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REVIEW

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Engineering strategies to enhance the research progress of mesenchymal stem cells in wound healing

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Abstract

Wound healing is a multifaceted biological process involving critical phases such as inflammation modulation, tissue regeneration, and angiogenesis. Traditional therapies often yield inconsistent results. Mesenchymal stem cells (MSCs)—with their abilities for self-renewal, tissue repair, angiogenesis, and immunomodulation—represent a promising avenue in regenerative medicine and wound healing. However, the efficacy of MSCs is frequently compromised by the hostile post-transplantation microenvironment. Recent advances in engineering strategies—including gene modification, preconditioning, biomaterial scaffolds, and hydrogels—have significantly enhanced the therapeutic potential of MSCs by improving their survival, proliferation, and migration. Moreover, the combined application of multiple engineering approaches further optimizes wound healing outcomes by accelerating tissue repair and reducing scar formation. In this review, we systematically summarize the mechanisms underlying MSC-mediated wound healing, their clinical applications, and the impact of various engineering strategies, with the aim of facilitating the clinical translation of engineered MSCs and providing more effective therapeutic solutions.

Keywords Mesenchymal stem cells, Engineering, Wound healing, Regenerative medicine

Introduction

Wounds, resulting from various internal and external factors, can compromise tissue integrity and function. The wound healing process unfolds in four overlapping phases—hemostasis, inflammation, proliferation, and remodeling—each involving coordinated interactions among different cell types [1]. Following injury, blood vessels constrict rapidly, triggering platelet aggregation and clot formation to minimize blood loss [2, 3]. Simultaneously, inflammatory cytokines and chemokines recruit immune cells to clear debris and prevent infection [4]. As inflammation subsides, extracellular matrix (ECM) synthesis bridges the wound gap and facilitates re-epithelialization [5]. Finally, a balance between collagen synthesis and degradation ensures the orderly organization of new fibers, culminating in tissue remodeling [6].

While conventional therapies help prevent infection and provide structural support, their efficacy is often limited [7–9]. In contrast, MSC-based therapies offer considerable potential due to the multipotent nature of these cells and their ability to modulate immune responses, stimulate cell proliferation, and differentiate into various tissue types [10]. However, systemic delivery of MSCs frequently results in their accumulation in the lungs, whereas localized delivery improves targeting

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but is hindered by the adverse wound microenvironment that reduces cell survival and engraftment [11, 12]. To overcome these limitations, researchers have developed engineering strategies—including the use of biomaterials, cytokines, and genetic modifications—to enhance MSCs survival, functionality, and therapeutic potential.

Mechanisms of MSCs in wound healing

MSCs facilitate wound healing through a variety of mechanisms, including homing to the site of injury, promoting directed differentiation, modulating immune cell activity, enhancing fibroblast and endothelial cell proliferation, and stimulating collagen synthesis. These synergistic processes collectively expedite wound healing while reducing scar formation (Fig. 1) [13–17].

During the inflammatory phase, dysregulated immune responses can delay healing [18]. MSCs can promote macrophage polarization to the M2 phenotype by secreting tumor necrosis factoralpha-stimulated gene/protein-6 (TSG-6), interleukin-6 (IL-6) and prostaglandin E2 (PGE2), thereby modulating the progression of inflammation at the wound site and facilitating wound healing [19]. Additionally, MSCs enhance the migration and phagocytic activity of neutrophils by increasing the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, and IL-8, thus promoting early bacterial clearance at the wound site [20]. Furthermore, MSCs encourage the differentiation of T cells into Th2 and regulatory T cells, further attenuating inflammation and facilitating the transition to the proliferative phase [21].

After inflammation subsides, MSCs detect damage signals from injured tissues and migrate to the wound site via peripheral circulation. Upon arrival, they facilitate wound healing through two primary mechanisms: directed differentiation and paracrine signaling [22]. MSCs differentiate into vascular endothelial and smooth muscle cells, aiding in the restoration of local blood circulation and improving the delivery of oxygen and nutrients to the wound [23, 24]. Additionally, MSCs secrete cytokines that stimulate the migration, proliferation, and differentiation of fibroblasts and endothelial cells in the surrounding tissue, thereby enhancing vascularization and epithelialization [25, 26]. MSC-derived exosomes further support ECM remodeling, TGF-β signaling, and epithelial-mesenchymal transition, promoting collagen deposition, epidermal layer formation, and re-epithelialization [1]. Through these coordinated processes, MSCs ensure a seamless transition from the proliferative phase to the remodeling phase, ultimately leading to effective tissue repair and regeneration.

