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Mesenchymal Stem Cells as Cornerstones of Regenerative Medicine: Mechanisms, Applications, and Future Perspectives

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REVIEW

Mesenchymal Stem Cells as Cornerstones of Regenerative Medicine: Mechanisms, Applications, and Future Perspectives

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ABSTRACT

Regenerative medicine is a multidisciplinary domain focused on restoring, repairing, or replacing damaged tissues and organs by harnessing the body's inherent healing abilities with sophisticated biological and technical techniques. Mesenchymal stem cells (MSCs) have become fundamental among many stem cell types because to their self-renewal, multipotency, paracrine signaling, and immunomodulatory capabilities. Their therapeutic adaptability has been shown in orthopedic, cardiovascular, neurological, dermatological, and immune-mediated illnesses, underscoring their clinical significance. Nonetheless, obstacles like donor heterogeneity, senescence during in vitro growth, restricted engraftment, and regulatory impediments persist in limiting repeatability and broad clinical use. Recent advancements are enhancing the capabilities of MSCs by using biomaterials, genetic modification, and cell-free methodologies, including MSC-derived extracellular vesicles. An intriguing domain is the interplay between MSCs and bioactive peptides, which can enhance cell adhesion, survival, differentiation, and targeted regenerative outcomes. This brief review outlines the fundamental principles of regenerative medicine, summarizes the unique attributes and therapeutic applications of MSCs, and highlights novel approaches that may overcome current limitations. These improvements collectively position MSCs as essentil catalysts for the next generation of regenerative therapies.

Keywords: Bioactive peptides, Extracellular vesicles (EVs), Mesenchymal stem cells (MSCs), Paracrine signaling, Regenerative medicine, Tissue engineering

1. Introduction

Regenerative medicine is an evolving multidisciplinary domain focused on restoring, replacing, or regenerating damaged tissues and organs to restore their normal functionality [1, 2]. Regenerative medicine targets the fundamental causes of illness by using the body's own healing mechanisms, unlike traditional medicines that often just mitigate symptoms [3]. It provides a revolutionary method for addressing degenerative illnesses, injuries, and organ failure by integrating concepts from cell biology, molecular medicine, biomaterials research, and tissue engineering, while also aligning with broader global health and environmental challenges [4–6]. The use of stem cells, notable for their ability to differentiate into

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various cell types and self-renew, is crucial to this domain [7]. Mesenchymal stem cells (MSCs) have attracted significant interest owing to their availability, multipotency, and advantageous safety profile compared to other stem cell types [8]. Various sources, such as bone marrow [9], adipose tissue [10], umbilical cord [11], and dental pulp [12], can be utilized to collect MSCs, making them widely relevant in clinical and research settings [13].

Besides their differentiation potential, MSCs have considerable paracrine effects by secreting bioactive substances, growth factors, and extracellular vesicles that modulate the immune response, enhance angiogenesis, and support endogenous repair [14]. Cytokines like IL-6 are crucial in influencing the inflammatory milieu, and new research suggests that the manipulation of IL-6–CXCL1 communication, for example by resveratrol, can markedly affect cellular survival and gene expression profiles [15]. These findings underscore the significance of cytokine modulation in the therapeutic uses of MSCs.

The combined mechanism of direct differentiation and indirect trophic signaling positions MSCs as a crucial element in modern regenerative approaches [16]. The multifaceted role of MSCs encompassing their differentiation potential, paracrine activity, and broad clinical applications is summarized in Fig. 1. Notwithstanding the swift advancements, regenerative medicine continues to encounter scientific and translational obstacles. Challenges like donor variability, restricted cell viability post-transplantation, and the necessity for standardized methods persist in obstructing the complete clinical implementation of MSC-based treatments [17, 18]. Nevertheless, continuous progress in biomaterials, genetic engineering, and manufacturing is facilitating more reliable and efficient uses.

This mini review presents an introduction of the fundamental concepts of regenerative medicine, emphasizes the distinctive characteristics of MSCs, and examines their current and prospective uses. Also, delineates the strengths, limits, and future prospects of MSC-based treatments to provide a succinct yet thorough overview of their pivotal role in regenerative medicine.

