cell heterogeneity in immunomodulatory profiles to improve cell-based therapies. Acta Biomater. 2021;133:114–25.
20. Yen BL, Liu KJ, Sytwu HK, Yen ML. Clinical implications of differential functional capacity between tissue-specific human mesenchymal stromal/stem cells. FEBS J. 2023;290(11):2833–44.
21. Wong KU, Zhang A, Akhavan B, Bilek MM, Yeo GC. Biomimetic culture strategies for the clinical expansion of mesenchymal stromal cells. ACS Biomaterials Science & Engineering; 2021.
22. Yea J-H, Kim Y, Jo CH. Comparison of mesenchymal stem cells from bone marrow, umbilical cord blood, and umbilical cord tissue in regeneration of a full-thickness tendon defect in vitro and in vivo. Biochem Biophys Rep. 2023;34:101486.
23. Sangeetha K, Vennila R, Secunda R, Sakthivel S, Pathak S, Jeswanth S, et al. Functional variations between mesenchymal stem cells of different tissue origins: a comparative gene expression profiling. Biotechnol Lett. 2020;42:1287–304.
24. Meyer MB, Benkusky NA, Sen B, Rubin J, Pike JW. Epigenetic plasticity drives adipogenic and osteogenic differentiation of marrow-derived mesenchymal stem cells. J Biol Chem. 2016;291(34):17829–47.
25. Chakraborty S, Sinha S, Sengupta A. Emerging trends in chromatin remodeler plasticity in mesenchymal stromal cell function. FASEB J. 2021;35(1):e21234.
26. Chiang CH, Lin Y-H, Kao Y-C, Weng S-C, Chen C-M, Liou Y-M. Mechanistic study of the Aldo-keto reductase family 1 member A1 in regulating mesenchymal stem cell fate decision toward adipogenesis and osteogenesis. Life Sci. 2024;336:122336.
27. Schooley JC, Kullgren B, Fletcher BL. Growth of murine bone marrow adherent stromal cells in culture without hydrocortisone in a low oxygen environment. Int J Cell Cloning. 1985;3(1):2–9.
28. Paquet J, Deschepper M, Moya A, Logeart-Avramoglou D, Boisson-Vidal C, Petite H. Oxygen tension regulates human mesenchymal stem cell paracrine functions. Stem Cells Translational Med. 2015;4(7):809–21.
29. Hu X, Xu Y, Zhong Z, Wu Y, Zhao J, Wang Y, et al. A large-scale investigation of hypoxia-preconditioned allogeneic mesenchymal stem cells for myocardial repair in nonhuman primates: paracrine activity without remuscularization. Circul Res. 2016;118(6):970–83.
30. Jiang RH, Wu CJ, Xu XQ, Lu SS, Zu QQ, Zhao LB, et al. Hypoxic conditioned medium derived from bone marrow mesenchymal stromal cells protects against ischemic stroke in rats. J Cell Physiol. 2019;234(2):1354–68.
31. Elabd C, Ichim T, Miller K, Anneling A, Grinstein V, Vargas V, et al. Comparing atmospheric and hypoxic cultured mesenchymal stem cell transcriptome: implication for stem cell therapies targeting intervertebral discs. J Translational Med. 2018;16(1):1–14.
32. Kim SH, Das A, Chai JC, Binas B, Choi MR, Park KS, et al. Transcriptome sequencing wide functional analysis of human mesenchymal stem cells in response to TLR4 ligand. Sci Rep. 2016;6(1):30311.
33. Haseli M, Pinzon-Herrera L, Hao X, Wickramasinghe SR, Almodovar J. Novel strategy to Enhance Human Mesenchymal Stromal Cell Immunosuppression: Harnessing Interferon-Gamma Presentation in Metal–Organic frameworks embedded on Heparin/Collagen multilayers. Langmuir. 2023;39(46):16472–83.
34. Luo F, Jiang W, Xu Y, Liu X-m, Wang W, Zhang W, et al. The mechanisms involved in mesenchymal stem cell alleviation of sepsis-induced acute lung injury in mice: a pilot study. Curr Therapeutic Res. 2020;93:100593.
35. Jin P, Zhao Y, Liu H, Chen J, Ren J, Jin J, et al. Interferon-γ and tumor necrosis factor-α polarize bone marrow stromal cells uniformly to a Th1 phenotype. Sci Rep. 2016;6(1):26345.
36. Gao Q, Wang L, Wang S, Huang B, Jing Y, Su J. Bone marrow mesenchymal stromal cells: identification, classification, and differentiation. Front Cell Dev Biology. 2022;9:787118.
37. Sivanathan KN, Rojas-Canales D, Grey ST, Gronthos S, Coates PT. Transcriptome profiling of IL-17A preactivated mesenchymal stem cells: a comparative study to unmodified and IFN-γ modified mesenchymal stem cells. Stem Cells International. 2017;2017.
38. Klinker MW, Marklein RA, Lo Surdo JL, Wei C-H, Bauer SR. Morphological features of IFN-γ–stimulated mesenchymal stromal cells predict overall immunosuppressive capacity. Proc Natl Acad Sci. 2017;114(13):E2598–607.
39. Pham HT, Ono M, Hara ES, Nguyen HTT, Dang AT, Do HT, et al. Tryptophan and kynurenine enhances the stemness and osteogenic differentiation of bone marrow-derived mesenchymal stromal cells in vitro and in vivo. Materials. 2021;14(1):208.
40. Hoang DM, Pham PT, Bach TQ, Ngo AT, Nguyen QT, Phan TT, et al. Stem cell-based therapy for human diseases. Signal Transduct Target Therapy. 2022;7(1):272.
41. Mannino G, Russo C, Maugeri G, Musumeci G, Vicario N, Tibullo D, et al. Adult stem cell niches for tissue homeostasis. J Cell Physiol. 2022;237(1):239–57.
42. Castro Nava A, Doolaar IC, Labude-Weber N, Malyaran H, Babu S, Chandorkar Y, et al. Actuation of Soft Thermoresponsive Hydrogels mechanically stimulates Osteogenesis in Human mesenchymal stem cells without biochemical factors. ACS Appl Mater Interfaces. 2024;16(1):30–43.
43. Witkowska-Zimny M, Wrobel E. Perinatal sources of mesenchymal stem cells: Wharton's jelly, amnion and chorion. Cell Mol Biology Lett. 2011;16(3):493–514.
44. Foo JB, Looi QH, Chong PP, Hassan NH, Yeo GEC, Ng CY et al. Comparing the therapeutic potential of stem cells and their secretory products in regenerative medicine. Stem Cells International. 2021;2021.