The remodeling phase, which can last from several months to years, plays a crucial role in scar formation and involves various cell types [27]. Dysfunction in repair cells can lead to excessive collagen deposition, resulting in scarring and impaired skin functionality. Key regulatory pathways, including TGF-β/Smad, JAK/STAT, MAPK, and PI3K/AKT, control fibroblast proliferation, collagen synthesis, and ECM deposition [28]. Studies have found that placenta-derived mesenchymal stem cells inhibit p38 MAPK signaling by secreting proenkephalin, thereby blocking the excessive proliferation of scar fibroblasts, a result that has been confirmed in mouse experiments [29]. Similarly, Meng et al. demonstrated that coculturing hypertrophic scar fibroblasts with human umbilical cord mesenchymal stem cells (HUC-MSCs) inhibited fibroblast proliferation, migration, and profibrotic phenotypic transition via the TGF-β1/Smad3 pathway, thereby reducing hypertrophic scar formation [30].

Despite their therapeutic potential, the effectiveness of MSCs in wound healing is often limited by the harsh post-transplantation microenvironment, characterized by hypoxia and excessive inflammatory mediators. To address these challenges, various engineering strategies have been developed to enhance MSCs survival, functionality, and therapeutic efficacy. These include genetic modifications to improve stress resistance, preconditioning strategies to better equip MSCs for adverse environments, and the incorporation of biomaterial scaffolds and hydrogels to provide structural and biochemical support.

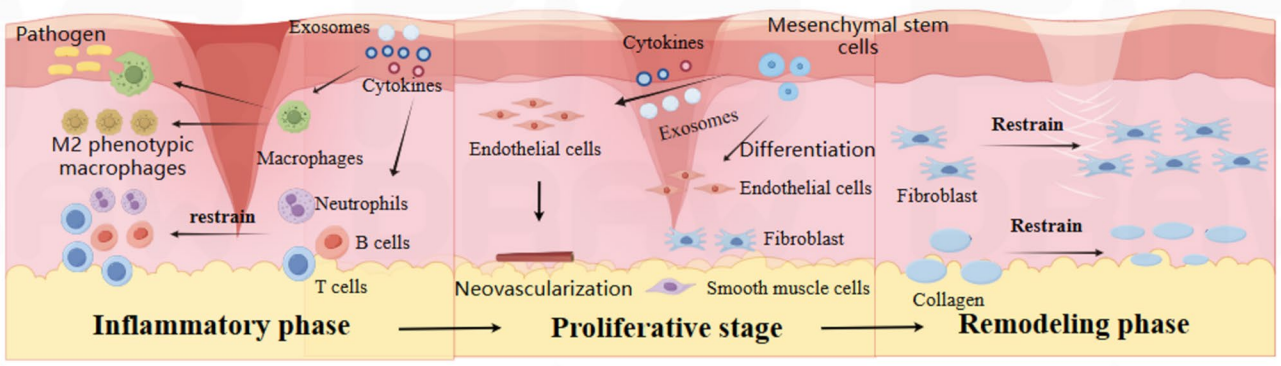

Fig. 1 The role of MSCs in each stage of wound healing

Clinical applications of MSCs in wound healing

MSC-based therapy has shown significant promise in treating various skin conditions, including diabetic foot ulcers, burns, and psoriasis. According to data from ClinicalTrials.gov, 96 clinical trials have been registered to date to evaluate the therapeutic potential of MSCs in skin-related disorders, primarily focusing on non-healing wounds caused by immune system imbalance, including diabetic wounds (39 trials), psoriasis (10 trials), and others [31]. Over the past five years, a growing number of clinical studies have further validated the efficacy of MSC-based interventions (Table 1) [32–35].

Despite these promising findings, the clinical application of MSCs faces considerable challenges, particularly in wound environments characterized by high levels of inflammatory cytokines, nutrient deprivation, and hypoxic-ischemic conditions. These adverse microenvironments often trigger oxidative stress-induced anoikis, significantly reducing MSCs survival [36]. Clinical studies indicate that MSCs are typically administered either systemically via intravenous injection or locally at the wound site. While both delivery methods support wound healing through immune modulation, angiogenesis stimulation, and scar formation reduction, their effectiveness is often limited by poor cell retention and low engraftment efficiency, which restricts the long-term therapeutic benefits of MSCs [37].

