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Mesenchymal stem cells in skin wound healing

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Abstract

The integrity of healthy skin plays a crucial role in maintaining physiological homeostasis of the human body. Chronic conditions such as diabetes mellitus or peripheral vascular diseases can lead to impaired wound healing. Skin wound healing purposes focusing on the main phases of wound healing, *i.e.*, inflammation, proliferation, epithelialization, angiogenesis, remodeling, and scarring. This is a complex process, which is dependent on many cell types and mediators interacting in a highly sophisticated temporal sequence. Although some interactions during the healing process are crucial, redundancy is high and other cells or mediators can adopt functions or signaling without major complications. Mesenchymal stem cells have an alternative role due to special properties such as the capacity for self-renewal and multi-lineage differentiation, immunomodulatory effect, alleviation of inflammatory response, induction of angiogenesis, regulation of extracellular matrix remodeling, excellent migration and secretion of growth factors and cytokines in wound healing. We summarized current research on the mechanisms of mesenchymal stem cells with their isolation, specific markers, differentiation capacity, and the functional activities to evaluate wound healing application.

Keywords: mesenchymal stem cell; skin; wound healing

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Introduction

The skin has a crucial role in protecting the body against external factors, such as mechanical strokes and infections. During the maintenance of the body homeostasis, integrity of skin is provided *via* fluid balance, flexibility, thermal regulation and keratinocytes exhibiting high mitotic activity. The keratinocytes in the basal layer of the skin generate the other epidermal layers and allow tissue renewal. They could fail to provide tissue regeneration in some chronic cases, especially diabetic wounds, peripheral vascular diseases and burn injuries.[1]

Wound healing is a complex process that depends on the presence of various types of cells, growth factors, cytokines and elements of the extracellular matrix. In condition of wound healing, alternative therapies are attempted such as mesenchymal stem cells because of the loss of skin tissue. For this purpose, stem cells have a potential use in wound healing treatments. Many growth factors such as epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), and vascular endothelial growth factor (VEGF) are also important for stem cell behavior in skin wound. The role of stem cells with biological activity of growth factors regulate skin environment during pathological conditions of skin. Therefore, knowledge concerning the mechanisms of wound healing is extremely essential from clinical point of view.[2]

Studies in recent years have reported various stem cells for chronic wound healing, *e.g.* skin-derived precursor cells (SKPs), epidermal stem cell (EpSCs), amnion-derived mesenchymal stem cells (AMSCs), synovium mesenchymal stem cells (SMSCs), bone marrow-derived stem cells (BMSCs) and adipose-derived stem cells (ASCs). These are effective in cell proliferation, promoting angiogenesis, granulation and immunomodulation. However, the researchers in agreement on the use of the MSCs due to their advantages.[3–9]

Mesenchymal stem cells (MSCs) have been a subject of an increased interest due to their ability to give rise to most of the tissues and their role in wound healing in organs has been extensively studied. Advances in the mechanism of these cells in promoting wound healing, including alleviation of inflammatory response, induc-

tion of angiogenesis, and promotion of migration of mesenchymal stem cells to the site of tissue injury show their potential use as tissue regenerative cells and tools for gene delivery.[10]

In the current review, we aimed to summarize the characteristic properties of MSCs and their potential use in skin wound healing clinically. Thereby, as an alternative therapy using MSCs is exhibitied with advantages in the dermatology area.

Mesenchymal Stem Cells

The potential of alternative methods to increase migration of MSCs into wound areas has also been demonstrated. Taking advantage of the association between MSCs with M2 macrophages and microRNA, methods to enhance the immunomodulatory capacity of MSCs have been successful. New measures to enhance angiogenic capabilities have also exhibited effectiveness, often demonstrated by increased levels of proangiogenic vascular endothelial growth factor. Also, hypoxia has been shown to have strong wound-healing potential in terms of increasing MSC efficacy.[11] There are many sources for MSCs such as bone marrow and adipose tissue. BMSCs and ASCs can be obtained practically with surgical operation. Derivation of MSCs from the source necessitate different culture substance such as the use of higher (>10%) concentrations of horse and bovine serum and addition of various hormonal supplements and extracellular matrix (ECM) proteins such as collagen and fibronectin. Their morphological shape is similar to fibroblasts *in vitro* during confluent stage (**Figure 1**). MSCs represent an extremely rare cell type within the bone marrow, comprising 0.01% to 0.001% of all mononuclear cells, compared to 1% for the hematopoetic stem cell (HSC). This rarity has made the identification of the MSCs niche within the bone marrow difficult, although surface marker expression analysis suggests a perivascular location. MSCs define pluripotent cells including stromal stem cells, multipotent stromal cells, mesenchymal stromal cells, and multipotent adult progenitor cells (MAPC).[10–12]