45. Khazaei S, Keshavarz G, Bozorgi A, Nazari H, Khazaei M. Adipose tissue-derived stem cells: a comparative review on isolation, culture, and differentiation methods. Cell Tissue Banking. 2022;23(1):1–16.
46. Petrenko Y, Vackova I, Kekulova K, Chudickova M, Koci Z, Turnovcova K, et al. A comparative analysis of multipotent mesenchymal stromal cells derived from different sources, with a focus on neuroregenerative potential. Sci Rep. 2020;10(1):4290.
47. Mohamed-Ahmed S, Fristad I, Lie SA, Suliman S, Mustafa K, Vindenes H, et al. Adipose-derived and bone marrow mesenchymal stem cells: a donor-matched comparison. Stem Cell Res Ther. 2018;9:1–15.

48. Han I, Kwon B-S, Park H-K, Kim KS. Differentiation potential of mesenchymal stem cells is related to their intrinsic mechanical properties. Int Neurourol J. 2017;21(Suppl 1):S24.
49. Lee RH, Pulin AA, Seo MJ, Kota DJ, Ylostalo J, Larson BL, et al. Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6. Cell Stem Cell. 2009;5(1):54–63.
50. Yeung CK, Yan Y, Yan L, Duan Y, Li E, Huang B, et al. Preclinical safety evaluation and tracing of human mesenchymal stromal cell spheroids following intravenous injection into cynomolgus monkeys. Biomaterials. 2022;289:121759.
51. Sierra-Parraga JM, Munk A, Andersen C, Lohmann S, Moers C, Baan CC, et al. Mesenchymal stromal cells are retained in the porcine renal cortex independently of their metabolic state after renal intra-arterial infusion. Stem Cells Dev. 2019;28(18):1224–35.
52. Sokal EM, Lombard CA, Roelants V, Najimi M, Varma S, Sargiacomo C, et al. Biodistribution of liver-derived mesenchymal stem cells after peripheral injection in a hemophilia a patient. Transplantation. 2017;101(8):1845–51.
53. Sood V, Mittal BR, Bhansali A, Singh B, Khandelwal N, Marwaha N, et al. Biodistribution of 18F-FDG-labeled autologous bone marrow–derived stem cells in patients with type 2 diabetes mellitus: exploring targeted and intravenous routes of delivery. Clin Nucl Med. 2015;40(9):697–700.
54. Chen L, Qu J, Kalyani FS, Zhang Q, Fan L, Fang Y, et al. Mesenchymal stem cell-based treatments for COVID-19: status and future perspectives for clinical applications. Cell Mol Life Sci. 2022;79(3):142.
55. Borow KM, Yaroshinsky A, Greenberg B, Perin EC. Phase 3 DREAM-HF trial of mesenchymal precursor cells in chronic heart failure: a review of biological plausibility and implementation of flexible clinical trial design. Circul Res. 2019;125(3):265–81.
56. Rodríguez-Fuentes DE, Fernández-Garza LE, Samia-Meza JA, Barrera-Barrera SA, Caplan AI, Barrera-Saldaña HA. Mesenchymal stem cells current clinical applications: a systematic review. Arch Med Res. 2021;52(1):93–101.
57. Kadri NA, Sylvie, Iacobaeus E, Boberg E, Le Blanc K. Current perspectives on mesenchymal stromal cell therapy for graft versus host disease. Cell Mol Immunol. 2023:1–13.
58. Carney B, Shah K. Migration and fate of therapeutic stem cells in different brain disease models. Neuroscience. 2011;197:37–47.
59. Yao P, Zhou L, Zhu L, Zhou B, Yu Q. Mesenchymal stem cells: a potential therapeutic strategy for neurodegenerative diseases. Eur Neurol. 2020;83(3):235–41.
60. Bonaventura G, Munafò A, Bellanca CM, La Cognata V, Iemmolo R, Attaguile GA, et al. Stem cells: innovative therapeutic options for neurodegenerative diseases? Cells. 2021;10(8):1992.
61. Mansoor SR, Zabihi E, Ghasemi-Kasman M. The potential use of mesenchymal stem cells for the treatment of multiple sclerosis. Life Sci. 2019;235:116830.
62. Chung J-W, Chang WH, Bang OY, Moon GJ, Kim SJ, Kim S-K, et al. Efficacy and safety of intravenous mesenchymal stem cells for ischemic stroke. Neurology. 2021;96(7):e1012–23.
63. Yamazaki K, Kawabori M, Seki T, Houkin K. Clinical trials of stem cell treatment for spinal cord injury. Int J Mol Sci. 2020;21(11):3994.
64. Xie B, Chen M, Hu R, Han W, Ding S. Therapeutic evidence of human mesenchymal stem cell transplantation for cerebral palsy: a meta-analysis of randomized controlled trials. Stem Cells International. 2020;2020.
65. McDonald CA, Djuliannisaa Z, Petraki M, Paton MC, Penny TR, Sutherland AE, et al. Intranasal delivery of mesenchymal stromal cells protects against neonatal hypoxic–ischemic brain injury. Int J Mol Sci. 2019;20(10):2449.
66. Liu Q, Chen M-X, Sun L, Wallis CU, Zhou J-S, Ao L-J, et al. Rational use of mesenchymal stem cells in the treatment of autism spectrum disorders. World J Stem Cells. 2019;11(2):55.
67. Fričová D, Korchak JA, Zubair AC. Challenges and translational considerations of mesenchymal stem/stromal cell therapy for Parkinson's disease. NPJ Regenerative Med. 2020;5(1):20.
68. Thayabaranathan T, Kim J, Cadilhac DA, Thrift AG, Donnan GA, Howard G, et al. Global stroke statistics 2022. Int J Stroke. 2022;17(9):946–56.
69. Li J, Zhang Q, Wang W, Lin F, Wang S, Zhao J. Mesenchymal stem cell therapy for ischemic stroke: a look into treatment mechanism and therapeutic potential. J Neurol. 2021;268:4095–107.
70. Rufino RA, Pereira-Rufino LS, Vissoto TCS, Kerkis I, Neves AC, da Silva MCP. The immunomodulatory potential role of mesenchymal stem cells in diseases of the central nervous system. Neurodegenerative Dis. 2023;22(2):68–82.
71. Liu K, Guo L, Zhou Z, Pan M, Yan C. Mesenchymal stem cells transfer mitochondria into cerebral microvasculature and promote recovery from ischemic stroke. Microvasc Res. 2019;123:74–80.
72. Bao X-J, Liu F-Y, Lu S, Han Q, Feng M, Wei J-J, et al. Transplantation of Flk-1 + human bone marrow-derived mesenchymal stem cells promotes behavioral recovery and anti-inflammatory and angiogenesis effects in an intracerebral hemorrhage rat model. Int J Mol Med. 2013;31(5):1087–96.