In summary, the local wound microenvironment and delivery strategies play a crucial role in determining the clinical efficacy of MSC-based therapies. To overcome these challenges, innovative engineering strategies are being developed to enhance MSCs resilience and therapeutic potential in wound healing. Recent advances in treating hard-to-heal wounds provide compelling evidence supporting the feasibility and effectiveness of these emerging approaches.

Application of various MSCs engineering strategies in wound healing

MSCs play a crucial role in wound healing through mechanisms such as homing, proliferation, differentiation, and the secretion of a diverse range of cytokines, which influence the wound site both directly and indirectly. However, wound healing is a highly complex and dynamic process that requires more effective therapeutic approaches. As a result, research on MSCs in wound healing has shifted from simply enhancing their inherent functions to developing strategies that maximize their therapeutic potential while minimizing external factors that hinder their efficacy. Emerging evidence suggests that preconditioning, biological scaffolds, and hydrogels can create a hydrated and supportive microenvironment for MSCs, thereby improving their proliferation, differentiation, homing, and cytokine secretion abilities to accelerate and enhance the wound healing process [38].

Microenvironmental preconditioning

Cytokine preconditioning

Exogenous cytokines have been shown to modulate MSCs gene and protein expression profiles, thereby optimizing their biological functions in tissue repair. For instance, IL-1β preconditioning enhances MSCs migration by upregulating matrix metalloproteinase-3 (MMP-3) expression [39]. Similarly, cotreatment with interferon-γ (IFN-γ) and TNF-α promotes macrophage polarization toward the M2 phenotype by upregulating C-C motif chemokine ligand 2 (CCL2) and IL-6 expression, creating an inflammatory microenvironment conducive to wound healing [40]. Moreover, transforming growth factor-β1 (TGF-β1) preconditioning has been shown to enhance the survival and engraftment of BMSCs post-transplantation, significantly reducing wound healing time in murine models [41]. These findings highlight the potential of cytokine preconditioning to mitigate MSC apoptosis while enhancing their proliferation and migratory capacities, thereby improving wound healing outcomes. However, the therapeutic efficacy of cytokine preconditioning is influenced by the specific cytokines used and their concentrations. Further research is needed to optimize preconditioning protocols and evaluate the synergistic effects of multiple cytokines on MSCs function.

Pharmacological preconditioning

Pharmacological preconditioning involves the in vitro modification of MSCs with chemical agents to enhance their biological properties, including proliferation, differentiation, and paracrine activity, ultimately improving their therapeutic efficacy in wound healing. For example, α-ketoglutarate, a key intermediate of the tricarboxylic acid cycle with potent antioxidant and anti-inflammatory properties, has been shown to significantly improve ADSCs survival in a chemically induced burn model. This effect is associated with increased expression of

Table 1 The main clinical applications of MSCs in wound healing

Author	Wound Type	Cell Type	Dosage	Administration method	Efficiency (time)	References
Michael Traub	abdominal fissures	MSCs	2×10^6 cells/kg	intravenous infusion	94% (1 year)	[32]
Carl I. Schulman	burns	BMSCs	5×10^3 cells/cm^2	local injection	100% (1 month)	[33]
Simona Ascanelli	anal fistula wounds	ADSCs	2 cc/cm length of each tract	local injection	63.8% (4 weeks)	[34]
Cecilia C Low Wang	diabetic foot ulcer	HUC-MSCs	1×10^5 cells/mm^3 ulcer surface area	local injection	100% (3 months)	[35]

VEGF and hypoxia-inducible factor-1α (HIF-1α), which promote angiogenesis and accelerate wound closure [42]. Similarly, collagen has been found to enhance MSCs activity by stimulating the secretion of chemokines and growth factors essential for wound healing. This process facilitates epidermal regeneration, collagen deposition, follicular angiogenesis, and inflammatory modulation, expediting wound healing in both murine and canine models [43]. Furthermore, caffeic acid has been shown to improve the viability and regenerative potential of HUC-MSCs under hypoxic conditions. Caffeic acid-preconditioned HUC-MSCs upregulate VEGF and stromal cell-derived factor-1 (SDF-1) secretion, enhancing angiogenesis [44]. Lipopolysaccharide (LPS) preconditioning has also been reported to improve ADSC viability and increase VEGF and DNA methyltransferase 1 expression, leading to accelerated epithelialization, angiogenesis, and diabetic wound healing [45].

