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Next-generation approaches for mesenchymal stem cell characterization and therapeutic application

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ABSTRACT

Mesenchymal stem cells (MSCs) have been the center of focus in the field of regenerative medicine owing to their intrinsic multipotency, ability for immunomodulation, and paracrine-mediated recovery processes. In spite of extensive research in the clinical setting, the therapeutic application of MSCs is still hindered by challenges from intrinsic heterogeneity, donor-to-donor variability, senescence of cells, and variability in potency. In this review, the recent biological understanding of MSCs is stringently evaluated concerning their role in immunomodulation, anti-apoptotic function, anti-fibrotic activity, angiogenesis, mitochondrial transfer, and antioxidant function. Additionally, it highlights the therapeutic potential of MSCs in osteoarthritis, cardiovascular disorders, and several neuropsychiatric, immunological, and dermatological ailments. Emphasis is placed on innovative approaches being generated for eroding the drawbacks of MSCs, which involve utilizing single-cell and spatial transcriptomics for deconvoluting cellular heterogeneity, applying CRISPR/Cas9 gene editing for genetic modification, and utilizing bioengineering approaches like 3D bioprinting and organ-on-a-chip systems. In addition, cell-free therapy from MSC-derived exosomes and secretomes is discussed as a novel substitute for conventional cell-based therapy, as they pose improved security, stability, and scalability. The integration of preconditioning, gene editing, and targeted delivery is also discussed as a strategic mechanism for enhanced therapeutic efficacy. In all, the review provides a well-integrated framework for MSC-based treatment mechanisms, clinical indications, and technological innovations, furthering the advancement of regenerative medicine.

INTRODUCTION

Friedenstein is credited with describing mesenchymal stem cells (MSCs) for the first time in 1968. The cells had self-renewal and the capability to differentiate into bone and stromal tissue [1]. In 1991, the term "MSCs" was first employed by Caplan. In the 2000s, the discovery that MSCs possess immunomodulatory functions brought great interest in their therapeutic usage [2]. In 2006, in a statement, the International Society for Cellular Therapy observed that the term MSCs is not interchangeable or synonymous with "mesenchymal stromal cell"[3]. First, MSCs are adherent to surfaces in the normal cultivation state [4, 5]. Secondly, MSCs express typical markers like CD105, CD73, and CD90, and are negative for CD45, CD34, CD14 or CD11b, CD79α or CD19, and HLA-DR [4]. Thirdly, the cells are multipotent and differentiate into mesenchymal lineages like osteoblasts, adipocytes, and chondroblasts in *in vitro* conditions [4, 5]. Additionally, some studies have shown that MSCs can differentiate into neural and muscle cells [6, 7]. The adherent nature of MSCs is regulated through the expression of adhesion

molecules like integrins, vinculin, and paxillin on the cells' surfaces [8]. To date, MSCs are present in tissues like adipose tissue [9], umbilical cord blood, dental pulp [9], and amniotic fluid [4].

In spite of increasing interest as well as significant clinical investigations, clinical translation of MSC therapies is delayed by reservations of cellular heterogeneity, donor-to-donor variation, loss of function while expanding, as well as variability of outcomes. Standardization of MSC identity, potency assays, as well as mechanism of action is still an open question. Next-generation technologies like single-cell RNA sequencing, spatial transcriptomics, CRISPR/Cas9 gene editing, 3D bioprinting, as well as organ-on-a-chip hold promise, yet a profound synthesis of the ways they facilitate MSC characterization as well as efficacy is yet distant.

The present review attempts to: i) outline superior MSC therapeutic mechanisms; ii) survey clinical applications under disease categories; iii) survey next-generation technologies for MSC research; as well as iv) outline prospects of enhancing therapeutic performance, including gene editing as well as cell-free techniques. In the union of biological understanding as well as innovation, an integrated framework is being outlined for guiding future MSC therapies.

IMMUNOMODULATORY MECHANISMS

MSCs have their immunomodulatory effects mainly through direct cell-to-cell interactions and secretion of bioactive molecules [10]. They suppress the survival and proliferation of T cells by arresting them in the G0/G1 phase, mediated through the inhibition of cyclin D2 [11]. This cell interaction also enables the induction of regulatory T cells (Tregs) through surface molecules like ICOSL [12]. In an inflammatory environment with high levels of pro-inflammatory cytokines like TNF-α and IFN-γ, the immunosuppressive MSC2 phenotype in MSCs is induced by the activation of toll-like receptor 3 (TLR3) [13, 14]. It is the MSC2 phenotype that secretes a range of anti-inflammatory soluble factors, which include indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), nitric oxide (NO), transforming growth factor-β (TGF-β), hepatocyte growth factor (HGF), and hemoxygenase (HO)[13]. These factors have the ability to suppress the proliferation of T cells. In addition, the MSC2 phenotype enhances the production of TGF-β, which in turn promotes the differentiation of regulatory T cells (Tregs) that suppress immune responses [13].

Additionally, MSC–T cell contact may indirectly suppress B cell activity through the release of soluble factors [15]. MSCs can inhibit the maturation and antibody production of B cells through the secretion of IL-1RA and CCL2, as well as suppress the expression of chemokine receptors on B cells, affecting their migration and function [16]. They also impair B-cell migration by downregulating chemokine receptors [17]. MSCs can also induce tolerogenic dendritic cells that facilitate Treg induction and suppress Th1/Th17 activity [18], [19]. Augello et al. showed that MSCs suppress lymphocyte division through PD-1/PD-L1 and PD-L2 interactions [17]. In addition, MSC-secreted factors influence macrophages by promoting anti-inflammatory M2 polarization. Key molecules such as TGF-β, IL-10, and PGE2 downregulate M1 activity and pro-inflammatory cytokines like TNF-α, IL-1α, IL-6, and IL-12p70, while increasing IL-10 secretion and enhancing phagocytosis [20, 21] (Figure 1).

