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Review Article

Bone-marrow-derived Mesenchymal Stem Cell-Based Therapy for Wound Healing

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ABSTRACT

Skin is the largest organ in the human and animal body and serves as the first line of defense against the external environment. The present study aimed to summarize the mechanisms underlying the effect of mesenchymal stem cells (MSCs) on wound healing and describe the latest strategies to enhance their therapeutic efficacy. Wounds caused by cuts, abrasions, or burns can disrupt the skin integrity, leading to severe consequences, such as infections, scarring, and reduced mobility. Therefore, effective wound healing therapies are essential to reduce the risk of complications and improve the quality of life for patients. In recent years, MSCs have emerged as promising therapy for wound healing due to their unique properties. The MSCs are found in various tissues, including the bone marrow, and can differentiate into multiple cell types, including skin cells. Additionally, MSCs can secrete substances with anti-inflammatory, anti-fibrotic, and pro-angiogenic properties, which play a critical role in the wound healing process. The MSCs can release these substances as soluble molecules, such as growth factors and cytokines, or enclosed within membrane vesicles like microparticles and exosomes. By releasing these substances, MSCs can reduce inflammation, prevent excessive scarring, and promote the growth of new blood vessels, which are crucial for effective wound healing. The MSC-based therapies have indicated promising results for wound healing. However, the optimal dosage, route of administration, and timing of MSC-based treatments for wound healing applications are yet to be determined. Despite the great potential of bone marrow-derived MSCs to improve the healing process of damaged skin caused by wounds and burns, more research is needed to fully understand how MSCs enhance wound healing and optimize their use in clinical settings.

1. Introduction

The skin is a complex and extensive organ that safeguards the body from many external stressors, such as chemical, mechanical, and thermal factors, infections, and dehydration[1]. The wound healing process comprises four overlapping phases, including hemostasis, inflammation, proliferation, and remodeling[2]. Numerous growth factors, cytokines, and chemokines play a crucial role in regulating the wound-healing process[3]. Stem cells have gained substantial interest in regenerative medicine due to their ability to self-renew and differentiate into multiple cell types, which is vital for physiologic tissue regeneration after injury[4]. One type of stem cell that has shown great potential for wound healing applications is mesenchymal stem cells (MSCs), which can be isolated from various adult tissues as multipotent progenitor cells[5]. MSCs can proliferate and differentiate into various mesenchymal lineages, including osteoblasts, adipocytes, mesodermal chondrocytes, tenocytes, and myocytes[6].

MSCs can be obtained from various sources, such as bone marrow, adipose tissue, umbilical cord blood, umbilical cord tissue, amniotic membrane, peripheral blood, and tendons. Following the discovery of increased numbers of cells with a similar phenotype to Bone Marrow Mesenchymal Stem Cells in burn patients, research on the effectiveness of stem cells in wound healing began[7]. Upon transplantation, MSCs release pro-angiogenic factors, such as vascular endothelial growth factor and angiopoietin-1, to promote the formation of epidermal keratinocytes, follicular epithelium, sebaceous glands, and dendritic cells[8,9]. The treatment and implantation of autologous MSCs have been found to have few adverse effects, primarily exerting anti-

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inflammatory and immunosuppressive effects[10]. However, the expansion of autologous MSCs takes up to 21 days by culturing, and their efficacy is reduced in elderly patients due to decreased proliferation, differentiation, and quantity[11].

To enhance the therapeutic value of MSCs in non-healing wounds, novel approaches have been developed to optimize their regenerative potential. This review aims to summarize the mechanisms underlying the effect of MSCs on wound healing and describe the latest strategies to enhance their therapeutic efficacy.

2. Skin anatomy

The skin is a vital organ in the human body, functioning as a protective barrier against external factors and maintaining body temperature[12]. This organ comprises two distinct layers: the epidermis and dermis[13]. The epidermis, positioned as the outermost layer, is pivotal in regulating body moisture levels and provides waterproofing. Keratinocytes comprise the bulk of the epidermal cells, while melanocytes, Langerhans cells, and Merkel cells account for the remaining population[14]. The dermis, a connective tissue, houses a variety of cells, including fibroblasts, vascular endothelial cells, adipose glands, sweat glands, hair follicles, blood vessels, and nerve endings[15]. Fibroblasts, the primary cells within the dermis, are responsible for producing elastin and collagen, which are critical for skin elasticity and mechanical strength[16]. Below the dermis is the hypodermis, composed of loose connective tissue and fat-storing cells, blood vessels, and nerves. This layer is rich in proteoglycan and glycosaminoglycans, which absorb fluid and provide the tissue with a mucous-like texture[17].