Although drug preconditioning shows great promise in optimizing MSCs therapeutic function, further research is needed to understand the effects of drug metabolites and their concentrations on MSCs and human tissues. Future studies should focus on evaluating concentration gradients to assess potential toxicities and ensure the safety of clinical applications.

Hypoxic preconditioning

Oxygen availability in the microenvironment is a critical determinant of MSCs survival and function. Studies have shown that oxygen levels within stem cell niches play a key role in maintaining MSCs self-renewal, proliferation, and migratory capacity [46]. Hypoxic conditions have been demonstrated to enhance MSCs function, including proliferation, survival, homing, differentiation, and paracrine activity [47, 48]. For example, MSCs cultured under 5% oxygen exhibit increased proliferation and elevated expression of various cytokines and growth factors. In murine models of alkali burns, hypoxia-preconditioned MSCs accelerated re-epithelialization and improved the histological architecture of repaired tissues [49]. Additionally, hypoxia-preconditioned ADSCs activate the PI3K/AKT signaling pathway by upregulating HIF-1α and insulin-like growth factor-1 receptor expression, increasing their proliferation, differentiation, and angiogenic potential, thereby reducing wound healing time [46].

Overall, hypoxic preconditioning has emerged as a promising strategy to enhance MSCs functionality in wound healing by improving their proliferation, survival, and angiogenic capacity. Further studies are needed to elucidate the molecular mechanisms underlying these effects and determine the optimal hypoxic conditions for therapeutic applications.

Cell culture and structural optimization

3D coculture

The three-dimensional (3D) microenvironment plays a crucial role in modulating MSC functionality, allowing cells to grow and interact with their surroundings in multiple dimensions. Studies have shown that, compared to traditional two-dimensional (2D) monolayer cultures, MSCs cultured as 3D spheroids exhibit increased viability, reduced apoptosis, increased quiescence, and enhanced expression of cytokines associated with immunomodulation and angiogenesis. Additionally, 3D spheroid MSCs demonstrate improved secretion of adhesion molecules and ECM proteins [47]. Notably, the proportion of MSCs in the G1 phase of the cell cycle increases within a 3D culture environment, accompanied by significant reductions in apoptosis and increased secretion of proteins involved in cell proliferation, migration, adhesion, and angiogenesis [48]. MSCs in a 3D microenvironment secrete higher levels of wound-healing-related proteins, promoting keratinocyte migration, inhibiting excessive dermal fibroblast proliferation, and reducing scar formation. These processes collectively facilitate rapid wound re-epithelialization [49]. In a murine burn model, Prakash et al. [50] demonstrated that MSCs cultured under 3D conditions exhibited significantly elevated secretion of proangiogenic cytokines, including IL-6, VEGFA, and interleukin-8, which collectively accelerated wound healing.

Application of biological scaffolds

The microenvironment plays a critical role in facilitating MSC-mediated molecular interactions essential for wound healing. Biological scaffolds, characterized by their porous structures that closely mimic the ECM, create a hydrated and supportive niche that promotes wound repair. These scaffolds not only enhance cell survival and proliferation but also provide essential mechanical, physical, and biochemical cues required for cellular function [51]. Recent studies have demonstrated that bilayer silk fibroin/alginate scaffolds effectively prolong HUC-MSCs survival in vitro [52]. Similarly, collagen scaffolds loaded with BMSCs have been shown to polarize macrophages toward the anti-inflammatory M2 phenotype, thereby suppressing the production of pro-inflammatory cytokines (IL-1β, TNF-α and MMP-9) while increasing anti-inflammatory cytokines (IL-10 and TGF-β3). This shift facilitates inflammation resolution and accelerates wound healing in diabetic mouse models [53]. Boron-enriched acellular scaffolds seeded with WJ-MSCs have been shown to upregulate genes related to epithelialization, expedite re-epithelialization, and improve burn wound healing in rat models [54]. Additionally, fibrous scaffolds stimulate MSCs to secrete critical bioactive factors, including PGE2, TSG-6 and inducible nitric oxide

synthase (iNOS), which regulate macrophage polarization and mitigate inflammation. These scaffolds further promote angiogenesis by enhancing the secretion of VEGF, bFGF, and human chorionic gonadotropin, as demonstrated in rat dorsal wound models [55]. Clinical studies support the therapeutic potential of biological scaffolds in wound management. For instance, amniotic scaffolds loaded with MSCs have been found to significantly reduce healing time in chronic diabetic ulcers, effectively promoting wound closure [56].