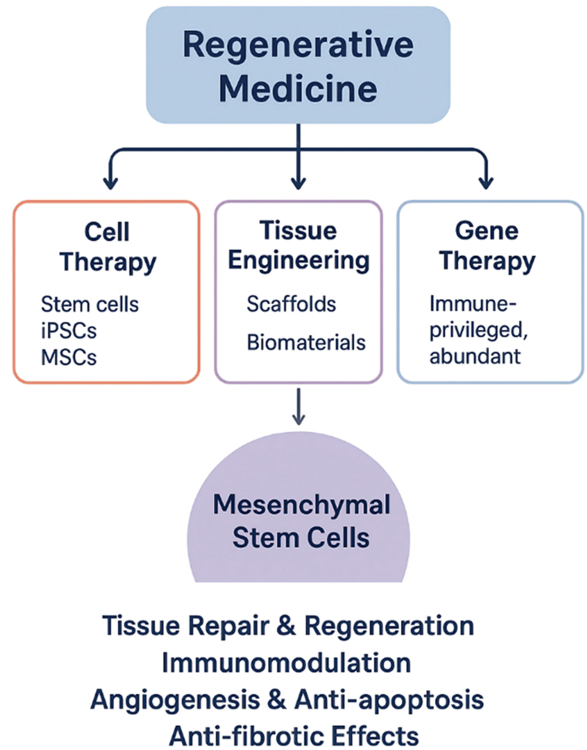

Fig. 1. Overview of regenerative medicine and the central role of MSCs.

2. Basic principles of regenerative medicine

Regenerative medicine has developed as a revolutionary paradigm in biomedical research, seeking to restore, repair, or replace damaged tissues and organs by biological and technological treatments. The conceptual framework is founded on the body's intrinsic ability for self-repair, which may be enhanced by external cells, bioactive chemicals, and manufactured materials [19]. In contrast to traditional treatments that typically offer only brief symptomatic relief, regenerative medicine aims for enduring functional recovery by addressing the underlying causes of tissue deterioration [20]. This characteristic highlights its capacity to tackle a wide array of ailments, from acute traumas to chronic degenerative disorders.

The basic theory of regenerative medicine is cell-based treatment. Stem and progenitor cells serve as the basis for regeneration owing to their capacity for self-renewal and differentiation into specialized cell types [21]. MSCs are particularly noteworthy due to their extensive tissue distribution, simplicity of separation, and excellent safety profile in both preclinical and clinical settings. MSCs demonstrate multipotency by developing into osteogenic, chondrogenic, and adipogenic lineages, thereby directly facilitating structural tissue regeneration [22]. In addition to differentiation, their paracrine activity facilitated by cytokines, chemokines, and extracellular vesicles significantly influences tissue healing [23].

The second concept involves the incorporation of biomaterials and scaffolds. Regeneration needs a conducive microenvironment that offers mechanical stability and biochemical direction. Biocompatible scaffolds, originating from natural (e.g., collagen, fibrin, chitosan) and synthetic (e.g., polylactic acid, polyethylene glycol) materials, function as transient matrices to promote cellular adhesion, proliferation, and differentiation. These scaffolds can be designed with nanoscale architecture, functional groups, or regulated porosity to replicate the extracellular matrix (ECM) [24, 25]. The capacity to provide bioactive substances in a geographically and temporally regulated fashion significantly amplifies their function in directing tissue remodeling.

The control of molecular and signaling pathways is equally significant. Regeneration necessitates meticulous synchronization of growth factors and signaling pathways that regulate inflammation, angiogenesis, and cellular recruitment. Molecules such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and fibroblast growth factor (FGF) are crucial in initiating vascularization and extracellular matrix (ECM) remodeling. Furthermore, exosomes and micro-vesicles produced from MSCs convey microRNAs and proteins that reprogram recipient cells and affect the regenerative niche [26–28]. This recognition has shifted the focus of the field from only cell replacement to a broader comprehension of the secretome and its therapeutic potential.

The immune system serves as a crucial foundation of regenerative medicine. The efficacy of tissue repair relies on the transition from pro-inflammatory to pro-healing immune responses [29]. MSCs are pivotal in this regulation by releasing immunoregulatory mediators, including prostaglandin E2, indoleamine 2,3-dioxygenase, and interleukin-10, which inhibit excessive immunological activation and facilitate the generation of regulatory T-cells. By modulating chronic inflammation and fibrosis, MSCs foster a conducive environment for tissue regeneration [30]. The immunomodulatory ability of MSC-based treatments differentiates them from traditional grafting methods, which frequently face limitations in long-term effectiveness due to immunological rejection [31].