Besides their direct effects on immune cells, MSCs also mitigate apoptosis-related damage through paracrine mechanisms. MSC apoptosis is essential for their immunomodulatory function. After infusion, many MSCs rapidly undergo apoptosis,

especially in the lungs. These apoptotic cells are phagocytosed by macrophages, which are then reprogrammed into an anti-inflammatory state. This process is a key mechanism underlying the therapeutic effects of MSCs [22]. These are now shown in Figure 1.

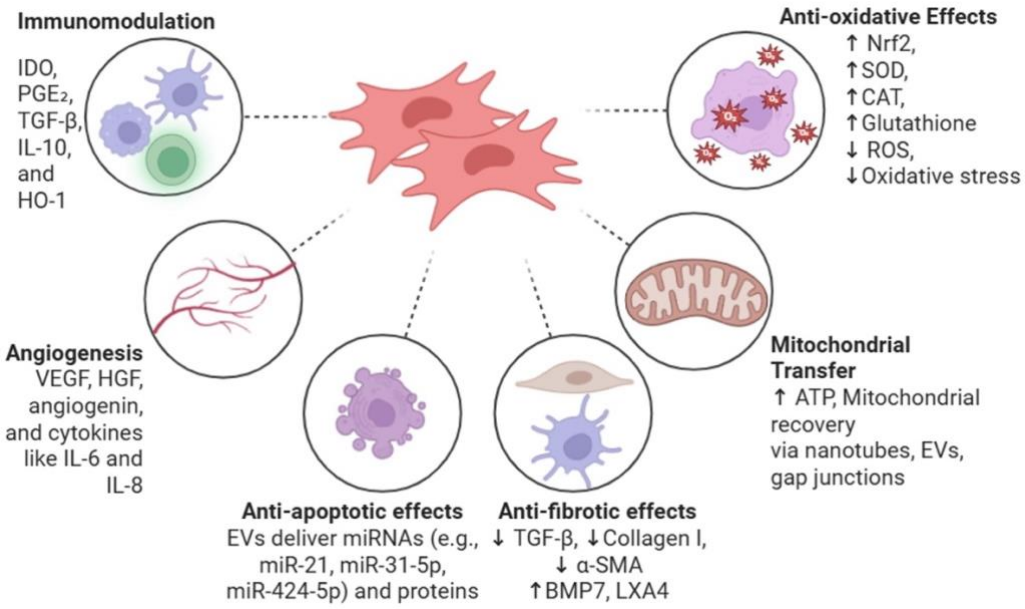

Figure 1. Therapeutic mechanisms of MSCs. MSCs exert therapeutic effects through multiple mechanisms, including immunomodulation, anti-apoptotic effects, anti-fibrotic activity, mitochondrial transfer, and anti-oxidative effects. Each pathway contributes to inflammation resolution, tissue repair, and regeneration (used Biorender.com).

Anti-apoptosis

MSCs exert anti-apoptotic effects via paracrine secretion of extracellular vesicles (EVs) containing miRNAs that regulate apoptosis-related genes. For example, miR-21 reduces ER stress and inhibits p38 MAPK phosphorylation, protecting beta cells from hypoxia-induced apoptosis [23]. EVs from umbilical cord MSCs also reduce granulosa cell apoptosis in premature ovarian failure models[24]. Similarly, miR-31-5p in MSC-derived exosomes inhibits apoptosis and calcification in endothelial progenitor cells by downregulating ATF6 and mitigating ER stress[25]. MSC-derived exosomes can reverse high glucose-induced apoptosis and epithelial-to-mesenchymal transition (EMT) in renal tubular epithelial cells. This effect is mediated by miR-424-5p, which suppresses YAP1 activation in HK2 cells, thereby reducing apoptosis and EMT in diabetic kidney disease models [26] (Figure 1).

Anti-fibrotic

Tissue injury triggers inflammation that promotes fibroblast differentiation into myofibroblasts, leading to fibrosis via excessive collagen I secretion. MSCs can mitigate fibrosis by modulating inflammation and secreting factors such as HGF, BMP7, and LXA4, which reduce TGF-β levels and inhibit TGF-β/Smad and Akt/mTOR/p70S6K pathways[27-29], EVs from BM-MSCs further downregulate fibrosis-related genes like TIMP, MMP3, collagen I, TGF-β, α-SMA, FASL, CCL3, and Snail in diabetic models [30] (Figure 1).

Angiogenesis

Angiogenesis is a key function of MSCs, primarily mediated via paracrine signaling. MSC-conditioned medium enhances endothelial proliferation and tube formation[31, 32]. MSCs secrete pro-angiogenic factors such as VEGF, bFGF, angiogenin, IL-6, IL-8, and HGF, which activate the PI3K/AKT/eNOS pathway in endothelial cells [31, 33, 34]. Stimuli such as co-culture with cardiac cells can further boost VEGF secretion via p38MAPK/pSTAT3 activation [35]. Additionally, angiogenesis-related miRNAs have been identified in MSCs [36]. While MSCs can form tubular structures on Matrigel, they lack endothelial markers like von Willebrand factor, indicating they do not transdifferentiate into endothelial cells [37] (Figure 1).