While biological scaffolds enhance MSCs functionality through material-cell interactions, the design and selection of scaffold materials should be tailored to the specific requirements of different wound types. Future research should focus on optimizing scaffold integration with MSCs to maximize therapeutic outcomes and facilitate clinical translation.

Application of hydrogels

Hydrogels, a class of novel functional polymer materials with three-dimensional network structures formed via chemical or physical cross-linking, provide MSCs with a supportive environment conducive to survival and proliferation. These materials enhance cell attachment and growth at wound sites [57]. The physicochemical properties of hydrogels—such as porosity, fiber alignment, surface roughness, and structural features—can modulate MSC behavior, improving their immunomodulatory and paracrine functions to accelerate wound healing [58]. Thermosensitive hydrogels composed of galloylated hydroxybutyl chitosan and soluble extracellular matrix have been shown to provide a favorable environment for HUC-MSCs survival and proliferation. These hydrogels increase the secretion of VEGF, IL-6 and PGE2, which regulate macrophage polarization, collagen deposition, and angiogenesis, ultimately promoting the healing of pressure ulcers in mice [59].

To further enhance the application of hydrogels in wound healing, Zhen Zhan et al. developed porous, multilayered, interconnected microgels with customizable sizes, pore diameters, and internal helical channels using a microfluidic approach. Compared to other gels, these microgels effectively promote MSCs adhesion, proliferation, and migration, enhance cell delivery, and improve cell viability in a post-transplantation environment by facilitating efficient nutrient exchange. Furthermore, in a Type 1 diabetes rat model, flow cytometry analysis of wound tissue sections after 14 days revealed that these microgels significantly increased MSCs retention at the wound site. They also more effectively inhibited wound infection, promoted re-epithelialization, collagen synthesis, and angiogenesis, thereby accelerating wound healing [60].

Hydrogels offer MSCs a protective and supportive microenvironment, extending their viability in vitro and enhancing their therapeutic efficacy by modulating intrinsic cellular properties. However, given the complex nature of wound healing, the ultimate clinical goal of scar-free regeneration, and the critical role of the microenvironment in influencing MSC behavior, optimizing the physicochemical characteristics of hydrogels is essential. Such advancements could lead to the development of biomaterials that more effectively promote wound repair and regeneration.

Genetic modification

Local injection remains the most common method for delivering MSCs in wound healing applications. However, their functionality is often influenced by the surrounding microenvironment. Therefore, genetic modification of MSCs can enhance their homing ability, enable precise exertion of their biological functions, and promote wound healing (Table 2). For example, PSGL-1-modified ADSCs exhibit increased adhesion to platelets and injured tissues, significantly improving their homing efficiency. Further investigations have revealed that PSGL-1 modification activates the Wnt/β-catenin signaling pathway, thereby promoting the release of therapeutic cytokines, angiogenesis, re-epithelialization, and granulation tissue formation to accelerate wound repair [61]. Lipocalin-2, a multifunctional protective factor with anti-inflammatory, antioxidative, and antimicrobial properties, is highly expressed in various cell types. HUC-MSCs overexpressing lipocalin-2 have been shown to significantly accelerate wound healing in rat dorsal wound models by promoting epithelialization, enhancing skin appendage formation, improving collagen alignment, and reducing scar formation [62]. Similarly, JAM-A-modified MSCs alleviate hyperglycemia-induced dysfunction, improve antioxidative capacity,

Table 2 Study of genetically modified MSCs in wound healing

Cell Type	Gene Modification Target	Gene Modification Method	Mechanism	Reference
ADSCs	IGF-1	mRNA Modification	corneal nerve repair↑; corneal stromal Fibrosis↓	[64]
HUC-MSCs	Cytokine Signaling Protein	DNA Modification	anti-inflammatory↑; reconstruction of the epidermis and dermis↑	[65]
HUC-MSCs	C-Jun	DNA Modification	PDGFA↑; HGF↑; proliferative and migratory capacities↑	[66]
BMSCs	Angiopoietin-1	DNA Modification	Akt pathway↑; Src↓	[67]
ADSCs	PDGFR-β	DNA Modification	Akt pathway↑	[68]

protect against apoptosis, and enhance paracrine signaling. These modifications collectively accelerate diabetic wound healing [63].