The vascularization of regenerated tissue is a crucial concept that influences therapeutic outcome [32]. In the absence of sufficient blood flow, transplanted cells and designed tissues experience hypoxia-induced apoptosis. Strategies to enhance angiogenesis, such as co-transplantation of MSCs with endothelial progenitor cells, functionalization of scaffolds with vascular endothelial growth factor, or genetic manipulation of mesenchymal stem cells to overexpress angiogenic factors, have been investigated to overcome this restriction [33]. The establishment of a stable and efficient vasculature is especially essential for big or metabolically intensive tissues, including the myocardial, liver, and bone.

Regenerative medicine is fundamentally interdisciplinary and integrative, amalgamating advancements in stem cell biology, biotechnology, nanotechnology, and gene editing [34]. Innovative methodologies, like CRISPR-mediated manipulation of mesenchymal stem cells, three-dimensional bioprinting of patient-specific scaffolds, and customized cell treatment platforms, illustrate the direction of the field [35]. These advances underscore the fundamental idea that regeneration is not accomplished by solitary intervention but by the interaction of cells, scaffolds, and molecular signals. The interplay among these elements constitutes the conceptual trinity of regenerative medicine and establishes the basis for translational advancement [36]. These concepts collectively highlight regenerative medicine's distinctive ability to restore biological function through the utilization of both endogenous and external repair processes. Despite ongoing hurdles related to repeatability, scalability, and regulatory approval, the amalgamation of MSCs with biomaterials and signaling networks persistently advances the research towards clinical use.

3. Mesenchymal stem cells (MSCs): The cornerstone of regenerative medicine

MSCs are adult multipotent stromal cells with the ability to self-renew and differentiate into several mesodermal lineages, such as osteoblasts, chondrocytes, and adipocytes [37, 38]. Following their initial characterization in bone marrow, MSCs have been extracted from diverse tissues including adipose tissue, umbilical cord, placenta, dental pulp, and peripheral blood [39]. A comparative summary of these MSCs sources, highlighting their advantages, limitations, and clinical relevance, is presented in Table 1, and a schematic overview of these MSCs sources is illustrated in Fig. 2. Extensive availability, together with straightforward separation techniques, establishes MSCs as one of the most pragmatic and therapeutically pertinent stem cell types for regenerative medicine [45]. Significantly, MSCs have been shown to maintain their regeneration capabilities across many tissue origins, but donor-specific variables and tissue origin may affect their potency and therapeutic reliability [46].

The characteristic biological attributes of MSCs encompass their capacity to stick to plastic in typical culture conditions [47], its expression of certain surface markers (e.g., CD73, CD90, CD105), and

Table 1. Sources of MSCs and comparative characteristics.

Source of MSCs	Advantages	Limitations	Clinical/Research Relevance	Reference
Bone marrow	Well-characterized; strong osteogenic potential	Painful collection, limited yield, age-related decline	Widely used in orthopedic applications	[40]
Adipose tissue	High yield; minimally invasive harvesting	Variable potency; donor metabolic state influences function	Popular for cosmetic & wound healing uses	[41]
Umbilical cord (Wharton's jelly, UC blood)	Non-invasive; high proliferation; low immunogenicity	Limited availability; ethical/logistical barriers	Increasingly applied in immunomodulation & cardiovascular trials	[42]
Dental pulp	Easy access during tooth extraction; neurotrophic potential	Small quantity; donor age dependent	Neuroregeneration, craniofacial repair	[43]
Placenta/Amniotic membrane	Abundant, immune-privileged	Variability in isolation & expansion	Emerging use in wound healing & immune disorders	[44]