Murine multipotent bone marrow MSCs were originally identified by Friedenstein on the basis of their adherence to tissue culture plastic *in vitro*, their ability to form colony-forming unit-fibroblasts (CFU-F) *in vivo*, and their potential for differentiation into adipocytic, osteocytic, chondrocytic, and muscular lineages. They were also shown to be able to differentiate following implantations *in vivo*. Depletion of hematopoietic cell contaminants by elimination of non-adherent cells or by surface marker-based negative selection is also routinely used to separate MSCs from HSCs. They show spindle, star-shaped, and large flattened cell morphology with surface markers indicative of self-renewal and multipotency. The identification of subpopulations of MSCs with varying degrees of commitment to one or more stromal cell types by specific antibodies is common during culture expansion *in vitro*.[13–15]

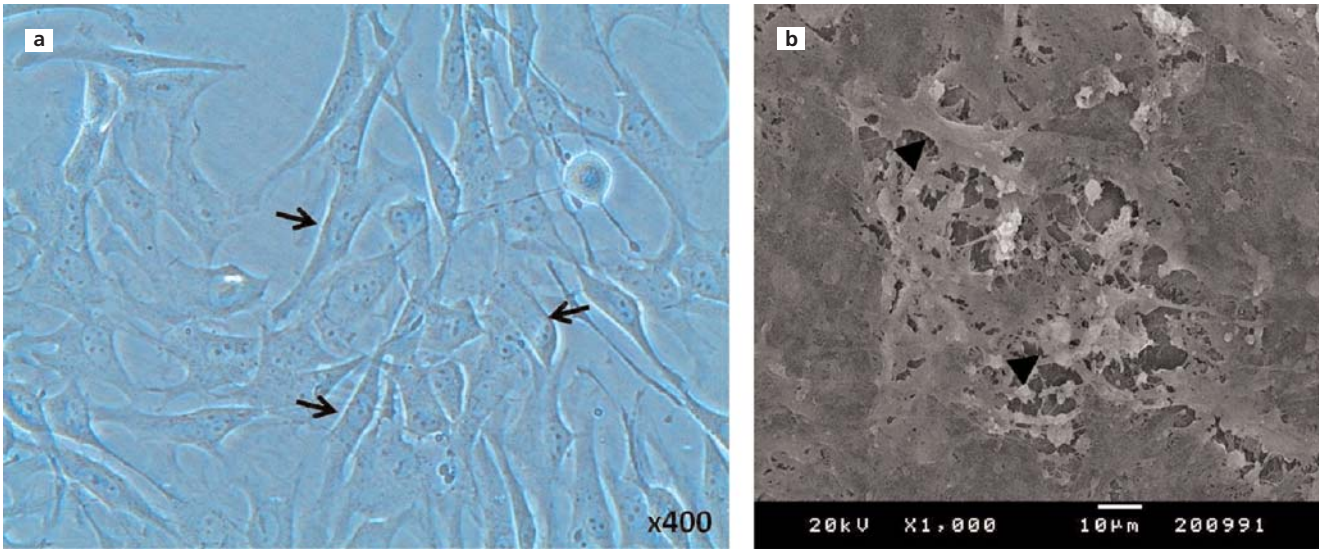

Figure 1. Inverted (**a**) and scanning electron microscope (**b**) images of MSCs *in vitro* culture conditions. MSCs were in shape of fibroblast-like on culture flask (**a**) and titanium disk (**b**). **Arrows** and **arrow heads**: MSCs. Magnification ×400 in a and Scale bar 10 µm in **b**. [Color figure can be viewed in the online issue, which is available at www.anatomy. org.tr]

MSCs share the expression of a number of key genes with embryonic stem cells (ESCs), namely, the transcription factors OCT-4 and SOX-2, which are involved in the maintenance of pluripotency. Additionally, MSCs are positive for the ESCs surface marker SSEA-4.[16,17]