Genetic engineering may endow MSCs with enhanced regenerative capabilities, thereby overcoming the clinical challenges of MSC-based wound healing therapies. However, previous genetic engineering efforts have mainly focused on individual specific genes, while wound healing requires the interaction of multiple mechanisms within the body. Studies have shown that, compared to MSCs overexpressing IL-4 alone, MSCs co-modified with PDGF-BB and IL-4 can enhance cell proliferation, activity, and osteogenic potential [69]. Furthermore, Di Wi et al. [70] introduced IL-4, IL-10 and IL-13 genes into HUC-MSCs via lentiviral transfection. The resulting MSCs-3IL increased the expression of anti-inflammatory cytokines, reduced the expression of pro-inflammatory cytokines, induced polarization of macrophages from M1 to M2, and promoted collagen regeneration, angiogenesis, and re-epithelialization, thereby accelerating wound healing in mice. Additionally, it was found that MSCs-3IL distributed normally in vivo without any observed chromosomal abnormalities or tumor risks, confirming their safety and feasibility.

Combination strategies for enhanced MSC-based wound healing

Wound healing is a complex and dynamic process regulated by a network of cells and molecular signaling pathways. Traditional approaches to engineering MSCs are relatively simplistic and often fail to address the diverse needs of wound microenvironments and the multifaceted demands of tissue repair. Combination strategies involving multiple engineering methods have emerged to overcome these challenges, offering synergistic improvements in the anti-inflammatory, immunomodulatory, angiogenic, and regenerative functions of MSCs, resulting in significant therapeutic advantages [71–75].

Compared with traditional MSC transplantation, nanopeptide hydrogels loaded with HUC-MSC spheroids have been shown to reduce the expression of inflammatory cytokines, including IL-6, IL-10, IL-1β, and TNF-α, in the wounds of diabetic rats. They also increase VEGF expression, thereby accelerating wound healing by modulating inflammation and promoting angiogenesis [76]. Similarly, collagen scaffolds embedded with MSCs genetically modified to express human bFGF significantly promote neovascularization through activation of the HIF-1 pathway. This enhances local blood perfusion, ensuring an adequate supply of oxygen and nutrients to damaged tissue and ultimately shortening the healing process [77]. Furthermore, compared with GelMA combined with non-preconditioned MSCs, GelMA combined with hypoxia-preconditioned ADSCs resulted in increased vascular density and enhanced blood perfusion in dorsal wounds of mice. This approach improves oxygen and nutrient delivery to repair sites, expediting wound healing [78].

The use of combination strategies has also demonstrated promise in promoting scar-free healing. For example, Irfan Khan et al. applied collagen scaffolds encapsulating jagged-1-preconditioned BMSCs to hypoxic wounds in rats. This method upregulated cytokines associated with cell proliferation, anti-inflammatory responses, and angiogenesis, resulting in complete epithelialization of the extracellular matrix, vascularized tissue frameworks, and improved tissue architecture, ultimately supporting scar-free healing [79].

In addition to integrating engineering strategies such as microenvironmental preconditioning or structural optimization with cell culture and biomaterials, MSCs can also be incorporated into biomaterials enriched with drugs or cytokines. This approach enhances MSC adaptability to the wound microenvironment, thereby promoting rapid wound healing. Research has shown that, compared with drug-free scaffolds, BMSCs seeded onto fibrous scaffolds loaded with atorvastatin exhibit superior paracrine functionality. Mechanistically, the release of atorvastatin from the scaffold activates the FAK/AKT pathway, enhancing the secretion and expression of pro-angiogenic cytokines in BMSCs [80]. In another study, Reza Sabzevari et al. demonstrated that applying hydrogels containing conditioned medium from NRF-2-overexpressing HEK-293 cells to MSC-treated wounds improved MSCs survival by creating an antioxidant niche. This strategy also facilitated angiogenesis, enhanced collagen alignment, and accelerated wound contraction [81]. Additionally, sodium ascorbyl phosphate embedded in PF-127 hydrogels reduced oxidative stress and mitochondrial damage, decreased the percentage of apoptotic MSCs, and improved post-transplantation survival. The combination of these strategies in diabetic rat models promoted M2 macrophage polarization, collagen deposition, and neovascularization, leading to faster wound closure [82].