Mitochondrial transfer

MSCs can transfer healthy mitochondria to damaged cells via tunneling nanotubes and extracellular vesicles [38-41]. This process restores mitochondrial function, enhances macrophage activity, increases ATP levels in alveolar epithelial cells, and supports surfactant secretion [40]. It also improves conditions like fatty liver disease by reducing lipid accumulation [42]. Moreover, mitochondrial transfer can induce Treg differentiation in T cells and aid tissue repair in the eye by targeting corneal and retinal cells [39, 41] (Figure 1).

Anti-oxidative

MSCs demonstrate significant antioxidant properties, offering therapeutic potential for various diseases associated with oxidative stress [43]. MSCs exert their antioxidant effects through multiple signaling pathways, including Nrf2, MAPK, and NF-κB [43]. Studies have shown that MSC transplantation can improve ovarian function and folliculogenesis in animal models by reducing oxidative stress [44]. MSC-derived conditioned medium (CM) has also demonstrated antioxidant and antiviral effects, potentially serving as a cell-free therapy [45]. The antioxidant capabilities of MSCs can be enhanced through preconditioning with probiotic metabolites, improving their wound healing potential [46]. However, prolonged exposure to oxidative stress may impair MSC functions [47]. Overall, MSCs and their derivatives show promise as antioxidant interventions for various conditions, including reproductive aging and vitiligo [48, 49] (Figure 1).

CLINICAL APPLICATIONS OF MSCS

These recent findings on MSC biology resulted in finding guidelines and quality controls for potentially viable clinical applications [50]. But there are also some challenges encountered in standardizing and optimizing MSC therapy, such as cells' survival, immunophenotype, and transplanted cells' efficacy [51]. In spite of all these challenges, MSCs are also being researched for all types of organ systems' clinical trials (Table 1).

Table 1. Clinical applications of MSCs.

Application Area	Key Points	Ref.
Bone and Cartilage	MSCs support cartilage and bone repair, primarily in osteoarthritis, either by scaffolds or through injections.	[52-57]
Cardiovascular Diseases	Improve cardiac function, enhance angiogenesis, lower infarct size; efficacy and safety established through clinical trials.	[58-60]
Neurological Disorders	Cross Blood-Brain Barrier, deliver neurotrophic factors, regulate inflammation; applied for stroke, Traumatic Brain Injury, Parkinson's, etc.	[61-66]
Immune/Autoimmune Diseases	MSCs regulate immune responses and have been experimentally tested in multiple sclerosis, rheumatoid arthritis, type 1 diabetes, systemic lupus erythematosus, inflammatory bowel disease, and graft-versus-host disease, etc.	[67-71]
Wound Healing & Skin	Promote healing of chronic ulcers, burns, and scars; reduce inflammation and scarring.	[72-74]
Gastrointestinal Disorders	Suppression of IBD inflammation; safe and efficacious double-gene therapy of malignancies.	[75, 76]
Respiratory Diseases	Safe in COPD and ARDS; systemic immune response control and quality of life enhancement.	[77-79]

IBD: Inflammatory Bowel Disease; COPD: Chronic Obstructive Pulmonary Disease; ARDS: Acute Respiratory Distress Syndrome

Bone and cartilage regeneration

Clinical trials have shown promising results for MSC-based therapies in bone regeneration and osteoarthritis (OA). In bone repair, MSCs are often combined with scaffolds to improve outcomes. For example, a Phase I/II study by Blanco et al. used autologous bone marrow-derived MSCs with tricalcium phosphate in spinal fusion, reporting reduced pain and better mobility after 12 months [52]. Other studies have successfully treated delayed or non-union fractures using MSCs with bioceramics [53], and dental pulp-derived MSCs with collagen scaffolds have shown potential in periodontal regeneration [54].

In OA, MSCs are being tested for cartilage repair through various delivery methods, including intra-articular injection and scaffold-based implantation [55]. A 7-year study using umbilical cord blood-derived MSCs with hyaluronic acid (Cartistem) showed encouraging results in OA management[56]. Additional trials are comparing the effects of bone marrow-derived MSCs with or without platelet-rich plasma, expanding therapeutic strategies for OA [57].

Cardiovascular diseases

MSCs have emerged as a promising therapeutic option for addressing the complex challenges posed by heart failure and myocardial infarction (heart attack). This cellular therapy has demonstrated therapeutic potential due to the inherent regenerative and immunomodulatory properties of MSCs. Several clinical trials have not only underscored the safety profile of MSCs but has also demonstrated their ability to tangibly improve cardiac function and reduce the size of the infarcted area in patients grappling with these conditions [58], [59].

Furthermore, clinical investigations have revealed that MSC therapy extends beyond mere symptom management. It actively contributes to the restoration of cardiac functionality by stimulating angiogenesis, the formation of new blood vessels, in individuals with ischemic heart disease [60].

Neurological disorders

Neurological disorders place a significant burden on healthcare systems worldwide, with none of these disorders having effective therapies. MSCs have emerged as a promising therapy for neurological disorders because of their multipotency, low degree of immunogenicity, and ability to pass through the blood-brain barrier [61, 62].

MSCs could be used in the disorders of diseases of the nervous system such as stroke, traumatic brain injury, spinal cord injury, multiple sclerosis, Alzheimer's disease, and Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and spinal cord injury [63, 64]. Their effects are primarily through paracrine and immunomodulatory effects with the release of neurotrophic factors and extracellular vesicles [65]. MSCs could modulate neuroinflammation through the regulation of interleukin-6 levels and other mediators of inflammation [66]. MSC treatment has proven its efficacy in clinical trials with mild side effects as the most common [63]. Further studies are needed to further improve manufacturing processes, modes of delivery, and overcome regulatory barriers for extended clinical application [65].