Human and murine MSCs are typically negative for hematopoietic markers CD34 and CD45, although freshly isolated MSCs often contain subpopulations of cells that express a low level of these markers (**Figure 2a**). Human MSCs typically are positive for surface markers CD44 (H cell adhesion molecule, HCAM), CD73 (5'-nucleotidase), CD90 (Thy-1 surface antigen), CD105 (endoglin), CD106 (vascular cell adhesion molecule-1, VCAM-1) and STRO-1 (**Figure 2b**).[18,19] Murine MSCs share this expression pattern, with the exception of STRO-1, but express the stem cell antigen-1 (Sca-1).[20] New surface markers with high differential expression on MSCs compared to other bone marrow cells have been recently proposed, including low-affinity nerve growth factor receptor (LNGFR/CD271) and integrin alpha-1 (CD49a), both of which have been used to purify a relativity homogeneous population of multipotent cells from bone marrow.[21]

Differentiation of MSCs into lineage specific cells is controlled by external factors in the environment, including cell–cell and cell–ECM adhesion and cytokine, chemokine, and growth factor availability. A number of genes expressed upon differentiation of MSCs into mature cells of mesenchymal bone marrow lineages such as adipocyte, osteocyte and chondrocyte have been well characterized. The transcription factors RUNX-2 and OSTERIX control the differentiation of osteoblasts and the formation of bone.[22,23] Differentiation of MSCs into adipocytes is highly dependent on the peroxisome proliferator-activated receptor gamma (PPARÁ) proteins, as well as the C/CAAT enhancer binding proteins.[24,25] A number of soluble mediators display powerful effects on MSCs proliferation and differentiation. Bone morphogenic proteins (BMP), which are members of the TGF-β family, stimulate the differentiation of MSCs into osteocytes, chondrocytes, and adipocytes. Selection of a particular lineage is dependent on the receptor engaged, with BMP receptor-IA and -IB inducing adipocyte or osteoblast differentiation, respectively. Additionally, BMP when coupled with Wnt inhibit the proliferation of undifferentiated MSCs. In contrast, transforming growth factor (TGF)-β1 stimulates the proliferation of MSCs, while suppressing differentiation. TGF-β activates inhibitory Smads which suppress BMP signaling, providing a molecular basis for the antagonistic effects of different TGF-β family members. The Wnt family of proteins influence MSC phenotype through both canonical and non-canonical signaling pathways, but their effect seems concentration dependent. Canonical Wnt3a increases proliferation of MSC, while non-canonical Wnt5a suppresses proliferation, although high levels of canonical Wnt may also have an inhibitory effect. The cytokines interleukin (IL)-1 and tumor necrosis factor (TNF)-α provide another example of antagonistic control over MSC phenotype, as these molecules suppress adipogenesis and enhance osteogenesis through PPARγ inhibition.[26] Platelet-derived growth factor (PDGF) mediates the differentiation of MSC into pericytes by activating through the receptors PDGFR-α,

