Stem Cells in Wound Healing

Subjects: Dermatology

Contributor: Banu Farabi, Katie Roster, Rahim Hirani, Katharine Tepper, Mehmet Fatih Atak, Bijan Safai

Wound healing is an intricate process involving coordinated interactions among inflammatory cells, skin fibroblasts, keratinocytes, and endothelial cells. Successful tissue repair hinges on controlled inflammation, angiogenesis, and remodeling facilitated by the exchange of cytokines and growth factors. Comorbid conditions can disrupt this process, leading to significant morbidity and mortality. Stem cell therapy has emerged as a promising strategy for enhancing wound healing, utilizing cells from diverse sources such as endothelial progenitor cells, bone marrow, adipose tissue, dermal, and inducible pluripotent stem cells.

Keywords: stem cells ; chronic wound ; wound healing ; dermatology

1. Introduction

Stem cells are used to modulate the progression of neurodegenerative diseases, ischemic damage in the tissues (peripheral artery disease, chronic diabetic wounds, venous ulcers, etc.), as well as for skin rejuvenation [1][2][3]. Recent studies have also shown that the secreted factors from stem cells (or cell-free extracts from stem cells) enhance various disorders through paracrine function in the tissues [4][5][6].

In the last decade, a significant rise in interest into chronic wound healing has occurred due to the increasing incidence of chronic ulcers, an aging population, the increasing incidence of diabetes, and healthcare inequalities. Non-healing ulcers can significantly reduce a patient's quality of life and increase healthcare costs due to recurrent admissions caused by chronically infected wounds, increased risk of osteomyelitis, prolonged intravenous antibiotic treatments, amputation, and eventually the need for supportive care measures for these individuals [7][8].

In contemporary healthcare, the alarming statistic that 70% of amputations stem from unhealed wounds underscores the urgency to address this pervasive issue. With an estimated six million individuals in the United States alone grappling with the consequences of non-healing wounds, the associated healthcare expenditures have surged to a staggering USD 25 billion. In the light of these compelling figures, there is a critical need to explore innovative research avenues to mitigate the human suffering and economic burden imposed by chronic wounds. It is within this context that the exploration of stem cell therapy emerges as a promising and potentially transformative approach. Regarding research into the unique regenerative capabilities of stem cells, further research in this domain has the potential to revolutionize wound care and contribute substantially to ameliorating the impact of non-healing wounds on both individuals and the healthcare system [8][9][10][11].

Stem cells harvested from different sources can be used for wound repair and regeneration such as endothelial progenitor cells (EPCs), adult stem cells in the forms of bone marrow-derived mesenchymal stem cells (BM-MSCs), adipose tissue stem cells (ASCs), dermal stem cells (DSCs), and inducible pluripotent stem cells (iPSs). These stem cells enhance wound healing via tissue regeneration through paracrine signaling and growth factor release, resulting in fibroblast proliferation and tissue remodeling [2].

Wound healing is a complex cascade involving the interaction of inflammatory cells, skin fibroblasts, keratinocytes, and endothelial cells in injured tissue. These cells contribute to wound healing by releasing various chemo-cytokines, growth factors that promote cell migration to the injured area and stimulate inflammation, angiogenesis, wound contraction, and remodeling, resulting in a healthy wound-healing process. The first phase of wound healing starts with the inflammation phase, which starts within 6–8 h after injury. During this phase, platelets migrate to the tissue and release chemo-attractive cytokines; next, macrophages arrive and phagocyte/debride the tissue/organisms and set the stage for the proliferative phase. The proliferative phase starts around 5–7 days after injury and is initiated by cytokines released from macrophages (PDGF, TGF-α/β, FGF, etc.). In this stage, the formation of granulation tissue occurs with fibroblast proliferation and extracellular matrix deposition. During this phase, angiogenesis occurs, which allows leukocyte migration and provides nutrients and oxygen to develop granulation tissue. The final stage is tissue remodeling, in which wound

contraction and extracellular matrix reorganization occurs over several months to years, transitioning into mature scar formation. Overall, an efficient wound-healing process results from a sufficient supply of growth factors, nutrients, cell–cell interactions, and adequate oxygenation to the tissue. Disruptions in these mechanisms, caused by conditions such as infection, malnutrition, chronic disease, or diabetes, can lead to delayed wound healing and chronic wound formation. Despite addressing systemic factors (controlling blood glucose levels, optimizing oxygenation to the tissue, providing local wound care), chronic wound care only achieves moderate success and treatment options are limited [12].

2. Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs)

Bone marrow-derived stem cells, encompassing both hematopoietic stem cells (HSCs) responsible for blood cell formation and mesenchymal stem cells (MSCs) with the capacity to differentiate into various cell types, including bone, cartilage, and fat cells, originate from the spongy tissue within bone cavities. While MSCs are not exclusive to bone marrow and are also found in tissues like adipose tissue, umbilical cord tissue, and synovial fluid, the bone marrow, particularly within long bones like the femur and tibia, serves as a valuable reservoir for these stem cells, making them instrumental for tissue repair across the body. Extraction of autologous bone marrow-derived cells involves a minimally invasive procedure known as bone marrow aspiration, with a specialized needle accessing the posterior iliac crest under local anesthesia. This aspirate, comprising a mix of hematopoietic and mesenchymal stem cells, holds promise for regenerative medicine. The unique regenerative properties of bone marrow-derived stem cells are crucial to optimizing their selection for the development of efficient wound-healing therapies.

Distinctive characteristics set bone marrow-derived stem cells apart from those derived from other tissues, especially in the realm of wound-healing therapy. Bone marrow serves as a rich source of diverse stem cells, including hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), each playing a unique role in blood cell formation and tissue regeneration. The advantageous attributes of bone marrow-derived stem cells lie in their innate ability to modulate the immune response, stimulate angiogenesis, and promote tissue repair, making them particularly well-suited for wound-healing applications. While stem cells can be sourced from alternative sites such as adipose tissue or the umbilical cord, the unique regenerative properties and versatile differentiation potential of bone marrow-derived stem cells position them as pivotal players in the development of effective therapeutic strategies for wound healing. Understanding these distinctions is essential for optimizing the selection of stem cell sources in the pursuit of targeted and efficient wound-healing therapies.

Bone marrow-derived mesenchymal stem cells (BM-MSCs) have emerged as a promising candidate for enhancing wound healing. These cells possess the ability to differentiate into multiple lineages, including cartilage, muscle, connective tissue, and adipose cells. Recent studies have demonstrated their capability to differentiate into various skin cell types, contributing significantly to wound repair. Additionally, research has shown that the application of BM-MSCs, whether through injection or topical occlusive dressing, accelerates wound healing by releasing proangiogenic factors and differentiating them into critical cell types. The therapeutic efficacy of BM-MSCs has been confirmed in human patients with chronic leg ulcers, demonstrating reduced wound size, increased vascularity, and dermal thickness. Notably, BM-MSC application has shown significant reductions in wound area as early as 2 weeks after application in patients with chronic lower-extremity wounds. These findings highlight the potential of BM-MSCs as a valuable and effective approach to advancing wound-healing therapies [8][9][12][13].

3. Adipose Tissue-Derived Mesenchymal Stem Cells

Adipose tissue-derived stem cells (ADSCs) are found in the stromal fraction of the adipose tissue. ADSCs were defined as CD45-negative, CD90-, CD73-, and CD105-positive cells [14]. Unlike other stem cells, ADSCs can easily be collected without any ethical problems and differentiate into different cell lines including adipogenic, osteogenic, chondrogenic, and myogenic cells. Thus, they are studied extensively as one of the leading sources in stem cell therapy for regenerative medicine [15][16].

ADSCs can easily adhere to plastic culture flasks and expand in vitro, and they have the capacity to differentiate into different cell lines. They have been reported to be effective in wound healing, acute graft versus host disease, and hematologic and immunologic disorders via their immunomodulatory properties [17]. In contrast to the intrusive methods required for harvesting BM-MSCs, adipose tissue is plentiful and can be easily obtained through liposuction, resulting in a less invasive process. Although flow cytometry is the conventional method for isolating AD-MSCs, autologous fat grafting can also be a valuable and practical alternative [18].