Immune disorders and autoimmune diseases

MSCs have shown clinical potential in treating autoimmune and immune-related disorders due to their immunomodulatory and anti-inflammatory properties. Clinical trials have explored their use in conditions such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes, lupus, IBD, and Sjögren's syndrome [67]. In a study by Dantas et al., adipose-derived MSCs combined with vitamin D3 were used in type 1 diabetes patients, potentially preserving insulin-producing cells [68].

MSCs have also been effective in managing graft-versus-host disease (GvHD), particularly steroid-refractory cases. Early clinical use in acute GvHD demonstrated therapeutic benefit [69], while recent studies, such as by Galleu et al., investigated early biomarkers of response following MSC infusion [70]. Long-term safety and efficacy of intravenous allogeneic MSCs have also been reported in pediatric GvHD [71]. Although encouraging, further research is needed to elucidate the mechanisms underlying MSC-mediated immune regulation and optimize therapeutic protocols.

Wound healing and tissue repair

MSCs are being investigated as a promising therapy for chronic wounds, scarring, and skin regeneration. Qin et al. reported that umbilical cord-derived MSCs, when applied post-angioplasty, were safe and effective for diabetic foot ulcers [72]. In a phase I/IIa trial, Kerstan et al. demonstrated that ABCB5^{+} skin-derived MSCs reduced venous leg ulcer size, potentially through suppression of IL-1β-driven M1 macrophage activation [73]. Hertegård et al. also showed encouraging results using autologous bone marrow MSCs to treat vocal fold scarring, improving phonation pressure and vocal fold function [74]. ClinicalTrials.gov lists at least 10 trials investigating MSCs for burn wound healing and 3 for skin aging. These efforts highlight the regenerative potential of MSCs in dermatological and reconstructive applications, though further validation is required to confirm efficacy and clinical utility.

Gastrointestinal disorders

One of the primary areas of interest is the use of MSCs in inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis. Several clinical trials have demonstrated the safety and potential efficacy of MSC therapy in reducing inflammation in IBD patients. MSCs that were injected into 10 Crohn's disease patients are supposed this be safe, well-tolerated, and may offer a benefit [75].

Additionally, MSCs have shown promise in treating gastrointestinal cancers. Phase 1/2 TREAT-ME-1 trial showed that MSC combined with ganciclovir was safe and tolerable in patients with advanced gastrointestinal adenocarcinoma. Half of the patients (5 out of 10) achieved stable disease, and some showed long-term survival. However, the lack of impact on tumor markers suggests the treatment may not be directly affecting tumor growth [76].

Respiratory diseases

MSCs have been clinically evaluated for pulmonary diseases, particularly chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS). A Phase I study by Armitage et al. showed that intravenous infusion of bone marrow-derived MSCs in stable COPD patients was safe and modulated systemic immune responses, potentially reducing inflammation and exacerbation frequency, though no improvement in lung function was observed [77].

Similarly, a Vietnamese pilot study using allogeneic umbilical cord-derived MSCs for moderate-to-severe COPD confirmed safety and reported improvements in patient quality of life, despite minimal changes in lung function or exercise capacity [78]. In ARDS, Wilson et al. conducted a dose-escalation Phase I trial using intravenous bone marrow MSCs at doses ranging from 1 to 10 million cells/kg predicted body weight. The treatment was well-tolerated, with no infusion-related adverse events, although two patient deaths were deemed unrelated to therapy. While the trial confirmed safety, it could not identify an optimal therapeutic dose [79].

EMERGING TECHNOLOGIES AND TECHNIQUES

Recent advances in bioengineering and emerging technologies have provided a portfolio of powerful tools for MSC research and clinical translation. These innovations not only significantly enhance our understanding of MSC heterogeneity, functions, and interactions with the microenvironment but also offer novel strategies to improve their regenerative potential. Those precious tools and platforms mentioned briefly in Table 2 are speeding up the development of MSC-based regenerative medicine. Each of those tools contributes differently to fine-tuning MSC isolation, characterization, and clinical efficacy.

Table 2. Emerging technologies and techniques in enhancing MSC research and application.

Technology/Technique	Key Points	Ref.
Single-cell RNA Sequencing	Deciphers heterogeneity, identifies subpopulations, and reveals differentiation potential and immune properties.	[78-89]
Spatial Transcriptomics	Preserves spatial context, maps MSC distribution and roles in tissue niches, useful in bone and cancer studies.	[90-95]
AI & Machine Learning	Used in cell image classification, predicting differentiation, and optimizing therapeutic outcomes.	[96-101]
CRISPR-Cas9 Gene Editing	Enables precise modification to enhance survival, migration, anti-inflammatory capacity, and reduce senescence.	[102-110]
3D Bioprinting	Fabricates tissue constructs using MSCs; applied in cartilage, bone, wound, and nerve regeneration.	[111-115]
Organoid/Organ-on-a-chip	Mimics human tissue complexity; evaluates MSC function and effects multi-organ interactions.	[116-118]
Engineering MSCs for Enhanced Therapeutic Efficacy	Includes genetic modification (e.g., overexpression of CXCR4, IL10), preconditioning (e.g., hypoxia, cytokines), and 3D culture to enhance efficacy.	[119–138]

AI: Artificial Intelligence; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; Cas9: CRISPR-associated protein 9; 3D: Three-Dimensional; CXCR4: C-X-C Motif Chemokine Receptor 4; IL10: Interleukin-10

Emerging technologies for decoding MSC heterogeneity

MSC Single-Cell RNA Sequencing

Single-cell RNA sequencing (scRNA-seq) is a technology that allows for the sequencing of RNA from individual cells. Unlike bulk RNA-seq, which measures the average gene expression levels within a cell population, scRNA-seq can capture the expression distribution of each gene in a single cell. Many studies have found that MSCs exhibit heterogeneity at various levels: individual, tissue, clone, and cell. Furthermore, the existing MSC markers do not provide information on the differentiation potential of each cell type. This poses challenges in determining the growth and transformation of cells in response to different conditions. Therefore, scRNA-seq is applied in the study of MSCs to discover new markers and functions of subpopulations.