3. The normal processes and characteristics of dermal wound repair

The process of skin wound repair is a complex and intricate interplay between epidermal and dermal cells, angiogenesis, the extracellular matrix, and plasma-derived proteins coordinated by a network of cytokines and growth factors[18]. The repair of skin ulcers occurs through four overlapping yet distinct phases, which are hemostasis, inflammation, proliferation, and remodeling[19]. During these phases, mesenchymal stem cells (MSCs) have shown promise in enhancing wound healing and reducing scarring[20]. MSCs have been found to assist in all stages of wound recovery by migrating to the cutaneous wound, inhibiting inflammation, and promoting the proliferation and differentiation of fibroblasts, epidermal cells, and endothelial cells [21].

Recent studies have highlighted the therapeutic potential of MSC-derived cultured media (MSCs-CM), extracellular matrix (ECM), exosomes, platelet-rich plasma (PRP), and cytokines for treating injuries in various tissues, including skin wounds[22,23]. MSCs-CM, for instance, contains many bioactive molecules, such as cytokines, chemokines, growth factors, and exosomes, which have been shown to enhance the migration and proliferation of dermal and epidermal cells[24]. Additionally, ECM, a scaffold composed of various extracellular matrix components, has been utilized in skin tissue engineering to promote wound healing and skin regeneration[25].

Platelet-rich plasma (PRP), a concentration of platelets obtained from the patient's blood, has also been shown to stimulate wound healing by releasing growth factors and cytokines. Cytokines, such as transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF), have also been found to play crucial roles in skin wound repair by promoting cell migration, proliferation, and angiogenesis[26,27].

In conclusion, the process of skin wound repair involves a complex interplay between various cellular and molecular components. The MSCs and their derived products, such as MSCs-CM, ECM, exosomes, PRP, and cytokines, have shown promise in enhancing the wound-healing process and reducing scarring. These emerging therapies represent a promising avenue for the development of new treatment options for skin wounds and other types of tissue injuries.

3.1. Inflammation

Inflammation is an essential physiological response immediately following tissue damage to prevent infection. This response involves the release of various cytokines, including TGF-β, PDGF, EGF, FGF, and IL8/CXCL-8, from the damaged tissue and fibrin clot, which recruit neutrophils to the wound site[28]. Neutrophils play a crucial role in removing foreign particles and bacteria through their phagocytic activity and releasing toxic substances, including eicosanoids, cationic peptides, and proteinases[29]. Oxygen-derived free radical species produced by neutrophils also have bactericidal properties. After approximately three days, macrophages replace neutrophils and support various functions, such as promoting and resolving inflammation, host defense, and tissue restoration[30]. The MSCs can modulate macrophages to polarize into M2-like phenotype macrophages (MMSC), which have immunosuppressive and anti-inflammatory functions[31]. Moreover, MMSCs can interact with NK cells and inhibit their activation-related proteins, such as NKp44, CD25, CD69, and IFN-γ[32].

3.2. Proliferation

The proliferative phase of healing, which typically occurs between 2-10 days after injury, involves the interaction of different cell types. Angiogenesis and keratinocyte migration are important factors in this phase, with VEGF and FGF playing a critical role in regulating angiogenesis[33]. Fibroblasts also play a crucial role in this phase by transforming into myofibroblasts, which contract and contribute to wound closure[34]. The MSCs play a vital role in this stage by manipulating macrophages to recruit keratinocytes and fibroblasts to the wound site and promote their migration and proliferation[35]. Additionally,

MSCs promote nerve regeneration by releasing signaling factors such as bFGF, NGF, and BDNF[36,37].

3.3. Remodeling

The final stage of healing, remodeling, starts 2-3 weeks after injury and can continue for up to two years[38]. This phase involves the removal of unneeded blood vessels, fibroblasts, and inflammatory cells, leading to scar maturation[39]. During this stage, the composition of the matrix changes, with type III collagen replaced by type I collagen. This process is mediated by matrix metalloproteinases (MMPs) produced by various cells, including fibroblasts, macrophages, and endothelial cells, to strengthen the scar[40].

One novel aspect of this process is the role of MSCs in promoting nerve regeneration, which is crucial for restoring the skin's protective ability and neuronal excitation functions. Another novel aspect is the impact of MSCs on the polarization of macrophages to the M2-like phenotype, which is important in reducing inflammation and promoting tissue restoration. These findings provide insights into potential therapeutic strategies for improving wound healing and tissue regeneration.