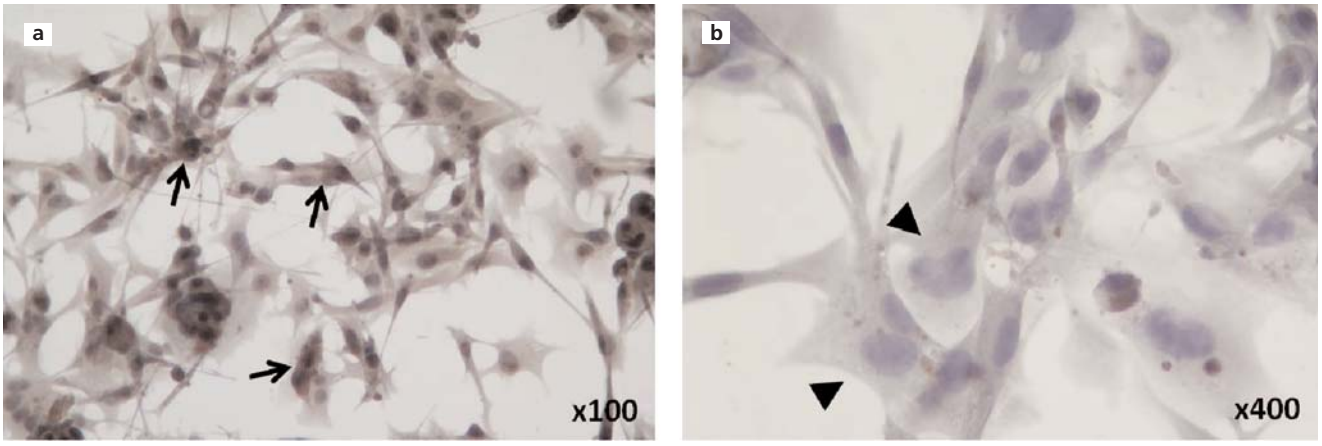

Figure 2. Immunohistochemistry staining of Stro-1 and CD45 in MSCs. MSCs were immunopositivity with Stro-1 (**a**), whereas CD45 staining was negative (**b**). **Arrows:** immunopositive cells, **arrows heads:** immunonegative cells. Magnification ×100 in **a** and ×400 in **b**. [Color figure can be viewed in the online issue, which is available at www.anatomy. org.tr]

ROCK, and the polymerization of α-SMA whereas PDGFR-β signaling inhibits ROCK and promotes α-SMA depolymerization.[27,28] Characterization, isolation and facilities of MSCs have been defined well, so utilization of MSCs are stil attempted.

Wound Healing and MSCs

The complex process of wound healing occurs in overlapping phases, including inflammation, proliferation, angiogenesis, epidermal restoration, and wound contraction and remodeling. As pro-inflammatory reactions play indispensable roles in initiating wound repair, sustained and prolonged inflammation exhibit detrimental effects on skin wound closure. Regeneration processes in wound healing are normally mediated through complex interactions among the extracellular matrix, cells and paracrine factors. Failed or disorganized healing processes caused by one or several impaired mechanisms would lead to difficulty in wound healing in many diseases.[29]

A number of the therapies developed for chronic wounds, including negative pressure therapy, hyperbaric oxygen therapy, antimicrobial therapy, bioengineered skin equivalents, maggot debridement therapy, growth factors, have limited success. The cell transplantation incorporated in the matrix material or implanted in the wound bed has gained recent interest. The stem and progenitor cells originally thought to replace organ-specific cells have recently been discovered to also deploy their potential for wound healing through chemotaxis of host cells and as a source for cell signaling molecules.[1,30]

In non-healing wounds, MSCs based therapies have the potential to activate a series of coordinated cellular processes, including angiogenesis, inflammation, cell migration, proliferation and epidermal terminal differentiation. As pro-inflammatory reactions play indispensable roles in initiating wound repair, sustained and prolonged inflammation exhibit detrimental effects on skin wound closure. Regeneration processes in wound healing are normally mediated through complex interactions among extracellular matrix, cells and paracrine factors. Failed or disorganized healing processes caused by one or several impaired mechanisms would lead to difficult-to heal wounds in many diseases. The beneficial effects of MSC in promoting wound repair have been widely supported by numerous studies.[31,32]

Prior studies have shown that MSCs can alter the cytokine secretion profile of a variety of immune cells towards anti-inflammatory behaviors. This feature of MSCs likely plays important functions in promoting wound repair beyond the inflammatory phase, and is particularly useful for inflammation-associated disorders such as infection, diabetes and critical limb ischemia.[33] Cells can contribute to tissue regeneration by effective and prolonged cytokine secretion at the wound site, immunomodulative properties, and cellular recruitments. Adipose-derived stromal cells (ASCs) have been described since 2002, are easily harvested by a subcutaneous biopsy, have high mesenchymal stem cell density per gram of adipose tissue, and possess differentiation, immunomodulative, and angiogenic properties similar to those of BMSCs. The ability of implanted ASCs to differentiate into endothelial cells was described, as was their capacity to release large amounts of proangiogenic growth factors (particularly SDF-1α and VEGF).[34]

Thus, the methods that potentially augment the immunomodulatory functions of MSCs may provide clinical benefits when treating chronic wounds in conjunction with MSCs. In clinical therapies to treat hard-to-heal and chronic lesions, MSCs present a promising opportunity, and fundamental understandings of MSC actions in wound healing are crucial for clinical success. Normal wound healing requires coordinated and dynamic tissue remodeling process, including coagulation and hemostasis, cell migration and proliferation, inflammation, angiogenesis, and extra cellular matrix remodeling. Failed or disrupted healing stages are often seen in chronic wounds due to a variety of underlying disorders, such as diabetes, vascular abnormalities or burns. Previous studies have reported that progenitor cells, particularly MSCs, could improve cutaneous repair, and MSCs could utilize multiple mechanisms to promote wound healing.[35]