Several studies have used scRNA to identify markers for bone marrow stem cells [80], osteochondroreticular cells [81], and adipose precursor cells [82]. Harman *et al.* demonstrated distinct marker expression differences among MSCs isolated from different sources in horses. Additionally, scRNA-seq can assess differential marker expression among cells from the same source [83, 84]. Studies have identified multiple MSC subpopulations, including those with enhanced wound repair, immunoregulatory, and osteogenic properties [85, 86]. ScRNA-seq has also provided insights into MSC differentiation trajectories and interactions with the cellular microenvironment [87].

Moreover, based on gene expression levels, differential gene expression can be identified to study immune regulation processes [88], proliferation, and environmental responses of MSCs [89, 90]. This allows for the characterization of disease mechanisms and evaluation of the therapeutic potential of MSCs. For instance, using single-cell RNA-seq technology, Hou et al. compared the differentiation potential of umbilical cord-derived MSCs, adipose-derived MSCs, and bone marrow-derived MSCs [91].

Spatial transcriptomics

Recent advancements in spatial transcriptomics (ST) have revolutionized our understanding of complex tissues by preserving spatial information during transcriptomic. This technology has been applied to various fields, including bone

research, where it has revealed novel cell clusters and their spatial organization within the bone marrow niche [86, 92]; ST has also been used to study MSCs in osteochondral repair, identifying distinct subpopulations with different functional roles [93]. In colorectal cancer research, ST has helped map the intratumoral heterogeneity of consensus molecular subtypes and their microenvironment [94]. To analyze ST data, new computational methods like Spatial PCA have been developed, enabling dimension reduction while preserving spatial correlation structure[95]. These advances have significantly improved our understanding of tissue complexity in various contexts, including oral pathogenesis[96] and hematopoiesis [97].

Artificial intelligence and machine learning

Artificial intelligence and machine learning (AI/ML) are increasingly applied in stem cell research, particularly for MSCs. These technologies have shown promise in cell classification, monitoring functionality, and genetic analysis [98]. AI and ML have been used to analyze stem cell images, predict cell types and differentiation efficiency, and enhance therapeutic outcomes [99]. Convolutional neural networks have been employed to classify MSC lines based on morphological features, achieving high accuracy [100]. AI and ML are also being utilized in drug development, disease modeling, and personalized medicine [101]. The integration of these technologies has led to improved understanding of cell heterogeneity, standardization of cell therapy quality, and advancements in tissue engineering [102]. However, ethical considerations and data quality remain important factors in their application [103].

CRISPR-Cas9 gene editing

CRISPR-Cas9 is a revolutionary gene-editing tool that allows scientists to make precise changes to an organism's DNA. This system can perform various operations on the genes of MSCs, including knock-in, knock-out, activation, or inactivation [104]. A study using CRISPR/Cas9 aimed to transfer the immortal gene into MSCs from bone marrow, thereby increasing the cells' immortality. This study also demonstrated that CRISPR/Cas9 is more efficient in gene transfer than retroviruses [105]. Another study showed that CRISPR/Cas9 can activate genes in stem cells by targeting regulatory regions, thereby altering the cell's phenotype [106].

Furthermore, due to its precise cutting ability, CRISPR/Cas9 can be used to remove any specific gene from a cell (knock out), allowing researchers to assess the gene's role in the cell. For example, scientists removed the C-X-C motif chemokine ligand 12 (CXCL12) from bone marrow stem cells to evaluate the role of this chemokine in the process of MSCs differentiation [107]. This method can also be applied in studying the role of miRNA [108].

In clinical applications, CRISPR/Cas9 includes the ability to regulate immunity [109] and reduce apoptosis [110]. Yeshai Schary et al. used CRISPR-based gene editing to disrupt the TLR4 gene in human cardiac MSCs. TLR4 deficiency in these cells enhances cell survival, left ventricular repair, and cardiac function after myocardial infarction (MI) in mice[111]. In addition to altering gene expression in cells, CRISPR/Cas9 can modify the gene expression of extracellular vesicles, thereby increasing therapeutic potential [112].

3D bioprinting

3D bioprinting is a technology that uses 3D printing to layer living cells, hydrogels, and stimulating chemicals to create complex tissues. It enables the creation of extracellular matrix (ECM) layers, the cultivation and differentiation of MSCs, and the production of customized tissues. Numerous studies have utilized 3D bioprinting in conjunction with MSCs for cartilage regeneration and joint function restoration [113, 114], bone tissue regeneration, and wound healing [115]. Notably, researchers are also exploring the use of bioprinting to generate nerve tissues from MSCs [116]. Additionally, this combination shows significant potential in the field of aesthetics, where co-culturing adipose-derived stem cells with chondrocytes can produce cartilage tissue for nasal augmentation [117].

This method addresses the challenges of organ transplantation shortages, inadequate tissue matching, and graft rejection. Scientists are continuously striving to discover new materials and printing techniques. It is hoped that in the future, 3D bioprinting will be able to create larger and more complex organs, thus alleviating the shortage of organ transplantation.