73. Hu H, Long H, Ren Z, Liu T, Xu J, Xiao F. Partially brain effects of injection of human umbilical cord mesenchymal stem cells at injury sites in a mouse model of thoracic spinal cord contusion. Front Mol Neurosci. 2023;16:1179175.
74. Qi L, Xue X, Sun J, Wu Q, Wang H, Guo Y, et al. The promising effects of transplanted umbilical cord mesenchymal stem cells on the treatment in traumatic brain injury. J Craniofac Surg. 2018;29(7):1689.
75. Shahror RA, Linares GR, Wang Y, Hsueh S-C, Wu C-C, Chuang D-M, et al. Transplantation of mesenchymal stem cells overexpressing fibroblast growth factor 21 facilitates cognitive recovery and enhances neurogenesis in a mouse model of traumatic brain injury. J Neurotrauma. 2020;37(1):14–26.
76. Shi W, Huang C, Xu X, Jin G, Huang R, Huang J, et al. Transplantation of RADA16-BDNF peptide scaffold with human umbilical cord mesenchymal stem cells forced with CXCR4 and activated astrocytes for repair of traumatic brain injury. Acta Biomater. 2016;45:247–61.
77. Enam SF, Kader SR, Bodkin N, Lyon JG, Calhoun M, Azrak C, et al. Evaluation of M2-like macrophage enrichment after diffuse traumatic brain injury through transient interleukin-4 expression from engineered mesenchymal stromal cells. J Neuroinflamm. 2020;17(1):1–24.
78. Harach T, Jammes F, Muller C, Duthilleul N, Cheatham V, Zufferey V, et al. Administrations of human adult ischemia-tolerant mesenchymal stem cells and factors reduce amyloid beta pathology in a mouse model of Alzheimer's disease. Neurobiol Aging. 2017;51:83–96.
79. Shin JY, Park HJ, Kim HN, Oh SH, Bae J-S, Ha H-J, et al. Mesenchymal stem cells enhance autophagy and increase β-amyloid clearance in Alzheimer disease models. Autophagy. 2014;10(1):32–44.
80. Hour FQ, Moghadam AJ, Shakeri-Zadeh A, Bakhtiyari M, Shabani R, Mehdizadeh M. Magnetic targeted delivery of the SPIONs-labeled mesenchymal stem cells derived from human Wharton's jelly in Alzheimer's rat models. J Controlled Release. 2020;321:430–41.
81. Zhao X, Li D, Zhang L, Niu Y, Wang W, Niu B. Mesenchymal stem cell therapies for Alzheimer's disease: preclinical studies. Metab Brain Dis. 2021;36(7):1687–95.
82. Hernández A, García E. Mesenchymal stem cell therapy for Alzheimer's disease. Stem Cells Int. 2021;2021(1):7834421.
83. Boika A, Aleinikava N, Chyzhyk V, Zafranskaya M, Nizheharodava D, Ponomarev V. Mesenchymal stem cells in Parkinson's disease: motor and nonmotor symptoms in the early posttransplant period. Surg Neurol Int. 2020;11.
84. Moradian H, Keshvari H, Fasehee H, Dinarvand R, Faghihi S. Combining NT3-overexpressing MSCs and PLGA microcarriers for brain tissue engineering: a potential tool for treatment of Parkinson's disease. Mater Sci Engineering: C. 2017;76:934–43.
85. Wang Y-L, Liu X-S, Wang S-S, Xue P, Zeng Z-L, Yang X-P et al. Curcumin-activated mesenchymal stem cells derived from human umbilical cord and their effects on MPTP-mouse model of Parkinson's disease: a new biological therapy for Parkinson's disease. Stem Cells International. 2020;2020.
86. Nakanishi M, Watanabe Y, Honda N, Une M, Kazuki K, Kazuki Y, et al. Dynamics of host and graft after cell sheet transplantation: basic study for the application of amyotrophic lateral sclerosis. Brain Res. 2019;1724:146444.
87. Yan L, Jiang B, Niu Y, Wang H, Li E, Yan Y, et al. Intrathecal delivery of human ESC-derived mesenchymal stem cell spheres promotes recovery of a primate multiple sclerosis model. Cell Death Discovery. 2018;4(1):89.
88. Jiang H, Zhang Y, Tian K, Wang B, Han S. Amelioration of experimental autoimmune encephalomyelitis through transplantation of placental derived mesenchymal stem cells. Sci Rep. 2017;7(1):41837.
89. Iacobaeus E, Kadri N, Lefsihane K, Boberg E, Gavin C, Törnqvist Andrén A, et al. Short and long term clinical and immunologic follow up after bone marrow mesenchymal stromal cell therapy in progressive multiple Sclerosis—A phase I study. J Clin Med. 2019;8(12):2102.
90. Connick P, Kolappan M, Crawley C, Webber DJ, Patani R, Michell AW, et al. Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. Lancet Neurol. 2012;11(2):150–6.
91. Uccelli A, Laroni A, Brundin L, Clanet M, Fernandez O, Nabavi SM, et al. MEsenchymal StEm cells for multiple sclerosis (MESEMS): a randomized, double blind, cross-over phase I/II clinical trial with autologous mesenchymal stem cells for the therapy of multiple sclerosis. Trials. 2019;20:1–13.

92. Uccelli A, Laroni A, Ali R, Battaglia MA, Blinkenberg M, Brundin L, et al. Safety, tolerability, and activity of mesenchymal stem cells versus placebo in multiple sclerosis (MESEMS): a phase 2, randomised, double-blind crossover trial. Lancet Neurol. 2021;20(11):917–29.
93. Zheng H, Zhang B, Chhatbar PY, Dong Y, Alawieh A, Lowe F, et al. Mesenchymal stem cell therapy in stroke: a systematic review of literature in pre-clinical and clinical research. Cell Transplant. 2018;27(12):1723–30.
94. Bang OY, Lee JS, Lee PH, Lee G. Autologous mesenchymal stem cell transplantation in stroke patients. Annals Neurology: Official J Am Neurol Association Child Neurol Soc. 2005;57(6):874–82.
95. Honmou O, Houkin K, Matsunaga T, Niitsu Y, Ishiai S, Onodera R, et al. Intravenous administration of auto serum-expanded autologous mesenchymal stem cells in stroke. Brain. 2011;134(6):1790–807.
96. Lee JS, Hong JM, Moon GJ, Lee PH, Ahn YH, Bang OY. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. Stem Cells. 2010;28(6):1099–106.