Impacts of ADSCs on neovascularization in ischemic tissue in animal models have been shown and these cells can release many potent angiogenic factors as well as the fact that they are capable of differentiating into endothelial cells, thus increasing tissue vascularization [19]. ADSCs secrete TGF-β, vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), fibroblast growth factor 2 (FGF2), PDGF, HGF, fibronectin, and collagen I, which have been previously shown to stimulate wound-healing processes previously [20]. Studies have suggested that ADSCs can promote wound healing with paracrine activity with the aforementioned chemokines [21][22][23]. Skin wounds treated with ADSCs have been shown to exhibit enhanced healing rates and less scar formation. It was shown that the human epidermal keratinocyte migration rate was increased when co-cultured with ADSCs [24].

Exosomes or extracellular vesicles have been defined as “particles naturally released from the cell that are delineated by lipid bilayer that cannot replicate or do not contain a functional nucleus” [25]. They can be secreted from various cell types and act as intercellular communications, delivering bioactive cargos, such as proteins, lipids, nucleic acids, miRNAs, and growth factors. They regulate cell-to-cell communication and regulate metabolism and homeostasis. Increasing evidence shows that exosomes derived from ADSCs exhibit anti-inflammatory properties through inducing the polarization of macrophages to the M2 type through the STAT-3 pathway and reducing inflammation. Exosomes contain microRNSAs, which reinforce the acceleration of wound healing [26]. Additionally, ADSC exosomes promote scarless wound healing by preventing fibroblasts from differentiating into myofibroblasts and resulting in better cosmesis. These exosomes can be delivered to the tissue with injections, by being loaded into alginate hydrogel or loaded into wound dressings [27].

It was shown that autologous ADSCs combined with atelocollagen accelerated wound healing in a diabetic chronic wound model on mice via increasing the healing time, epithelization rate, granulation tissue, and vascular formation compared to a control group [28]. Altman et al. reported enhanced wound healing when full-thickness wounds were sutured with ADSC-seeded silk sutures in mice [29]. Furthermore, Blanton et al. reported better cosmesis and vascularization on porcine skin when ADSCs and platelet-rich plasma were applied together topically compared to only ADSCs or PRP applications in mice [30]. ADSCs appear to enhance wound healing via differentiation to other cell lines and paracrine activity.

4. Inducible Pluripotent Stem Cells

Inducible pluripotent stem cells (iPSCs) are pluripotent stem cells derived from somatic donor cells that are generated via overexpression of Oct4, Klf4, Sox2, and c-myc transcription factors in adult somatic cells harvested from healthy objects. iPSCs have the capacity to differentiate into and repopulate all cell types found in the skin [9]. Although there are some concerns regarding their safety and regenerative capacity, iPSCs have been investigated in clinical trials of disease modeling, including cardiomyopathy, autism spectrum disorder, coronary artery disease, and cystic fibrosis [31]. Human-induced pluripotent fibroblasts, human-induced pluripotent mesenchymal stem cells, and human-induced pluripotent stem-cell-derived vesicles have the potential to accelerate wound healing [32]. Two recent studies from Sebastiano et al. and Umegaki-Arao et al. reported the successful use of human keratinocyte-derived iPSCs to reconstitute skin in vitro for recessive dystrophic epidermolysis bullosa [33][34]. Clayton et al. showed that injection of iPSC-derived endothelial cells promoted angiogenesis and accelerated wound closure in a murine excisional wound model [34]. These findings can enable the generation of iPSC-based cutaneous substitutes that include epidermal appendages and may be attractive as a therapeutic option in wound healing. However, there are concerns regarding the safety of iPSCs: since iPSCs can differentiate into cells from any of the three germ layers, they carry a risk for teratoma formation. Different strategies, including using viral vectors to deliver induced pluripotent stem cell vesicles, are under investigation to overcome this risk [32].

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