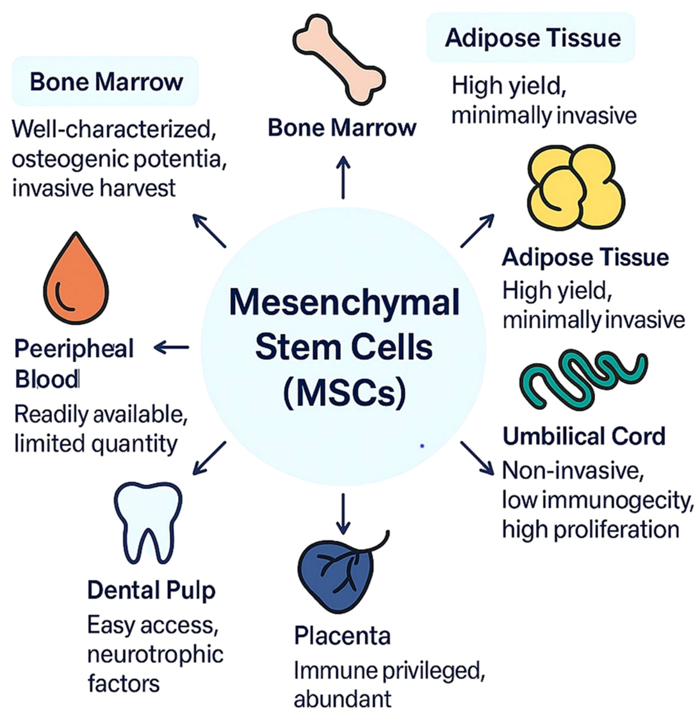

Fig. 2. Sources of MSCs.

the absence of hematopoietic antigens (CD34, CD45, CD14, CD11b, CD19, HLA-DR) [48]. The standards set by the International Society for Cellular Therapy (ISCT) constitute a fundamental standard for the characterization of MSCs and are crucial for assuring comparability across research investigations. Nonetheless, mounting data suggests that MSCs constitute a diverse population, with functional disparities emerging based on culture circumstances, donor age, and epigenetic history [49]. This variance offers both opportunities and challenges for clinical translation.

In addition to their multipotency, MSCs are recognized for their paracrine and immunomodulatory properties, which often eclipse their therapeutic benefits. MSCs release a diverse range of growth factors, cytokines, and chemokines, including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), and stromal cell-derived factor-1 (SDF-1), which promote angiogenesis, inhibit apoptosis, and recruit endogenous progenitor cells. Moreover, MSCs release extracellular vesicles (EVs), including exosomes and microvesicles, that convey bioactive compounds such as proteins, lipids, and microRNAs [50]. These extracellular vesicles function as mediators that modulate inflammation, facilitate tissue repair, and reprogram neighboring cells to adopt regenerative traits [51].

This recognition has generated heightened interest in “cell-free MSC therapies,” in which exosomes may serve as standardized, scalable alternatives to live cell transplantation.

The immunomodulatory capacity of MSCs is among their most notable contributions. MSCs can diminish T-cell proliferation, obstruct dendritic cell maturation, promote the expansion of regulatory T-cells, and transform macrophages from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype. The effects are facilitated by soluble substances such as prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), nitric oxide, and transforming growth factor-β (TGF-β) [52]. The immune-privileged properties of MSCs make them highly attractive for treating immune-mediated disorders, such as graft-versus-host disease, Crohn’s disease, and systemic lupus erythematosus. Furthermore, their reduced expression of major histocompatibility complex (MHC) class II molecules promotes allogeneic transplantation with a decreased chance of immunological rejection, hence enabling off-the-shelf therapeutic alternatives [53].

From a translational standpoint, the therapeutic uses of MSCs encompass many organ systems. In orthopedic medicine, MSCs have been utilized to rectify bone deficiencies, regenerate cartilage in osteoarthritis, and improve tendon and ligament regeneration [54]. In cardiovascular situations, MSCs are studied for myocardial infarction, heart failure, and peripheral ischemia, mostly because of their pro-angiogenic and anti-apoptotic paracrine effects [55]. MSCs have been investigated for their neurological applications in stroke, spinal cord injury, and neurodegenerative disorders, including Parkinson’s and Alzheimer’s disease, where they demonstrate neuroprotective and neurotrophic properties [56]. MSCs have potential in wound healing, liver cirrhosis, renal damage, and pulmonary disorders, highlighting their adaptability as a therapeutic modality [57].

Notwithstanding these benefits, several constraints impede the practical use of MSC treatments. Variability across donors, cellular senescence during in vitro growth, and varying potency across manufacturing processes result in disparate results in clinical studies [58]. Furthermore, although MSCs are typically regarded as safe, long-term concerns include ectopic differentiation, undesirable fibrosis, or pro-tumorigenic effects are still being examined [59]. Standardizing standards for isolation, expansion, and quality control is essential for attaining reproducible results and regulatory approval. The absence of agreement about the ideal cell dosage, method of administration, and criteria for patient selection exacerbates the complexity of clinical trial design and analysis [60].