97. Levy ML, Crawford JR, Dib N, Verkh L, Tankovich N, Cramer SC. Phase I/II study of safety and preliminary efficacy of intravenous allogeneic mesenchymal stem cells in chronic stroke. Stroke. 2019;50(10):2835–41.
98. Ballen K, Kurtzberg J. Exploring new therapies for children with autism:do no harm does not mean do not try. Stem Cells Translational Med. 2021;10(6):823–5.
99. Reyhani S, Abbaspanah B, Mousavi SH. Umbilical cord-derived mesenchymal stem cells in neurodegenerative disorders: from literature to clinical practice. Regen Med. 2020;15(4):1561–78.
100. Gu J, Huang L, Zhang C, Wang Y, Zhang R, Tu Z, et al. Therapeutic evidence of umbilical cord-derived mesenchymal stem cell transplantation for cerebral palsy: a randomized, controlled trial. Stem Cell Res Ther. 2020;11:1–12.
101. Tsao CW, Aday AW, Almarzooq ZI, Anderson CA, Arora P, Avery CL, et al. Heart disease and stroke statistics—2023 update: a report from the American Heart Association. Circulation. 2023;147(8):e93–621.
102. Davidson BT, Dunham S. The perfect storm: barriers to Heart failure treatment optimization. Crit Care Nurs Clin. 2022;34(2):141–50.
103. Arjmand B, Abedi M, Arabi M, Alavi-Moghadam S, Rezaei-Tavirani M, Hadavandkhani M, et al. Regenerative medicine for the treatment of ischemic heart disease; status and future perspectives. Front Cell Dev Biology. 2021;9:704903.
104. Malihi G, Nikoui V, Elson EL. A review on qualifications and cost effectiveness of induced pluripotent stem cells (IPSCs)-induced cardiomyocytes in drug screening tests. Arch Physiol Biochem. 2023;129(1):131–42.
105. Chong JJ, Yang X, Don CW, Minami E, Liu Y-W, Weyers JJ, et al. Human embryonic-stem-cell-derived cardiomyocytes regenerate non-human primate hearts. Nature. 2014;510(7504):273–7.
106. Mirotsou M, Jayawardena TM, Schmeckpeper J, Gnecchi M, Dzau VJ. Paracrine mechanisms of stem cell reparative and regenerative actions in the heart. J Mol Cell Cardiol. 2011;50(2):280–9.
107. Guo Y, Yu Y, Hu S, Chen Y, Shen Z. The therapeutic potential of mesenchymal stem cells for cardiovascular diseases. Cell Death Dis. 2020;11(5):349.
108. Gubert F, da Silva JS, Vasques JF, de Jesus Gonçalves RG, Martins RS, de Sá MPL, et al. Mesenchymal stem cells therapies on fibrotic heart diseases. Int J Mol Sci. 2021;22(14):7447.
109. Bolli R, Solankhi M, Tang X-L, Kahlon A. Cell therapy in patients with heart failure: a comprehensive review and emerging concepts. Cardiovascular Res. 2022;118(4):951–76.
110. Azizidoost S, Farzaneh M. MicroRNAs as a novel player for differentiation of mesenchymal stem cells into cardiomyocytes. Curr Stem Cell Res Therapy. 2023;18(1):27–34.
111. Peng C, Yan J, Jiang Ya, Wu L, Li M, Fan X. Exploring cutting-edge approaches to Potentiate Mesenchymal Stem Cell and Exosome Therapy for myocardial infarction. J Cardiovasc Transl Res. 2023:1–20.
112. Grobbelaar S, Mercier AE, Van den Bout I, Durandt C, Pepper MS. Considerations for enhanced mesenchymal stromal/stem cell myogenic commitment in vitro. Clin Transl Sci. 2023.
113. Peng X, Wang S, Chen H, Chen M. Role of the Notch1 signaling pathway in ischemic heart disease. Int J Mol Med. 2023;51(3):1–13.
114. Cortés-Morales VA, Vázquez-González WG, Montesinos JJ, Moreno-Ruíz L, Salgado-Pastor S, Salinas-Arreola PM, et al. Human bone marrow mesenchymal stem cells promote the M2 phenotype in Macrophages Derived from Stemi patients. Int J Mol Sci. 2023;24(22):16257.
115. Li J, Chen Q, Zhang R, Liu Z, Cheng Y. The phagocytic role of macrophage following myocardial infarction. Heart Fail Rev. 2023:1–15.
116. Miteva K, Pappritz K, El-Shafeey M, Dong F, Ringe J, Tschöpe C, et al. Mesenchymal stromal cells modulate monocytes trafficking in coxsackievirus B3-induced myocarditis. Stem Cells Translational Med. 2017;6(4):1249–61.
117. Arabpour M, Saghazadeh A, Rezaei N. Anti-inflammatory and M2 macrophage polarization-promoting effect of mesenchymal stem cell-derived exosomes. Int Immunopharmacol. 2021;97:107823.
118. Barrère-Lemaire S, Vincent A, Jorgensen C, Piot C, Nargeot J, Djouad F. Mesenchymal stromal cells for improvement of cardiac function following acute myocardial infarction: a matter of timing. Physiol Rev. 2023.
119. Shao L, Shen Y, Ren C, Kobayashi S, Asahara T, Yang J. Inflammation in myocardial infarction: roles of mesenchymal stem cells and their secretome. Cell Death Discovery. 2022;8(1):452.
120. Moeinabadi-Bidgoli K, Babajani A, Yazdanpanah G, Farhadihosseinabadi B, Jamshidi E, Bahrami S, et al. Translational insights into stem cell preconditioning: from molecular mechanisms to preclinical applications. Biomed Pharmacother. 2021;142:112026.
121. Zhu Y. Advances in CRISPR/Cas9. Biomed Res Int. 2022;2022(1):9978571.
122. Jang J, Park H-J, Kim S-W, Kim H, Park JY, Na SJ, et al. 3D printed complex tissue construct using stem cell-laden decellularized extracellular matrix bioinks for cardiac repair. Biomaterials. 2017;112:264–74.
123. Wang H, Yu H, Zhou X, Zhang J, Zhou H, Hao H, et al. An overview of extracellular matrix-based bioinks for 3D bioprinting. Front Bioeng Biotechnol. 2022;10:905438.
124. Bulcha JT, Wang Y, Ma H, Tai PW, Gao G. Viral vector platforms within the gene therapy landscape. Signal Transduct Target Therapy. 2021;6(1):53.
125. Nowak I, Madej M, Secemska J, Sarna R, Strzalka-Mrozik B. Virus-based biological systems as next-generation carriers for the therapy of central nervous system diseases. Pharmaceutics. 2023;15(7):1931.