The application of exosomes and engineered exosomes in wound healing

Exosomes are nanoscale vesicles secreted by various cell types. They are rich in growth factors, cytokines, proteins, and microRNAs, playing a crucial role in the wound healing process. Compared to MSCs, exosomes offer several advantages. For example, they can effectively prevent tumor formation and progression, inhibit immune-induced rejection, and avoid genetic instability associated with limited cell survival, functional decline, or aging [83]. Due to these benefits, research in wound healing is increasingly shifting toward cell-free therapies.

Studies have shown that human umbilical cord mesenchymal stem cell-derived exosome (HucMSC-ex) can effectively regulate the inflammatory response by modulating the HIF-1α/TGF-β/Smad signaling pathway, enhance collagen synthesis and angiogenesis, and regulate the intestinal microbiota, thereby promoting the repair of complex perianal fistula wounds in rats. Furthermore, HucMSC-ex at a concentration of 10 μg/100μl has been identified as the optimal dosage for treating complex anal fistulas [84]. Clinically, exosomes have demonstrated similar therapeutic efficacy. In multiple cases involving post-cosmetic surgery, facial trauma, and non-Crohn's disease anal fistulas, local application of HucMSC-ex significantly shortened wound healing time and facilitated effective tissue repair [85, 86].

Despite their therapeutic promise, the clinical translation of exosomes is hindered by several challenges. First, exosome production yields are relatively low, making it difficult to meet the demands of large-scale clinical applications. Second, exosomes lack intrinsic targeting abilities, reducing the precision of their therapeutic effects. Additionally, exosomes exhibit a short residence time on the wound surface, limiting their full therapeutic potential [87].

Nonetheless, due to their advantages in intracellular communication and biocompatibility, exosomes have emerged as a highly promising delivery vector. Bioengineering techniques allow for the modification of exosome phenotypes and the introduction of specific biological substances to enhance cell migration and viability during wound repair. Moreover, with the aid of computational tools and biomaterials, exosome delivery can be optimized for targeted applications, thereby accelerating wound healing [88–91]. For instance, Sheng Meng et al. [92] discovered that MiR-141-3p can inhibit hypertrophic scar formation by downregulating the TGF-β2/Smad pathway in vitro. To enable efficient and safe delivery of MiR-141-3p, researchers transfected miR-141-3p lentivirus into ADSCs and successfully extracted engineered exosomes encapsulating MiR-141-3p. When these engineered exosomes were applied via a dissolvable microneedle array to a rabbit-ear hypertrophic scar model, the scar's color significantly lightened, and the surface became smoother after 21 days. Additionally, when a collagen-rich/platelet-rich plasma biomaterial scaffold loaded with exosomes from keratinocytes, fibroblasts, and ADSCs was applied to dorsal wounds in mice, complete wound closure was achieved within 12 days—substantially faster than with the scaffold alone. Further analysis indicated that the exosome-loaded scaffold promoted efficient wound healing by enhancing angiogenesis, cell proliferation, immune microenvironment modulation, and collagen fiber organization [93].

MSC-derived exosomes represent a promising cell-free therapeutic approach with broad application potential, offering distinct advantages in wound healing. These exosomes not only facilitate tissue regeneration and reduce fibrosis but also present a lower risk of immune rejection, making them particularly suitable for treating chronic and complex wounds. However, challenges related to production, targeting, and clinical application persist, necessitating further research and technological advancements. In the future, with improvements in exosome production techniques and targeted delivery strategies, MSC-derived exosomes are expected to become a key therapeutic modality in wound healing.

Challenges and future perspectives

Wound healing is a dynamic and highly regulated biological process in which MSCs play a crucial role in facilitating tissue regeneration. Since adverse wound microenvironment conditions, including hypoxia and inflammation, can undermine the reparative efficacy of MSCs, advanced MSC engineering technologies have emerged as a pivotal focus in tissue repair research to surmount these challenges and maximize their therapeutic potential.

On one hand, strategies such as pretreatment, optimized cultivation, and biomaterial integration enhance MSC function by improving adhesion, survival, and differentiation through cell-material interactions—effectively countering the challenges of harsh wound microenvironments. On the other hand, precision engineering via genetic modification enables targeted regulation of specific MSCs functions (e.g. anti-inflammatory effects, angiogenesis, re-epithelialization) tailored to wound repair needs. Additionally, exosome-based therapies are emerging as promising acellular approaches that bypass issues like cell senescence and immune rejection while actively promoting healing (Table 3).