Novel strategies are being explored to overcome these challenges. Preconditioning mesenchymal stem cells using hypoxia, inflammatory cytokines, or pharmaceutical interventions has shown enhanced survival and paracrine effectiveness [61]. Genetic engineering, encompassing the overexpression of angiogenic or anti-apoptotic genes, might augment their therapeutic effectiveness [62]. Combinatorial techniques, involving the administration of MSCs within biocompatible scaffolds or hydrogels, improve cell retention and facilitate accurate tissue integration. The increasing focus on MSC-derived exosomes offers a standardized, cell-free therapeutic option, potentially reducing risks associated with live cell therapy while maintaining regenerative efficacy [63].

MSCs embody the core principles of regenerative medicine, encompassing cellular plasticity, paracrine signaling, and immune regulation. Their unique attributes have propelled them from laboratory settings to clinical applications, with over a thousand registered clinical trials worldwide investigating their therapeutic benefits. Notwithstanding current challenges, progress in cell engineering, nanomaterials, and exosome-based therapeutics is solidifying MSCs as essential to regenerative medicine. Their concurrent capacity for direct tissue regeneration and systemic immunomodulation positions them as one of the most versatile and promising tools in the regenerative arsenal.

4. Applications of MSCs in regenerative medicine

The therapeutic versatility of MSCs has been demonstrated in several clinical contexts, due to their capacity for differentiation, secretion of bioactive substances, and modulation of immune responses. Unlike pluripotent stem cells, which are constrained by safety and ethical concerns, MSCs offer a pragmatic balance of multipotency, safety, and accessibility [64]. This discourse emphasizes their relevance in regenerative medicine across principal organ systems, emphasizing both preclinical findings and clinical application.

4.1. Orthopedic and musculoskeletal disorders

Orthopedic regeneration is one of the earliest and most extensively studied applications of MSCs. MSCs intrinsic osteogenic and chondrogenic differentiation capabilities make them optimal candidates for bone and cartilage regeneration [65]. Clinical trials have shown that intra-articular delivery of MSCs enhances pain relief and functional results in osteoarthritis, partially through cartilage rebuilding and partially by modulating inflammatory cytokines in the joint milieu [66]. Likewise, mesenchymal stem cells (MSCs) implanted on biomaterial scaffolds or hydrogel matrices have been effectively utilized to repair critical-sized bone lesions, facilitate spinal fusions, and address tendon injuries. The combined use of MSCs with osteoinductive growth factors, including bone morphogenetic proteins (BMPs), significantly improves their restorative effectiveness [67].

4.2. Cardiovascular regeneration

In cardiovascular medicine, MSCs are being studied for myocardial infarction, ischemic cardiomyopathy, and peripheral arterial disease [68]. MSCs therapeutic advantages are generally ascribed to paracrine pathways rather than direct cardiomyogenic differentiation. MSCs release VEGF, HGF, and angiopoietins, which promote neovascularization, diminish cardiomyocyte death, and enhance perfusion in ischemic tissues [69–71]. Clinical investigations have indicated moderate enhancements in left ventricular ejection fraction and quality of life subsequent to MSCs transplantation in individuals with heart failure [72]. Strategies such the genetic modification of MSCs to overexpress pro-angiogenic factors or the co-delivery with endothelial progenitor cells are being investigated to improve clinical effectiveness.

4.3. Neurological disorders

The central nervous system (CNS) poses distinct hurdles for regeneration owing to its restricted intrinsic healing capability [73]. MSCs, via the release of neurotrophic factors such as brain-derived neurotrophic factors and glial cell-derived neurotrophic factors, have demonstrated potential in models of stroke, spinal cord injury, and neurodegenerative disorders [74]. MSCs diminish subsequent damage cascades, mitigate neuroinflammation, and facilitate axonal sprouting and remyelination [75]. Initial clinical trials have demonstrated promising results regarding motor recovery and functional enhancement in patients with spinal cord injury and ischemic stroke following MSC transplantation [76]. Although MSCs capacity to traverse the blood–brain barrier is restricted, delivery methods such intrathecal injection or encapsulation in biomaterial carriers are being developed to enhance targeting and retention within the central nervous system.