126. Li X, Zhao H, Qi C, Zeng Y, Xu F, Du Y. Direct intercellular communications dominate the interaction between adipose-derived MSCs and myofibroblasts against cardiac fibrosis. Protein Cell. 2015;6(10):735–45.
127. Kishore R, Verma SK, Mackie AR, Vaughan EE, Abramova TV, Aiko I, et al. Bone marrow progenitor cell therapy-mediated paracrine regulation of cardiac miRNA-155 modulates fibrotic response in diabetic hearts. PLoS ONE. 2013;8(4):e60161.
128. Silva DN, Souza BS, Azevedo CM, Vasconcelos JF, de Jesus PG, Feitoza MS et al. IGF-1-Overexpressing mesenchymal stem/stromal cells promote immunomodulatory and proregenerative effects in chronic experimental chagas disease. Stem Cells International. 2018;2018.
129. Chen Y, Zhao Y, Chen W, Xie L, Zhao Z-A, Yang J, et al. MicroRNA-133 overexpression promotes the therapeutic efficacy of mesenchymal stem cells on acute myocardial infarction. Stem Cell Res Ther. 2017;8(1):1–11.
130. Davani S, Marandin A, Mersin N, Royer B, Kantelip B, Hervé P, et al. Mesenchymal progenitor cells differentiate into an endothelial phenotype, enhance vascular density, and improve heart function in a rat cellular cardiomyoplasty model. Circulation. 2003;108(10suppl1):II–253.
131. Gomes SA, Rangel EB, Premer C, Dulce RA, Cao Y, Florea V et al. S-nitrosoglutathione reductase (GSNOR) enhances vasculogenesis by mesenchymal stem cells. Proceedings of the National Academy of Sciences. 2013;110(8):2834-9.
132. Tang Y, Gan X, Curran E, Lamberti G, Krynska B, Kiani MF, et al. Targeted delivery of vascular endothelial growth factor improves stem cell therapy in a rat myocardial infarction model. Nanomed Nanotechnol Biol Med. 2014;10(8):1711–8.
133. Ju C, Shen Y, Ma G, Liu Y, Cai J, Kim I-m, et al. Transplantation of cardiac mesenchymal stem cell-derived exosomes promotes repair in ischemic myocardium. J Cardiovasc Transl Res. 2018;11:420–8.
134. Bartunek J, Behfar A, Dolatabadi D, Vanderheyden M, Ostojic M, Dens J, et al. Cardiopoietic stem cell therapy in heart failure: the C-CURE (cardiopoietic stem cell therapy in heart failURE) multicenter randomized trial with lineage-specified biologics. J Am Coll Cardiol. 2013;61(23):2329–38.
135. Bartunek J, Terzic A, Davison BA, Filippatos GS, Radovanovic S, Beleslin B, et al. Cardiopoietic cell therapy for advanced ischaemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 clinical trial. Eur Heart J. 2017;38(9):648–60.
136. Hare JM, DiFede DL, Rieger AC, Florea V, Landin AM, El-Khorazaty J, et al. Randomized comparison of allogeneic versus autologous mesenchymal stem cells for nonischemic dilated cardiomyopathy: POSEIDON-DCM trial. J Am Coll Cardiol. 2017;69(5):526–37.
137. Mathiasen AB, Qayyum AA, Jørgensen E, Helqvist S, Kofoed KF, Haack-Sørensen M, et al. Bone marrow-derived mesenchymal stromal cell treatment in patients with ischaemic heart failure: final 4-year follow-up of the MSC-HF trial. Eur J Heart Fail. 2020;22(5):884–92.

138. Florea V, Rieger AC, DiFede DL, El-Khorazaty J, Natsumeda M, Banerjee MN, et al. Dose comparison study of allogeneic mesenchymal stem cells in patients with ischemic cardiomyopathy (the TRIDENT study). Circul Res. 2017;121(11):1279–90.
139. Ngo AT, Le HM, Trinh NT, Jun APG, Bach TQ, Bui HT, et al. Clinically relevant preservation conditions for mesenchymal stem/stromal cells derived from perinatal and adult tissue sources. J Cell Mol Med. 2021;25(22):10747–60.
140. Bartolucci J, Verdugo FJ, González PL, Larrea RE, Abarzua E, Goset C, et al. Safety and efficacy of the intravenous infusion of umbilical cord mesenchymal stem cells in patients with heart failure: a phase 1/2 randomized controlled trial (RIMECARD trial [randomized clinical trial of intravenous infusion umbilical cord mesenchymal stem cells on cardiopathy]). Circul Res. 2017;121(10):1192–204.
141. Ulus AT, Mungan C, Kurtoglu M, Celikkan FT, Akyol M, Sucu M, et al. Intramyocardial transplantation of umbilical cord mesenchymal stromal cells in chronic ischemic cardiomyopathy: a controlled, randomized clinical trial (HUC-HEART trial). Int J Stem Cells. 2020;13(3):364–76.
142. He X, Wang Q, Zhao Y, Zhang H, Wang B, Pan J, et al. Effect of intramyocardial grafting collagen scaffold with mesenchymal stromal cells in patients with chronic ischemic heart disease: a randomized clinical trial. JAMA Netw Open. 2020;3(9):e2016236–e.
143. Murray CJ. COVID-19 will continue but the end of the pandemic is near. Lancet. 2022;399(10323):417–9.
144. Lignelli E, Palumbo F, Myti D, Morty RE. Recent advances in our understanding of the mechanisms of lung alveolarization and bronchopulmonary dysplasia. Am J Physiology-Lung Cell Mol Physiol. 2019;317(6):L832–87.
145. Behnke J, Kremer S, Shahzad T, Chao C-M, Böttcher-Friebertshäuser E, Morty RE, et al. MSC based therapies—new perspectives for the injured lung. J Clin Med. 2020;9(3):682.
146. Lopes-Pacheco M, Rocco PR. Functional enhancement strategies to potentiate the therapeutic properties of mesenchymal stromal cells for respiratory diseases. Front Pharmacol. 2023;14:1067422.
147. Antunes MA, Abreu SC, Cruz FF, Teixeira AC, Lopes-Pacheco M, Bandeira E, et al. Effects of different mesenchymal stromal cell sources and delivery routes in experimental emphysema. Respir Res. 2014;15(1):1–14.
148. Li J-H, Li Y, Huang D, Yao M. Role of stromal cell-derived factor-1 in endothelial progenitor cell-mediated vascular repair and regeneration. Tissue Eng Regenerative Med. 2021;18(5):747–58.