4. Adult stem cells related to the wound-healing process

To be classified as stem cells, two criteria must be met: prolonged self-renewal and asymmetric division leading to the production of specialized cell types[41]. These characteristics provide unique abilities that could be leveraged to facilitate the regeneration and repair of damaged skin. Injury models have demonstrated that severe damage significantly increases the number of circulating stem cells in the blood, which can then migrate and differentiate into non-hematopoietic skin structures at the wound site[42]. These findings suggest that stem cells are crucially involved in wound healing, but the underlying mechanisms are not yet fully understood.

Several studies have examined the role of stem cells in wound healing and have highlighted their potential therapeutic applications[43-45]. For instance, recent research has shown that stem cells derived from adipose tissue, bone marrow, and umbilical cord blood can accelerate wound healing by promoting re-epithelialization and reducing inflammation[46]. Moreover, stem cells can also differentiate into skin appendages, such as hair follicles and sweat glands, which could be beneficial for repairing skin defects caused by burns or trauma[47].

Using stem cells in wound healing also presents a unique opportunity to overcome current challenges in tissue engineering. Traditional tissue engineering approaches have struggled to create functional and durable skin substitutes due to limitations in cell sourcing and expansion and inadequate vascularization. Stem cells provide a promising alternative, as they can be obtained from various sources, including the patient's body, and can be expanded *in vitro* to produce large quantities of cells[48]. Furthermore, stem cells can be genetically modified to enhance their therapeutic potential and enable the production of more complex skin structures[49].

Despite these promising advances, several challenges must be addressed before stem cell therapy can become a routine treatment for skin wounds. These challenges include identifying the optimal source and type of stem cells, understanding their mechanisms of action, and ensuring their safety and efficacy in clinical trials. Nevertheless, stem cells hold enormous potential for improving wound healing outcomes and transforming regenerative medicine.

5. Mesenchymal stem cells characterization

Among the various types of stem cells, MSCs are currently considered the most suitable for therapeutic purposes. This is because of their ease of isolation and culturing techniques and the absence of ethical concerns surrounding their usage[50]. In contrast to induced pluripotent stem cells (iPSCs), MSCs carry a lower risk of teratoma formation. As a result of their exceptional immunomodulatory abilities, MSCs are increasingly being recognized as a valuable tool in veterinary medicine[51]. This section will explore noteworthy findings regarding wound healing applications of mesenchymal stem cells (Figure 1).

The MSCs are adult and multipotent stem cells derived from mesodermal tissue, which possess unique biological characteristics that have piqued researchers' interest in regenerative medicine. Additionally, these cells can differentiate into osteoblasts, adipocytes, and chondrocytes *in vitro*[52]. The MSCs are capable of secreting various chemokines that recruit and regulate the function of numerous cell types, as well as growth factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), or leukemia inhibitory factor (LIF), which promote survival and stimulate the proliferation of resident cells[53]. Some of these growth factors, such as VEGF, also induce pro-angiogenic effects, which are crucial for restoring blood supply and recovering damaged tissues[54]. Furthermore, MSCs produce various cytokines and

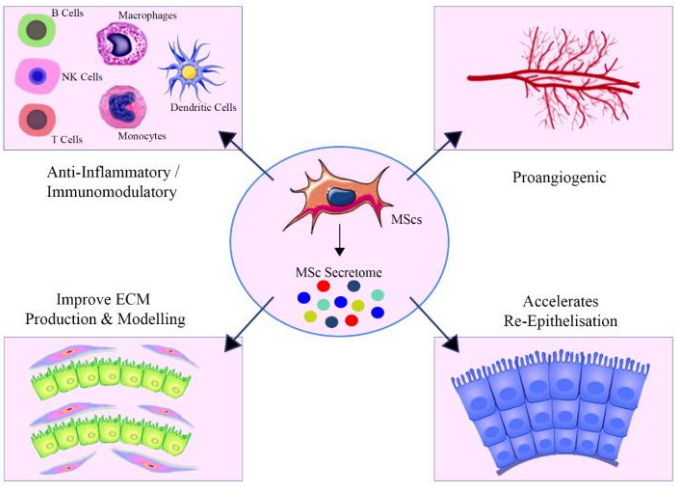

Figure 1. Mesenchymal stem cell properties

mediators, such as interleukin (IL)-6 and 10, prostaglandin E-2 (PGE-2), transforming growth factor (TGF-β), and nitric oxide (NO)[55]. These substances elicit immunomodulatory actions that include inhibiting the proliferation of lymphocytes T, preventing lysis mediated by cytotoxic T cells, suppressing the activation of natural killer (NK) cells and macrophages, and modulating B cell proliferation[56]. Recent studies have shown that MSCs play an important role in wound healing by promoting cell migration, reducing inflammation, and stimulating angiogenesis[57]. The use of MSCs is effective in treating chronic wounds, diabetic foot ulcers, and burns[58]. Additionally, MSCs have been combined with various biomaterials and scaffolds to enhance their regenerative potential in wound healing applications[59].