4.4. Immune and inflammatory disorders

The immunomodulatory potential of MSCs has been most firmly shown in the management of immune-mediated disorders. MSCs are now the sole cell therapy product sanctioned in specific regions for the treatment of graft-versus-host disease (GvHD), a perilous complication arising from hematopoietic stem cell transplantation. Their release of prostaglandin E2, indoleamine 2,3-dioxygenase, and interleukin-10 inhibit alloreactive T-cell proliferation while facilitating the formation of regulatory T cells [77, 78]. In addition to GvHD, MSCs have been investigated in Crohn's disease, systemic lupus erythematosus, and rheumatoid arthritis, with several trials indicating clinical efficacy [79, 80]. These findings underscore their ability to reestablish immunological homeostasis in conditions where traditional immunosuppressive treatments frequently prove inadequate.

4.5. Wound healing and dermatology

MSCs expedite wound closure by augmenting fibroblast proliferation, increasing angiogenesis, and facilitating extracellular matrix deposition [81]. MSCs utilization in chronic wounds, including diabetic ulcers, has led to increased healing rates, less scarring, and enhanced re-epithelialization. In dermatological applications, MSCs have been tested for burn injuries and skin graft integration, where MSCs paracrine activity facilitates vascularization and tissue remodeling [82, 83]. The cosmetic and reconstructive capabilities of MSCs are gaining recognition, especially with the emergence of adipose-derived MSCs in skin rejuvenation and scar reduction treatments.

4.6. Visceral organ regeneration

MSCs-based treatments have shown promise in the regeneration of essential organs such as the liver, kidney, and lung. In liver illness, MSCs demonstrate anti-fibrotic properties by suppressing the activation of hepatic stellate cells and enhancing hepatocyte proliferation [84]. In acute kidney damage and chronic kidney disease, MSCs promote renal recovery by diminishing oxidative stress and apoptosis, but in pulmonary fibrosis, they alleviate inflammation and fibrotic remodeling [85]. Despite the majority of research being in preclinical or early-phase clinical phases, the variety of organ systems addressed demonstrates the systemic relevance of MSCs.

4.7 Emerging frontiers

Along with conventional uses, MSCs are being progressively investigated alongside biomaterials, gene editing, and bio-fabrication technologies [86]. For example, mesenchymal stem cells integrated into three-dimensional printed scaffolds provide personalized regeneration of bone and cartilage abnormalities [87]. Gene-modified MSCs, designed to overexpress angiogenic, anti-fibrotic, or neurotrophic factors, have enhanced regeneration capabilities relative to unmodified cells [88]. Furthermore, MSCs-derived extracellular vesicles (EVs) are emerging as next-generation, cell-free therapies, providing benefits in scalability, safety, and regulatory adherence [89]. These advances are transforming the field of regenerative medicine, transitioning from cell transplantation to precision-engineered biologics.

In summary, MSCs have exhibited therapeutic effectiveness in a wide array of clinical applications, including musculoskeletal and cardiovascular repair, immunological diseases, and organ regeneration. Their methods vary according to the target tissue, including direct differentiation and paracrine immunomodulation; yet their consistent safety profile and versatility underscore their essential role in regenerative medicine. Translating these findings into consistent treatment results requires careful modification of delivery methods, dosing strategies, and patient selection, which remain active areas of study. Collectively, these findings highlight the broad therapeutic versatility of MSCs across multiple organ systems. The principal mechanisms of MSC action are schematically illustrated in Fig. 3, A consolidated overview of the principal clinical applications, underlying mechanisms, and representative clinical outcomes is provided in Table 2.