149. Strizova Z, Benesova I, Bartolini R, Novysedlak R, Cecrdlova E, Foley LK, et al. M1/M2 macrophages and their overlaps–myth or reality? Clin Sci. 2023;137(15):1067–93.
150. Rahbarghazi R, Keyhanmanesh R, Aslani MR, Hassanpour M, Ahmadi M. Bone marrow mesenchymal stem cells and condition media diminish inflammatory adhesion molecules of pulmonary endothelial cells in an ovalbumin-induced asthmatic rat model. Microvasc Res. 2019;121:63–70.
151. Dai R, Yu Y, Yan G, Hou X, Ni Y, Shi G. Intratracheal administration of adipose derived mesenchymal stem cells alleviates chronic asthma in a mouse model. BMC Pulm Med. 2018;18:1–9.
152. Shi Y, Wang Y, Li Q, Liu K, Hou J, Shao C, et al. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. Nat Rev Nephrol. 2018;14(8):493–507.
153. Böttcher M, Hofmann D, Bruns A, Haibach H, Loschinski M, Saul R. Mesenchymal stromal cells disrupt mTOR-signaling and aerobic glycolysis during T-cell activation. Stem Cells. 2016;34(2):516–21.
154. Jitschin R, Böttcher M, Saul D, Lukassen S, Bruns H, Loschinski R, et al. Inflammation-induced glycolytic switch controls suppressivity of mesenchymal stem cells via STAT1 glycosylation. Leukemia. 2019;33(7):1783–96.
155. Jiang W, Xu J. Immune modulation by mesenchymal stem cells. Cell Prolif. 2020;53(1):e12712.
156. Huang Y, Wu Q, Tam PKH. Immunomodulatory mechanisms of mesenchymal stem cells and their potential clinical applications. Int J Mol Sci. 2022;23(17):10023.
157. Shin JW, Ryu S, Ham J, Jung K, Lee S, Chung DH, et al. Mesenchymal stem cells suppress severe asthma by directly regulating Th2 cells and type 2 innate lymphoid cells. Mol Cells. 2021;44(8):580–90.
158. Cao C, Zhang L, Liu F, Shen J. Therapeutic benefits of mesenchymal stem cells in Acute Respiratory Distress Syndrome: potential mechanisms and challenges. J Inflamm Res. 2022:5235–46.
159. Kletukhina S, Mutallapova G, Titova A, Gomzikova M. Role of mesenchymal stem cells and extracellular vesicles in idiopathic pulmonary fibrosis. Int J Mol Sci. 2022;23(19):11212.
160. Singh PV, Singh PV, Anjankar A. Harnessing the therapeutic potential of stem cells in the management of Chronic Obstructive Pulmonary Disease: a Comprehensive Review. Cureus. 2023;15(8).
161. Martí-Chillón GJ, Muntión S, Preciado S, Osugui L, Navarro-Bailón A, González-Robledo J, et al. Therapeutic potential of mesenchymal stromal/stem cells in critical-care patients with systemic inflammatory response syndrome. Clin Translational Med. 2023;13(1):e1163.
162. Lohan P, Treacy O, Griffin MD, Ritter T, Ryan AE. Anti-donor immune responses elicited by allogeneic mesenchymal stem cells and their extracellular vesicles: are we still learning? Front Immunol. 2017;8:1626.
163. Wang M-y, Zhou T-y, Zhang Z-d, Liu H-y. Zheng Z-y, Xie H-q. current therapeutic strategies for respiratory diseases using mesenchymal stem cells. MedComm. 2021;2(3):351–80.
164. Ren G, Zhang L, Zhao X, Xu G, Zhang Y, Roberts AI, et al. Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide. Cell Stem Cell. 2008;2(2):141–50.
165. Mohamed T, Abdul-Hafez A, Gewolb IH, Uhal BD. Oxygen injury in neonates: which is worse? Hyperoxia, hypoxia, or alternating hyperoxia/hypoxia. J Lung Pulmonary Respiratory Res. 2020;7(1):4.
166. Chang YS, Ahn SY, Yoo HS, Sung SI, Choi SJ, Oh WI, et al. Mesenchymal stem cells for bronchopulmonary dysplasia: phase 1 dose-escalation clinical trial. J Pediatr. 2014;164(5):966–72. e6.
167. Ahn SY, Chang YS, Lee MH, Sung SI, Lee BS, Kim KS, et al. Stem cells for bronchopulmonary dysplasia in preterm infants: a randomized controlled phase II trial. Stem Cells Translational Med. 2021;10(8):1129–37.
168. Berg K, Wright JL. The pathology of chronic obstructive pulmonary disease: progress in the 20th and 21st centuries. Arch Pathol Lab Med. 2016;140(12):1423–8.
169. Li X, Wang J, Cao J, Ma L, Xu J. Immunoregulation of bone marrow-derived mesenchymal stem cells on the chronic cigarette smoking-induced lung inflammation in rats. Biomed Res Int. 2015;2015.
170. Melo MM, Cruz FF, Rocco PRM. Mesenchymal stromal cell therapy for chronic lung diseases: experimental and clinical evidence. Expert Rev Respir Med. 2023;17(3):223–35.
171. Stessuk T, Ruiz MA, Greco OT, Bilaqui A, Ribeiro-Paes MJdO, Ribeiro-Paes JT. Phase I clinical trial of cell therapy in patients with advanced chronic obstructive pulmonary disease: follow-up of up to 3 years. Revista Brasileira De Hematologia E Hemoterapia. 2013;35:352–7.
172. Weiss DJ, Casaburi R, Flannery R, LeRoux-Williams M, Tashkin DP. A placebo-controlled, randomized trial of mesenchymal stem cells in COPD. Chest. 2013;143(6):1590–8.
173. de Oliveira HG, Cruz FF, Antunes MA, Macedo Neto AV, Oliveira GA, Svartman FM, et al. Combined bone marrow-derived mesenchymal stromal cell therapy and one-way endobronchial valve placement in patients with pulmonary emphysema: a phase I clinical trial. Stem Cells Translational Med. 2017;6(3):962–9.
174. Glassberg MK, Csete I, Simonet E, Elliot SJ. Stem cell therapy for COPD: hope and exploitation. Chest. 2021;160(4):1271–81.
175. Le Thi Bich P, Nguyen Thi H, Dang Ngo Chau H, Phan Van T, Do Q, Dong Khac H, et al. Allogeneic umbilical cord-derived mesenchymal stem cell transplantation for treating chronic obstructive pulmonary disease: a pilot clinical study. Stem Cell Res Ther. 2020;11(1):1–14.
176. Karaoz E, Kalemci S, Ece F. Improving effects of mesenchymal stem cells on symptoms of chronic obstructive pulmonary disease. Bratislava Med Journal-Bratislavske Lekarske Listy. 2020;121(3):188–91.