In summary, MSCs possess unique biological properties that make them ideal candidates for regenerative medicine, particularly in wound healing. Their ability to secrete various bioactive factors, such as growth factors, chemokines, and cytokines, allows them to modulate immune responses and promote tissue repair. Further research is needed to understand the potential of MSCs in wound healing applications fully and to develop more effective therapies (Figure 1).

6. Bone marrow-derived mesenchymal stem cells

Mesenchymal stem cells derived from bone marrow, or BM-MSCs, are a promising tool in regenerative medicine due to their ability to differentiate into various tissue types[60]. They are particularly advantageous because of their ease of accessibility and non-invasive nature of acquisition[61]. Moreover, BM-MSCs have a greater capacity to differentiate into skin system tissue types when compared to other MSCs[62]. As a result, they have garnered a great deal of scientific attention and have been extensively characterized.

Despite their numerous advantages, BM-MSCs do have some drawbacks. One significant disadvantage is the time lag associated with culture-expanded BM-MSCs, which can take 3 to 6 weeks from bone marrow aspirate until treatment[63]. This delay may limit the effectiveness of BM-MSC therapy in cases where immediate treatment is necessary, such as acute injuries or wounds.

Researchers have explored different strategies to reduce the time required for BM-MSC expansion to overcome this limitation. One approach involves the use of alternative culture conditions and growth factors to enhance the proliferation and differentiation potential of BM-MSCs. For instance, some studies have shown that hypoxic culture conditions can improve the regenerative potential of BM-MSCs by promoting angiogenesis and enhancing their immunomodulatory properties[64]. Additionally, specific growth factors, such as basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF), can also enhance the proliferation and differentiation potential of BM-MSCs [65].

Another promising approach is the use of pre-expanded BM-MSCs. Pre-expanded BM-MSCs can be obtained by culturing bone marrow aspirates before transplantation, thereby reducing the time required for expansion. This approach is effective in various preclinical and clinical studies, demonstrating the feasibility and safety of using pre-expanded BM-MSCs in regenerative medicine [66].

In conclusion, BM-MSCs are a promising tool for regenerative medicine, particularly in skin system tissue regeneration.

7. Animal studies

MSCs have emerged as a promising therapeutic option for wound healing due to their ability to differentiate into various cell types and secrete trophic factors that promote tissue regeneration. Animal studies have been crucial in assessing the potential of MSCs in wound healing and identifying the most effective ways to deliver these cells.

One major variation among animal studies is the source of MSCs[67,68]. Bone marrow is the most commonly used source due to the extensive knowledge of MSC biology obtained from previous research. However, adipose tissue and umbilical cord-derived MSCs are also being explored, as they have shown similar wound-healing potential in some animal studies[69,70]. Furthermore, researchers are investigating the possibility of combining MSCs from multiple sources to enhance their therapeutic efficacy.

Another variation in animal studies is the method of cell delivery. Systemic cell delivery methods have been widely used as they are easy to operate, but they have low efficiency in cell engraftment at the wound site[71]. To improve cell retention at the wound site, researchers have explored alternative methods such as local cell suspension injection or scaffold-assisted cell grafting[72]. Scaffold-assisted cell grafting involves using a scaffold that mimics the extracellular matrix and provides structural support to the cells. This method has shown promising results in improving the survival and function of MSCs at the wound site[73].

Although rodent models are commonly used in MSC-based wound healing studies, there are significant differences between the healing mechanisms of rodent and human wounds. In rodents, skin wounds heal mainly by wound contraction, whereas human skin wounds heal primarily by re-epithelialization and granulation[74]. Furthermore, rodents' and humans' innate and acquired immune systems are quite different, and the number and type of cell infiltrate and response in wound healing differ between species[75]. Hence, researchers should consider these species variations when interpreting the results of animal studies and choosing an appropriate animal model.

Reproducible animal models that closely mimic human wound healing are crucial for the translational potential of animal studies[76]. For instance, porcine skin wound models have been proposed as better models for human wound healing due to the similarities in wound healing mechanisms and immune responses[77]. However, it is

essential to note that none of the existing animal models can replicate the complexity and heterogeneity of chronic wounds in humans. Therefore, future research should focus on developing more sophisticated animal models that closely resemble human wounds and on conducting clinical trials to assess the safety and efficacy of MSC-based therapies in humans.