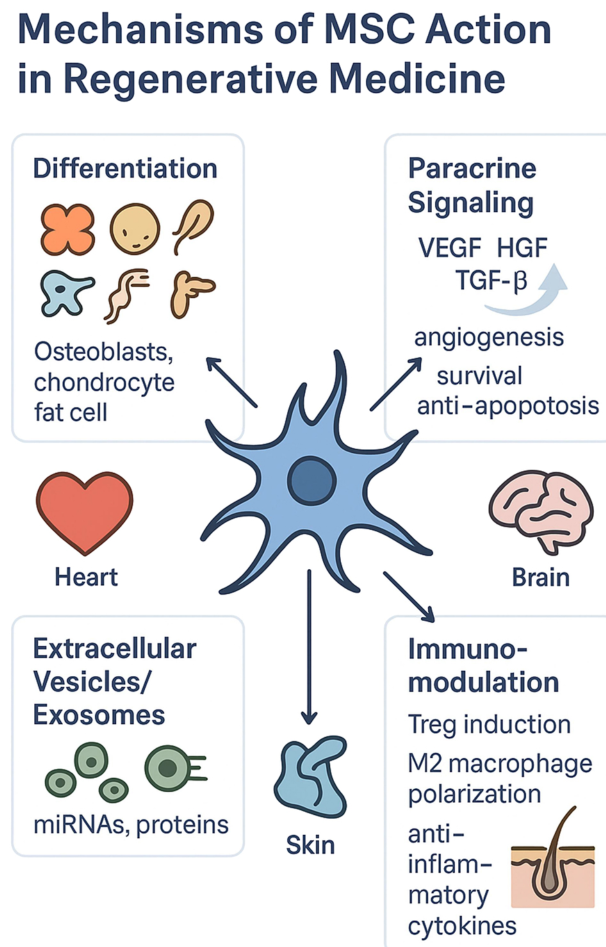

Fig. 3. Mechanisms of MSCs action in regenerative medicine.

5. Challenges and limitations of MSC-based regenerative medicine

The extensive clinical use of MSCs is impeded by several scientific, technical, and regulatory challenges [96]. These limits underscore the complexity of moving from preclinical successes to reliable clinical outcomes. A comprehensive grasp of these challenges is essential for improving treatment

Table 2. Clinical applications of MSCs in regenerative medicine.

Target System/Disease	Mechanism of Action	Example Clinical Findings	Reference
Orthopedic (Osteoarthritis, bone defects)	Chondrogenic/osteogenic differentiation; anti-inflammatory cytokine release	Improved pain scores, cartilage regeneration, enhanced bone healing	[90]
Cardiovascular (MI, heart failure)	Paracrine angiogenic signaling (VEGF, HGF); anti-apoptotic effects	Improved LVEF, reduced infarct size, better perfusion	[91]
Neurological (Stroke, SCI, Parkinson's)	Neurotrophic factor secretion (BDNF, GDNF); anti-inflammatory modulation	Enhanced motor recovery, neuroprotection, partial remyelination	[92]
Immune-mediated (GvHD, Crohn's, SLE, RA)	Immunomodulation: Treg induction, macrophage M2 polarization	Reduced disease severity, steroid-sparing effects	[93]
Dermatology & Wound Healing	Fibroblast activation, angiogenesis, ECM remodeling	Faster closure of chronic wounds, reduced scarring	[94]
Liver/Kidney/Pulmonary Disorders	Anti-fibrotic and anti-apoptotic paracrine effects	Reduced fibrosis, improved organ function (preclinical & early clinical)	[95]

methodologies and developing standardized protocols for practical use.

In MSC-based treatment, primary obstacles are donor variability and heterogeneity. The proliferation, differentiation potential, and secretory characteristics of MSCs are significantly affected by parameters including donor age, sex, health state, and tissue origin [97]. MSCs obtained from older donors often have diminished immunomodulatory function and decreased proliferation relative to those sourced from younger individuals. Umbilical cord-derived MSCs, akin to their bone marrow-derived equivalents, have superior proliferative potential and reduced immunogenicity [98]. This biological diversity hinders the creation of uniform effectiveness and potency among patient populations.

A second constraint relates to cellular senescence and in vitro proliferation. To generate therapeutically pertinent doses, MSCs often require substantial culture growth, leading to the accumulation of DNA damage, telomere shortening, and phenotypic variation. Not only do senescent MSCs lose their regenerative capacity, but they may also adopt a pro-inflammatory secretory phenotype, which could potentially compromise the efficacy of therapeutic interventions [99]. It is imperative to maintain the potency of MSCs during proliferation by establishing optimal culture conditions, which include oxygen tension, growth factor supplementation, and three-dimensional culture systems.

Engraftment and survival following transplantation continue to be significant challenges. A significant number of MSCs are either promptly removed from the host microenvironment or undergo apoptosis upon administration as a result of immune surveillance, hypoxia, or oxidative stress. Research suggests that less than 10% of transplanted MSCs remain in vivo for more than a few days, which raises concerns about whether the clinical benefits observed are the result of durable engraftment or transient paracrine signaling [100]. Preconditioning strategies, genetic modifications, and biomaterial scaffolds are being investigated to improve the persistence and integration of MSCs within target tissues.