Although current research has made notable progress, several critical issues remain that require further attention. Firstly, the use of a single strategy for MSCs engineering still faces significant limitations in clinical applications, particularly regarding the survival rate and functional maintenance of MSCs in trauma repair, which need further optimization. Consequently, future research should focus on the development and clinical validation of combination strategies, employing various engineering approaches such as genetic modification, microenvironmental preconditioning, biomaterial scaffolds, and exosomes, to maximize the functional enhancement of MSCs and improve the overall efficacy of trauma repair. Secondly, clinical translation remains another major challenge for MSCs engineering technologies. While most current studies focus on in vitro experiments and small animal models, with encouraging results,

Table 3 Strategies to enhance MSC therapeutic efficacy in wound healing

Strategy		Mechanism	Efficacy	References
Microenvironmental Preconditioning	cytokine preconditioning pharmacological preconditioning hypoxic preconditioning	PI3K/AKT↑; VEGF↑; HIF-1α↑; MMP-3↑; apoptosis↓	biological characteristics↑	[39–46]
Cell Culture And Structural optimization	3D Coculture biological Scaffolds hydrogels	modulate cell morphology or mimic ECM 3D structure	cell viability, paracrine function↑; cell apoptosis↓; pro-inflammatory cytokine secretion↓	[47–60]
Genetic Modification	-	Wnt/β-catenin signaling pathway↑; regulate cell cycle; normalize intercellular signaling	homing efficiency↑; expression of anti-inflammatory factors↑; angiogenesis↑; re-epithelialization↑; pro-inflammatory cytokine secretion↓	[61–70]
Combination Strategies	-	multi-target regulation	cell proliferation↑; anti-inflammatory capacity↑; angiogenesis↑; survival rate ↑; apoptosis rate↓	[71–82]
Engineered Exosomes	-	precise single-gene regulation	delivery efficiency↑; immune microenvironment modulation ↑	[83–93]

substantial difficulties persist regarding MSCs delivery, long-term survival, and therapeutic efficacy in clinical settings. Therefore, optimizing MSCs delivery methods and addressing MSCs apoptosis in the trauma microenvironment should be prioritized in future research. Additionally, with the emergence of exosome-based therapies as cell-free treatments, improving the production, delivery, and targeting capabilities of exosomes will be critical directions for future research. Advances in bioengineering techniques can further enhance exosome functionality and their application in wound healing.

In summary, with continuous advancements in MSCs engineering technology, personalized treatments that combine multiple engineering strategies are expected to represent a significant breakthrough in the field of trauma healing. Future research should continue to strengthen interdisciplinary collaboration, promote the clinical translation of MSCs engineering treatment strategies, and develop more efficient and safer treatment options to achieve broader clinical applications in trauma repair and ultimately improve patients' quality of life.

Abbreviations

2D	Two-dimensional
3D	Three-dimensional
ADSCs	Adipose mesenchymal stem cells
BMSCs	Bone marrow mesenchymal stem cells
CCL2	C-C motif chemokine ligand 2
ECM	Extracellular matrix
GMSCs	Gingival mesenchymal stem cells
HIF-1α	Hypoxia-inducible factor-1α
HUC-MSCs	Human umbilical cord mesenchymal stem cells
HucMSC-ex	Human umbilical cord mesenchymal stem cell-derived exosome
IFN-γ	Interferon-γ
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
iNOS	Inducible nitric oxide synthase
LPS	Lipopolysaccharide
MMP-3	Matrix metalloproteinase-3
MSCs	Mesenchymal stem cells
PGE-2	Prostaglandin E2
SDF-1	Stromal cell-derived factor-1
TGF-β1	Transforming growth factor-β1
TGF-β	Transforming growth factor-beta
TNF-α	Tumor necrosis factor-alpha
TSG-6	Tumor necrosis factor-alpha-stimulated gene/protein-6
VEGF	Vascular endothelial growth factor
WJ-MSCs	Wharton's jelly derived mesenchymal stem cells

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Author contributions
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Declarations

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Not applicable.

Consent for publication
All authors read and approved the final manuscript and consent for publication was obtained from all participants.

Competing interests
The authors declare that they have no conflicts of interest with the contents of this article.

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