177. Hoang DM, Nguyen KT, Nguyen AH, Nguyen BN, Nguyen LT. Allogeneic human umbilical cord-derived mesenchymal stem/stromal cells for chronic obstructive pulmonary disease (COPD): study protocol for a matched case–control, phase I/II trial. BMJ Open. 2021;11(5):e045788.
178. Chen J, Hu C, Chen L, Tang L, Zhu Y, Xu X, et al. Clinical study of mesenchymal stem cell treatment for acute respiratory distress syndrome induced by epidemic influenza A (H7N9) infection: a hint for COVID-19 treatment. Engineering. 2020;6(10):1153–61.
179. Atluri S, Manchikanti L, Hirsch JA. Expanded umbilical cord mesenchymal stem cells (UC-MSCs) as a therapeutic strategy in managing critically ill COVID-19 patients: the case for compassionate use. Pain Physician. 2020:E71–83.
180. Lopes-Pacheco M, Robba C, Rocco PRM, Pelosi P. Current understanding of the therapeutic benefits of mesenchymal stem cells in acute respiratory distress syndrome. Cell Biol Toxicol. 2020;36:83–102.

181. Liang B, Chen J, Li T, Wu H, Yang W, Li Y et al. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells: a case report. Medicine. 2020;99(31).
182. Glenn JD, Whartenby KA. Mesenchymal stem cells: emerging mechanisms of immunomodulation and therapy. World J Stem Cells. 2014;6(5):526.
183. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Disease. 2020;11(2):216.
184. Zhang Y, Ding J, Ren S, Wang W, Yang Y, Li S, et al. Intravenous infusion of human umbilical cord Wharton's jelly-derived mesenchymal stem cells as a potential treatment for patients with COVID-19 pneumonia. Stem Cell Res Ther. 2020;11:1–6.
185. Shi L, Huang H, Lu X, Yan X, Jiang X, Xu R, et al. Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: a randomized, double-blind, placebo-controlled phase 2 trial. Signal Transduct Target Therapy. 2021;6(1):58.
186. Wang M, Ty Z, Zd Z, Hy L, Zy Z. Xie Hq. Current therapeutic strategies for respiratory diseases using mesenchymal stem cells. MedComm. 2021;2(3):351–80.
187. Schifter M, McLean M, Sukumar S. Disorders of the endocrine system and of metabolism. Burket's Oral Med. 2021:817–902.
188. Qi X, Yun C, Pang Y, Qiao J. The impact of the gut microbiota on the reproductive and metabolic endocrine system. Gut Microbes. 2021;13(1):1894070.
189. Liu X, Li J, Wang W, Ren X, Hu J-F. Therapeutic restoration of female reproductive and endocrine dysfunction using stem cells. Life Sci. 2023;322:121658.
190. Rodrigues Oliveira SM, Rebocho A, Ahmadpour E, Nissapatorn V, de Lourdes Pereira M. Type 1 diabetes mellitus: a review on advances and challenges in creating insulin producing devices. Micromachines. 2023;14(1):151.
191. Morran MP, Vonberg A, Khadra A, Pietropaolo M. Immunogenetics of type 1 diabetes mellitus. Mol Aspects Med. 2015;42:42–60.
192. Peloso A, Citro A, Zoro T, Cobianchi L, Kahler-Quesada A, Bianchi CM, et al. Regenerative medicine and diabetes: targeting the extracellular matrix beyond the stem cell approach and encapsulation technology. Front Endocrinol. 2018;9:445.
193. Wan X-X, Zhang D-Y, Khan MA, Zheng S-Y, Hu X-M, Zhang Q, et al. Stem cell transplantation in the treatment of type 1 diabetes mellitus: from insulin replacement to beta-cell replacement. Front Endocrinol. 2022;13:859638.
194. Carlsson P-O, Schwarcz E, Korsgren O, Le Blanc K. Preserved β-cell function in type 1 diabetes by mesenchymal stromal cells. Diabetes. 2015;64(2):587–92.
195. Dantas JR, Araújo DB, Silva KR, Souto DL, Pereira MFC, Luiz RR, et al. Adipose tissue-derived stromal/stem cells + cholecalciferol: a pilot study in recent-onset type 1 diabetes patients. Archives Endocrinol Metabolism. 2021;65:342–51.
196. Hu J, Yu X, Wang Z, Wang F, Wang L, Gao H, et al. Long term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells from the umbilical cord for newly-onset type 1 diabetes mellitus. Endocr J. 2013;60(3):347–57.
197. Cai J, Wu Z, Xu X, Liao L, Chen J, Huang L, et al. Umbilical cord mesenchymal stromal cell with autologous bone marrow cell transplantation in established type 1 diabetes: a pilot randomized controlled open-label clinical study to assess safety and impact on insulin secretion. Diabetes Care. 2016;39(1):149–57.
198. Huang Q, Huang Y, Liu J. Mesenchymal stem cells: an excellent candidate for the treatment of diabetes mellitus. International Journal of Endocrinology. 2021;2021.
199. Nguyen LT, Hoang DM, Nguyen KT, Bui DM, Nguyen HT, Le HT, et al. Type 2 diabetes mellitus duration and obesity alter the efficacy of autologously transplanted bone marrow-derived mesenchymal stem/stromal cells. Stem Cells Translational Med. 2021;10(9):1266–78.
200. Alicka M, Major P, Wysocki M, Marycz K. Adipose-derived mesenchymal stem cells isolated from patients with type 2 diabetes show reduced stemness through an altered secretome profile, impaired anti-oxidative protection, and mitochondrial dynamics deterioration. J Clin Med. 2019;8(6):765.
201. An S-M, Cho S-H, Yoon JC. Adipose tissue and metabolic health. Diabetes Metabolism J. 2023;47(5):595.
202. Agarwal A, Baskaran S, Parekh N, Cho C-L, Henkel R, Vij S, et al. Male infertility. Lancet. 2021;397(10271):319–33.
203. Farquhar C, Marjoribanks J. Assisted reproductive technology: an overview of Cochrane Reviews. Cochrane Database Syst Reviews. 2018(8).
204. Chang Z, Zhu H, Zhou X, Zhang Y, Jiang B, Li S et al. Mesenchymal stem cells in preclinical infertility cytotherapy: a retrospective review. Stem Cells International. 2021;2021.
205. Fenton AJ. Premature ovarian insufficiency: Pathogenesis and management. J Mid-Life Health. 2015;6(4):147.
206. Huhtaniemi I, Hovatta O, La Marca A, Livera G, Monniaux D, Persani L, et al. Advances in the molecular pathophysiology, genetics, and treatment of primary ovarian insufficiency. Trends Endocrinol Metabolism. 2018;29(6):400–19.