Organoid and organ-on-a-chip, and microfluidics

Drug activity testing with traditional two-dimensional (2D) cell culture, while useful, cannot define tissue structure and tends to provide misleading information. Animals, while capable of showing differences from humans through interspecies variation of functional organs, are also beset with undue expense. MSCs have emerged as powerful tools for the creation of biologically relevant in vitro models that bear close similarities with tissue and organs in humans. By exploiting MSCs' unique features such as the capacity for differentiation into diverse cells and for regenerating tissue, researchers are able to create three-dimensional (3D) organoid or organ-on-a-chip models. Such sophisticated in vitro systems provide not only a more physiologically relevant microenvironment but also provide the means of studying intricate cell interactions, disease processes, and treatment responsiveness in controlled and economical ways.

By combining cell technology and chip manufacturing technology, researchers have developed microfluidic organ-on-a-chip devices that mimic various organs in the body. These chips feature channels and fluid delivery systems to recreate the survival environment and interactions between organs. Unlike organoids, organ-on-a-chip models are much smaller in scale and do not require replicating the exact structure of the actual organ, while still allowing for the representation of multi-organ interactions. With their potential to differentiate into multiple cell types and self-renewal capabilities, stem cells are one of the primary cell sources employed in the creation of organ-on-a-chip (OOC) models [118]. Embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and MSCs can all be utilized as cell sources; however, due to their limited differentiation potential, MSCs have less promising applications compared to pluripotent stem cells [119]. Moreover, OOC models can also be employed in the study of MSCs themselves. For instance, one study evaluated the impact of bone marrow stem cell secretions on kidney and liver organoid-based multi-organ-on-a-chip models. Through this experiment, researchers could assess the therapeutic effects of the secretions on injured kidneys while simultaneously observing their influence on the liver [120].

ENGINEERING MSCS FOR ENHANCED THERAPEUTIC EFFICACY

Some studies have shown that MSC therapy does not achieve the desired results due to the unfavorable environment in the damaged tissue areas, causing cell atrophy and death [121]. Therefore, measures are needed to increase the survival ability of MSCs after transplantation, thereby increasing the effectiveness of treatment.

Genetic modification can be an effective method to solve the above problem. In this method, researchers use vectors to insert genes encoding the necessary factors to enhance cell survival ability [122-124]. Some factors that can be introduced into cells include enhancing the expression of anti-inflammatory cytokines or inhibiting the apoptosis process [125, 126]. miRNAs can be used to regulate gene expression, thereby enhancing the expression of certain genes or reducing the expression of undesired genes. Some studies have shown that the gene editing process can also prevent aging [122, 127, 128] and increase the adhesion ability of MSCs.

One of the other major challenges in using MSCs for treatment is ensuring their ability to migrate to the desired location in the body. After injection, a significant number of MSCs may be trapped in pulmonary circulation and unable to access the areas in need of intervention. In addition, MSCs often exhibit heterogeneous expression of chemokine receptors, reducing their ability to migrate accurately to specific locations in the body [129, 130]. To enhance the therapeutic efficacy of MSCs, researchers have attempted to improve their migration ability by enhancing the expression of important chemokine receptors [130]. A research by Xiu et al. showed that by increasing CXCR4 expression on MSCs, these cells were able to migrate more accurately to the site of liver injury in a mouse model, leading to higher therapeutic efficacy [131]. Li et al. used mRNA to express the CXCR2 receptor on MSCs, allowing them to recognize CXCL2 and CXCL5 chemokines in the colitis environment [132].

In addition to enhancing cell survival after transplantation, genetic modification can also increase the therapeutic potential of MSCs. For example, mRNA encoding CXCR4 and IL10 has been transferred into adipose-derived stem cells. CXCR4 helps improve the migration ability of stem cells towards the site of inflammation, while IL10 helps reduce inflammation compared to normal MSCs [123]. Han et al. transferred the IFN-β gene into adipose-derived stem cells. The gene-transferred cells showed the ability to fight against canine melanoma, a type of cancer in dogs [133]. Another study showed that MSCs transferred with the manganese superoxide dismutase (MnSOD) gene accelerated the recovery from radiation-induced lung injury [134].

Preconditioning can also enhance the therapeutic potential of MSCs. This is a process of treating the cells before using them in therapy by exposing them to specific biological, physical or chemical agents. Wang et al. showed that MSCs treated with N-methyldopamine and norepinephrine increased exosome secretion threefold without altering exosome characteristics [135]. Additionally, supplementing the culture medium with certain components can modify the exosome composition and increase therapeutic potential. For instance, a group led by Liming Li reported a study focusing on using exosomes derived from hypoxic preconditioned human umbilical vein endothelial cells to stimulate angiogenic MSCs for spinal cord injury treatment [136]. The study of Zhang et al found that treatment with interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) can resolve variations in cell proliferation and immunomodulatory functions of human umbilical cord-derived MSCs obtained from different donors [137].

3D culture can be employed to increase cell culture density, while enhancing cell-cell and cell-environment interactions. Consequently, 3D culture increases the yield of

secreted products [138, 139]. Furthermore, research shows that 3D culture can enhance the activity of cytokines and growth factors from MSCs compared to 2D culture [140]. These are shown in Figure 2.