8. The safety of mesenchymal stem cells

The use of MSCs for therapeutic purposes is not without its potential risks, which must be considered when developing clinical protocols. One of the key concerns is the possibility of cells undergoing malignant transformation or promoting tumor growth in vivo, as well as the potential for mal-differentiation of the cells[78]. Therefore, it is crucial to consider certain factors when developing clinical trials involving MSCs.

One potential risk associated with the administration of MSCs is the accumulation of genomic instability during ex vivo expansion, particularly in later passages of the cells[79]. This instability may increase the likelihood of malignant transformation of the graft cells, so it is essential to determine the appropriate cell passages for clinical trials and analyze the genotype of the graft cells before transplantation. This step is necessary to minimize the risk of malignant transformation.

Another potential risk associated with MSC administration is the possibility of the cells homing to tumor sites and promoting tumor growth and progression. Although there have been no reports of adverse tumor formation cases after MSC administration in clinical trials, it is important to exercise strict cell-quality control and conduct long-term follow-ups to ensure no negative effects.

Although the paracrine action of MSCs is the primary mechanism of wound healing in MSC-based therapy, there is still a potential risk of cell mal-differentiation or malignant transformation *in vivo*. As a result, researchers have developed a promising strategy to aid in chronic wound healing using an MSC-conditioned medium, which contains various paracrine factors secreted by MSCs during in vitro culture. Compared to direct transplantation of MSCs *in vivo*, the use of an MSC-conditioned medium avoids the potential risks of mal-differentiation or malignant transformation of grafted cells, making it a safer approach to therapy. However, more research is necessary to fully understand the efficacy and safety of this approach in clinical settings.

9. Conclusion

The skin is one of the most crucial organs in the human body, and when it becomes damaged by wounds caused by cutting, breaking, or burning, it can lead to severe consequences such as infections, scarring, and reduced mobility. The wound-healing process involves complex interactions between various cells and biochemical signals, and any disruption of these processes can lead to delayed or impaired wound healing. Therefore, there is a significant need for effective therapies that can improve the wound-healing process and minimize the risk of complications. Mesenchymal stem cells (MSCs) have emerged as a promising therapy for wound healing applications. The MSCs are found in many tissues throughout the body, including the bone marrow, and can differentiate into various cell types, including skin cells. Additionally, MSCs have been shown to have other beneficial properties that make them attractive for wound healing applications. These cells have a potent immunomodulatory effect and can regulate the immune response, resulting in a reduced inflammatory response and increased anti-inflammatory cytokine levels.

One of the main ways MSCs promote wound healing is by secreting various substances with anti-inflammatory, anti-fibrotic, and pro-angiogenic properties. These substances can be released as soluble molecules, such as growth factors and cytokines, or enclosed within membrane vesicles like microparticles and exosomes. By releasing these substances, MSCs can reduce inflammation, prevent excessive scarring, and promote the growth of new blood vessels, all essential for effective wound healing. Several clinical trials have explored the potential of MSC-based therapies for wound healing, with promising results. In one study, MSCs were found to promote the healing of chronic wounds in diabetic patients. Additionally, MSCs have been shown to accelerate the healing of acute and chronic injuries, including burns and surgical wounds. However, further research is necessary to optimize the use of MSC-based therapies for wound healing applications, including identifying the optimal dose, route of administration, and timing of treatment.

In conclusion, MSC-based therapies have significant potential for improving the healing process of damaged skin caused by wounds and burns. The beneficial properties of MSCs, including their ability to secrete substances with anti-inflammatory, anti-fibrotic, and pro-angiogenic activities, make them an attractive option for wound healing applications. However, more research is needed to fully understand how MSCs enhance wound healing and optimize their use in clinical settings. With continued investigation, MSC-based therapies could become essential for treating a wide range of wound types and improving patient outcomes.

Declarations

Competing interests

The authors have declared no conflicts of interest.

Authors' contributions

Mahsa Khiyabani wrote the draft of the manuscript. Hossein Kazemi Mehrjerdirevised the draft of the manuscript and check the final version of the article. All authors have read and approved the final version of the manuscript for publication in the present journal.

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Ethical considerations

The authors declare that this manuscript is original and has not been submitted elsewhere for possible publication. The authors also declare that the data used/presented in this manuscript has not been fabricated.

Availability of data and materials

The data presented in this study are available on request from the corresponding author.

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