MSC-based treatments have additional limitations due to difficulty in cell engraftment and survival, dangers of abnormal differentiation, and concerns regarding pro-tumorigenic effects, alongside these inherent obstacles [101]. Regulatory clearance is further hindered by manufacturing limitations, including the lack of defined potency testing, variability in culture reagents, and challenges in scalability. Moreover, although the immune-privileged attributes of MSCs, their immunosuppressive properties may, in some situations, promote tumor growth, and recurrent allogeneic treatments may provoke immunological responses [102]. These problems underscore the urgent need for sophisticated engineering techniques, standardized protocols, and improved biomaterial support to ensure the safety and repeatability of clinical translation.

6. Future perspectives

The next generation of regenerative medicine is progressively concentrating on enhancing efficacy, safety, and scalability, transcending the direct transplantation of mesenchymal stem cells (MSCs). The advancement of MSC-derived extracellular vesicles (EVs), especially exosomes, as cell-free therapies represent a crucial frontier [103]. These vesicles encompass regulatory RNAs, lipids, and proteins that mimic various paracrine functions of MSCs, including angiogenesis and immunomodulation. Exosomes have greater stability, reduced immunogenicity, and enhanced ease of storage and distribution compared to live cells, making them optimal candidates for standardized biological therapy [104]. Genetic and epigenetic engineering are concurrently utilized to augment the resilience and efficacy of MSCs. CRISPR-Cas9 and other methodologies provide accurate alterations that enhance the release of regenerative factors or confer tolerance to adverse conditions [105]. For example, MSCs expressing VEGF or anti-apoptotic genes demonstrate improved tissue healing capabilities and increased survival rates [106]. Similarly, preconditioning methods, such hypoxia or inflammatory priming, might augment immunomodulatory activity and maintain stemness, therefore mitigating the limitations of senescence and donor variability [107].

A key area of emphasis is the incorporation of sophisticated manufacturing technologies and biomaterials. Engineered scaffolds, hydrogels, and 3D bioprinting techniques supply structural and biochemical signals that promote MSC development and tissue integration [108]. The prospect of repairing bone, cartilage, and intricate tissue abnormalities is notably encouraging when functionalized scaffolds are created by integrating MSCs with growth hormones or nanomaterials [109]. The imperative for transdisciplinary collaboration across stem cell biology, biomaterials research, and tissue engineering is highlighted by these bioengineered platforms.

The integration of MSC-based therapies with peptides is a particularly promising frontier. By activating integrin-mediated signaling pathways and mimicking extracellular matrix motifs, bioactive peptides, including RGD, IKVAV, and YIGSR, can improve MSC adhesion, migration, and differentiation. Encapsulating or conjugating MSCs with peptide-functionalized scaffolds enhances their targeted regenerative activity, engraftment, and survival [110]. Moreover, MSC secretomes can be integrated with therapeutic peptides exhibiting anti-inflammatory or angiogenic characteristics to accelerate tissue regeneration [111]. The collaboration of MSCs and peptides presents a viable strategy to overcome current challenges, hence creating regeneration platforms that are more accurate, effective, and customized to specific application requirements.

7. Conclusion

Regenerative medicine is emerging as a transformative paradigm in modern healthcare, with MSCs at its core. Their unique capacity for multilineage differentiation, together with strong paracrine and immunomodulatory functions, has established MSCs as versatile therapeutic agents in orthopedic, cardiovascular, neurological, and immune-mediated disorders. The comprehensive array of preclinical and clinical studies underscores their ability to address disorders inadequately managed by conventional medication. Significant barriers continue to impede their practical use. Donor variability, cellular senescence during expansion, inconsistent engraftment, and unresolved long-term safety concerns result in heterogeneous outcomes. The absence of established manufacturing protocols and potency assessments obstructs regulatory approval and large-scale deployment. Addressing these challenges through improved culture procedures, rigorous quality control measures, and careful patient selection will be essential for achieving consistent and reliable treatment outcomes. Emerging methodologies are currently altering the parameters of MSC-based therapies. Innovations encompass MSC-derived extracellular vesicles, genetic engineering, advanced biomaterial scaffolds, and the integration of bioactive peptides, addressing current limitations. The interaction between peptides and MSCs has promise for enhancing cell adhesion, survival, differentiation, and immunomodulatory capabilities, hence advancing the creation of more precise and efficient regenerative platforms. These improvements are steering the field towards customized, cell-free, and peptide-enhanced approaches that might establish MSC-based therapies as mainstream, clinically reliable interventions in regenerative medicine.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

Not applicable.

Data availability

Not applicable.

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Author contributions

All authors contributed equally to the conception and design of the study.

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