207. Gupta S, Lodha P, Karthick MS, Tandulwadkar SR. Role of autologous bone marrow-derived stem cell therapy for follicular recruitment in premature ovarian insufficiency: review of literature and a case report of world's first baby with ovarian autologous stem cell therapy in a perimenopausal woman of age 45 year. J Hum Reproductive Sci. 2018;11(2):125.
208. Igboeli P, El Andaloussi A, Sheikh U, Takala H, ElSharoud A, McHugh A, et al. Intraovarian injection of autologous human mesenchymal stem cells increases estrogen production and reduces menopausal symptoms in women with premature ovarian failure: two case reports and a review of the literature. J Med Case Rep. 2020;14(1):1–11.
209. Ulin M, Cetin E, Hobeika E, Chugh RM, Park H-S, Esfandyari S, et al. Human mesenchymal stem cell therapy and other novel treatment approaches for premature ovarian insufficiency. Reproductive Sci. 2021;28(6):1688–96.
210. Herraiz S, Romeu M, Buigues A, Martínez S, Díaz-García C, Gómez-Seguí I, et al. Autologous stem cell ovarian transplantation to increase reproductive potential in patients who are poor responders. Fertil Steril. 2018;110(3):496–505. e1.
211. Ding L, Yan G, Wang B, Xu L, Gu Y, Ru T, et al. Transplantation of UC-MSCs on collagen scaffold activates follicles in dormant ovaries of POF patients with long history of infertility. Sci China Life Sci. 2018;61:1554–65.
212. Wang M-Y, Wang Y-X, Li-Ling J, Xie H-Q. Adult stem cell therapy for premature ovarian failure: from bench to bedside. Tissue Eng Part B: Reviews. 2022;28(1):63–78.
213. Kaddoura I, Abu-Sittah G, Ibrahim A, Karamanoukian R, Papazian N. Burn injury: review of pathophysiology and therapeutic modalities in major burns. Annals Burns Fire Disasters. 2017;30(2):95.
214. Jeschke MG, van Baar ME, Choudhry MA, Chung KK, Gibran NS, Logsetty S. Burn injury. Nat Reviews Disease Primers. 2020;6(1):11.
215. Mansilla E, Marín GH, Berges M, Scafatti S, Rivas J, Núñez A et al. Cadaveric bone marrow mesenchymal stem cells: first experience treating a patient with large severe burns. Burns Trauma. 2015;3.
216. Yoshikawa T, Mitsuno H, Nonaka I, Sen Y, Kawanishi K, Inada Y, et al. Wound therapy by marrow mesenchymal cell transplantation. Plast Reconstr Surg. 2008;121(3):860–77.
217. Abo-Elkheir W, Hamza F, Elmofty AM, Emam A, Abdl-Moktader M, Elsherefy S, et al. Role of cord blood and bone marrow mesenchymal stem cells in recent deep burn: a case-control prospective study. Am J Stem Cells. 2017;6(3):23.
218. Zhou Y, Zhao B, Zhang X-L, Lu Y-j, Lu S-T, Cheng J, et al. Combined topical and systemic administration with human adipose-derived mesenchymal stem cells (hADSC) and hADSC-derived exosomes markedly promoted cutaneous wound healing and regeneration. Stem Cell Res Ther. 2021;12(1):257.
219. Li L, Ngo HT, Hwang E, Wei X, Liu Y, Liu J, et al. Conditioned medium from human adipose-derived mesenchymal stem cell culture prevents UVB-induced skin aging in human keratinocytes and dermal fibroblasts. Int J Mol Sci. 2019;21(1):49.
220. Andrzejewska A, Dabrowska S, Lukomska B, Janowski M. Mesenchymal stem cells for neurological disorders. Adv Sci. 2021;8(7):2002944.
221. Chen Y, Shen H, Ding Y, Yu Y, Shao L, Shen Z. The application of umbilical cord-derived MSCs in cardiovascular diseases. J Cell Mol Med. 2021;25(17):8103–14.
222. Chen X-Y, Chen Y-Y, Lin W, Chen C-H, Wen Y-C, Hsiao T-C, et al. Therapeutic potential of human umbilical cord-derived mesenchymal stem cells in recovering from murine pulmonary emphysema under cigarette smoke exposure. Front Med. 2021;8:713824.
223. Tencerova M, Okla M, Kassem M. Insulin signaling in bone marrow adipocytes. Curr Osteoporos Rep. 2019;17:446–54.
224. Umer A, Khan N, Greene DL, Habiba UE, Shamim S, Khayam AU. The therapeutic potential of human umbilical cord derived mesenchymal stem cells for the treatment of premature ovarian failure. Stem Cell Reviews Rep. 2023;19(3):651–66.
225. Shpichka A, Butnaru D, Bezrukov EA, Sukhanov RB, Atala A, Burdukovskii V, et al. Skin tissue regeneration for burn injury. Stem Cell Res Ther. 2019;10:1–16.
226. Fellows CR, Matta C, Zakany R, Khan IM, Mobasheri A. Adipose, bone marrow and synovial joint-derived mesenchymal stem cells for cartilage repair. Front Genet. 2016;7:234346.

227. Zhou T, Yuan Z, Weng J, Pei D, Du X, He C, et al. Challenges and advances in clinical applications of mesenchymal stromal cells. J Hematol Oncol. 2021;14(1):1–24.
228. Moll G, Ankrum JA, Kamhieh-Milz J, Bieback K, Ringdén O, Volk H-D, et al. Intravascular mesenchymal stromal/stem cell therapy product diversification: time for new clinical guidelines. Trends Mol Med. 2019;25(2):149–63.
229. He X, Hong W, Yang J, Lei H, Lu T, He C, et al. Spontaneous apoptosis of cells in therapeutic stem cell preparation exert immunomodulatory effects through release of phosphatidylserine. Signal Transduct Target Therapy. 2021;6(1):270.
230. Stroncek DF, Jin P, McKenna DH, Takanashi M, Fontaine MJ, Pati S, et al. Human mesenchymal stromal cell (MSC) characteristics vary among laboratories when manufactured from the same source material: a report by the cellular therapy team of the biomedical excellence for safer transfusion (BEST) collaborative. Front cell Dev Biology. 2020;8:458.
231. Wright A, Arthaud-Day ML, Weiss ML. Therapeutic use of mesenchymal stromal cells: the need for inclusive characterization guidelines to accommodate all tissue sources and species. Front cell Dev Biology. 2021;9:632717.

## Publisher's note