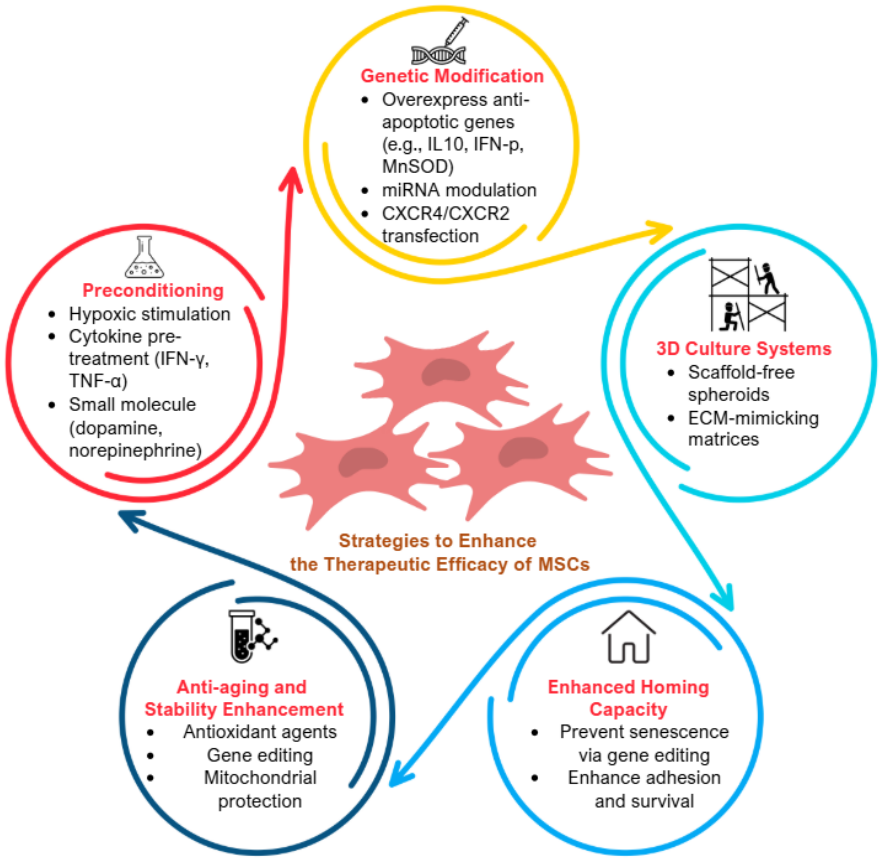

Figure 2. Strategies to enhance the therapeutic efficacy of MSCs. These include preconditioning, genetic modification, 3D culture systems, enhanced homing, and anti-aging/stability enhancement. Together, they improve MSC survival, functional stability, and therapeutic outcomes.

CHALLENGES AND FUTURE PERSPECTIVES

Challenges

One of the major challenges in the application of MSCs is their inherent heterogeneity. MSCs can be isolated from various tissue sources, such as adipose tissue, bone marrow, umbilical cord, or dental pulp, and the source significantly affects their proliferation rate, differentiation capacity, and immunomodulatory profile [141]. Furthermore, donor variability, including age and health status, may also influence therapeutic outcomes [142]. In vitro expansion conditions are another critical factor, as prolonged culture can lead to genetic and epigenetic alterations that impair MSC functionality [143].

The lack of standardized protocols in the production and characterization of MSCs remains a major regulatory barrier. Regulatory bodies like the FDA emphasize the importance of harmonized methods to ensure the safety, efficacy, and consistency of MSC-based therapies. Variations in isolation, expansion, and quality control procedures complicate the approval process and hinder clinical translation [144]. Moreover, the mechanisms of action of MSCs remain incompletely understood, and in many cases, therapeutic benefits have been observed without clear mechanistic explanations, limiting scientific advancement. Additional challenges include limited long-term safety

data, inconsistent clinical trial outcomes, and issues related to cell homing, phenotype stability during culture, and functional maintenance post-transplantation [145].

To address these concerns, it is essential to develop globally harmonized guidelines for MSC production, clinical use, and post-transplant monitoring. Countries currently employ diverse regulatory frameworks [146], creating inconsistencies in safety and quality standards. Simultaneously, further research is needed to elucidate MSC behavior in vivo, ensure long-term safety, and mitigate adverse effects. Healthcare providers must also strictly comply with ethical and legal regulations concerning cell sourcing, donor consent, and traceability, while policies around intellectual property, clinical trial transparency, and equitable access to MSC therapies remain equally critical [147]. In parallel, clear policies regarding intellectual property, clinical trials, and ensuring equitable access to stem cell therapies for all citizens are needed.

Future perspectives

Personalized medicine and biomarker discovery

With their high adaptability and potential to differentiate into various cell types, MSCs can be optimized to treat specific diseases for individual patients. They can be derived from a patient's own body, such as bone marrow or adipose tissue, eliminating the risk of immune rejection. Additionally, the banking of perinatal MSCs is gaining increasing attention. This process involves storing MSCs, particularly from perinatal tissue, in stem cell banks, contributing to the advancement of personalized medicine [145]. Currently, researchers are still searching for additional biomarkers related to MSCs and exploring their roles. Feng et al. conducted a study that identified potential biomarkers involved in modulating osteogenic differentiation in MSCs. Most of these markers are associated with inflammation and immunity [148]. Choi et al. discovered novel markers in cerebrospinal fluid that have potential applications in predicting and monitoring the response of Alzheimer's disease patients to MSCs. Specifically, reticulocalbin-3 (RCN3) and follistatin-related protein 3 (FSTL3) can predict the response to MSCs, while scrapie-responsive protein 1 (SCRG1), neural proliferation differentiation and control protein (NPDC1), apolipoprotein E (ApoE), and cystatin C (CysC) are potential biomarkers for monitoring MSC response in patients with Alzheimer's disease [149].

Furthermore, several studies have been conducted to identify new biomarkers associated with the aging process of MSCs. Qian Lei et al. attempted to evaluate MSC aging through the analysis of microvesicles released by these cells [150]. Another study identified TBX15, IGF1, GATA2, PITX2, SNAI1, and VCAN as potential biomarkers for diagnosing the aging state of donor MSCs [151]. These studies provide a potential approach to control the quality of MSCs before transplanting patients.

Applications for cancer treatment

MSCs are attracted to sites of tissue damage and the tumor microenvironment due to inflammatory mediators. Cell migration is influenced by various signals, like immune cells responding to injury [152]. This homing ability has drawn attention to investigating MSCs as a vector for delivering drugs and biological products for targeted treatment of damaged tissues and organs, particularly cancer.

MSCs have been shown to be capable of migrating to tumor sites and inhibiting the growth of cancer cells. One study demonstrated that when cultured in a high concentration of the chemotherapeutic drug gemcitabine, MSCs not only took up the

drug but also acquired the ability to migrate to tumors and suppress the proliferation of cancer cells [153]. Additionally, researchers have utilized MSCs to deliver a prodrug called G114 for the targeted treatment of prostate cancer. G114 is an inactive form of the drug and becomes activated when it reaches the tumor. An enzyme protease that has high levels in tumors can activate G114. Therefore, the drug can be targeted directly to the tumor, reducing the risk of side effects on healthy cells [154]. Moreover, exosomes secreted by MSCs have also been studied as drug delivery vectors. Bagheri and colleagues loaded doxorubicin into exosomes derived from bone marrow MSCs using electroporation and then administered the exosomes to mice with colon cancer. The results showed a reduction in tumor growth in mice injected with exosomes. Additionally, the authors conjugated aptamers onto the exosomes [155].

Based on these characteristics and research findings, MSCs have demonstrated the potential to serve as vectors for delivering drugs, prodrugs, and other biological products to target damaged tissues and organs, particularly tumors. This approach helps minimize undesirable effects on healthy tissues and organs, enhancing therapeutic efficacy while reducing side effects of the treatment.

"Off-the-shelf" technology

Beyond traditional therapeutic approaches, efforts are underway to develop stem cells, particularly MSCs, into drug formulations. In this form, stem cells can be harvested, preserved, and pre-packaged, ready for administration when needed without requiring further processing. The process of introducing stem cells into the patient's body is non-invasive.

Currently, several countries have approved certain stem cell-derived drugs. Remestemcel-L, originating from bone marrow stem cells, was the first to be approved for the treatment of steroid-refractory Graft-versus-Host Disease (GVHD) in Canada [156]. and was subsequently approved by the U.S. FDA. South Korea has also approved Cupistem for the treatment of anal fistulas and Cartistem for the treatment of cartilage injury and osteoarthritis [157]. Another approved product in Europe is Alofisel, derived from adipose-derived stem cells, used for the treatment of complex perianal fistulas in Crohn's disease patients [158]. Recently, India has successfully produced a stem cell drug called Stempeucel for the treatment of Critical Limb Ischemia [159]. In the future, many more MSC-derived drugs are expected to be researched and manufactured to meet the growing demand for effective treatments.

Cell-free therapy

MSCs exert therapeutic effects mainly through secreted factors such as cytokines, chemokines, and EVs, especially exosomes. These products possess anti-inflammatory, anti-fibrotic, antioxidant, and regenerative properties, and offer advantages in storage, safety, and immune tolerance compared to whole-cell therapies [160, 161].

Exosomes are widely applied due to their small size and ability to interact with target cells via fusion or receptor binding. They have shown efficacy in treating cardiovascular, neurological, and autoimmune diseases, including supporting stroke recovery and reducing inflammation [162]. Recent studies highlight their potential in organ preservation [163], COVID-19 therapy by preventing cytokine storms [164], and antiviral action, such as inhibiting HCV replication via miRNAs [165]. These findings could open new applications for treatment using cell-free therapies with MSCs.

Bioinformatics applied

Transcriptomic tools are widely used to explore MSC differentiation, identify key genes/miRNAs involved in osteogenic and adipogenic pathways, and understand BMP-9-induced differentiation [166]. They also aid in discovering surface markers to classify MSC subpopulations, such as nine non-classical markers found in adipose-derived MSCs (AMSCs) [167]. Additionally, transcriptomics helps assess MSC roles in disease contexts, revealing reduced therapeutic potential in type 2 diabetes and associations with conditions like adolescent idiopathic scoliosis. It also complements proteomic analyses to evaluate the therapeutic relevance of MSCs and their vesicles [167].

CONCLUSIONS

MSCs have emerged as a cornerstone in regenerative medicine due to their multipotency, immunomodulatory capacity, and paracrine effects. Over the past decades, substantial progress has been made in understanding their biological mechanisms and clinical potential. However, challenges such as cell heterogeneity, limited engraftment, and the lack of standardized potency assays continue to hinder their widespread clinical application. The integration of emerging technologies, including single-cell transcriptomics, CRISPR-based gene editing, 3D bioprinting, and organ-on-chip platforms, offers new opportunities to enhance MSC functionality, precision, and safety. Additionally, strategies such as preconditioning, biomaterial encapsulation, and secretome optimization may further improve therapeutic outcomes. To translate MSC-based therapies from bench to bedside effectively, future research must focus on unraveling their in vivo mechanisms of action, identifying reliable biomarkers, and establishing harmonized regulatory frameworks. By addressing these scientific and translational barriers, MSCs may fulfill their promise in a wide range of clinical indications, from immune disorders to tissue regeneration and personalized medicine.

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AUTHOR CONTRIBUTIONS

PDH conceptualized the review topic, developed the outline, and finalized the manuscript. DHTV prepared the initial draft based on the outline, while KVTN was responsible for updating the literature and enriching the content with relevant data. NBV contributed by reviewing the manuscript for clarity, grammar, and consistency. NCN contributed by preparing tables and figures, drafting responses to reviewers, thoroughly reviewing the manuscript, and managing reference formatting. All authors contributed to the critical revision of the work and approved the final version for submission.

CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

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