MSCs provide many key growth factors to induce cell migration and proliferation. Particularly, pro-angiogenic factors secreted by MSCs can stimulate the survival, proliferation and branching of vascular cells *in vitro* and *in vivo*. MSC-induced neovascularization through VEGF and bFGF could be a crucial step in directing efficient supplies of the cells required for the effective healing processes. MSCs can also maintain an optimal context for tissue remodeling by dynamically modulating the immune environment. Stem cells have been used successfully to treat both chronic and acute wounds by accelerating wound healing, enhancing re-epithelialization, promoting angiogenesis, exhibiting plasticity, and releasing paracrine signaling molecules. These cells can be delivered to the wounds either directly (*e.g.*, through spraying, injecting, or systemic administration) or *via* skin scaffolds. For example, successful delivery of autologous MSCs using a fibrin spray system directly to acute and chronic wounds in mice and humans has been reported.[36,37]

MSCs were also shown to increase vascular density in the wounds along with the rate of re-epithelialization. The effect of activin signaling on the homing of stem cells to skin wound has been reported. It was also found that JNK and ERK signaling pathways were involved in activin signaling and eventually the homing of stem cells. The role of stem cells in wound healing has been shown to be performed through several pathways, such as JNK and ERK59, and with the involvement of different factors and mediators, such as KGF-1 and PDGF-BB.[38]

The properties of the extracellular matrix (ECM) and its contribution to wound-healing changes throughout the lifespan. Younger skin can mount a robust response by producing ECM that can adapt to the mechanical demands of an injury, whereas older skin shows considerable atrophy and a prolonged and blunted healing response with heightened inflammation and differences in signal transduction that results in decrease in ECM production. The healing in older animals also involves a protective and non-inflammatory response characterized by reduced matrix molecule production and reduced scarring. The study about an *in vitro* model of aged rat skin suggests that age-associated disadvantages in healing may arise from overexpression of MMPs, particularly MMP2, consistent with findings that protease expression and activity are increased in older human adults. Age-related changes in hormonal status affect repair. MMPs, particularly MMP2, are elevated principally in older postmenopausal females, and estrogen replacement therapy can stimulate the migration and proliferation of keratinocytes and elaboration of matrix.[39,40]

The important cell types in this process include platelets which recruit inflammatory cells and form a provisional matrix, and macrophages which include several phenotypes and regulate the cytokine environment in the wound influencing proliferative responses and wound closure. Matrix metalloproteinases (MMPs) are active throughout wound healing, aiding in phagocytosis, angiogenesis, cell migration during epidermal restoration, and tissue remodeling.[39]

In chronic wounds, resident cells proliferate less and show morphology similar to that seen in senescent cells. Fibroblasts from chronic VLU, particularly ulcers of long duration, show poorer responses to platelet-derived growth factor (PDGF), alterations in transforming growth factor beta (TFG-β) and TGF-β type II receptor expression, and abnormal phosphorylation of key signal transduction proteins. Decreased receptor expression in cells in these wounds is similar to that in cells exposed to low oxygen tension, suggesting chronic wounds are hypoxic.[41]

There are some FDA-approved cellular treatment products for wound healing. One of them is Gintuit, a product based on an allogeneic cultured keratinocytes and fibroblasts in bovine collagen. It is an allogeneic cellularized scaffold product indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults. The active ingredients of GINTUIT are the allogeneic keratinocytes, allogeneic dermal fibroblasts, and bovine Type I collagen. *In vitro* studies have shown that GINTUIT secretes human growth factors and cytokines, and contains extracellular matrix proteins. The efficacy analysis of GINTUIT was based on two six-month, prospective, randomized, within-subject controlled (matched for teeth and gingival condition), treatment comparison clinical trials. Another FDA-approved cellular treatment product is Apligraf. It is a living cell-based product for chronic venous leg ulcers and diabetic foot ulcers. Apligraf is supplied as a living, bi-layered skin substitute. The lower dermal layer combines bovine type 1 collagen and human fibroblasts (dermal cells), which produce additional matrix proteins. The upper epidermal layer is formed by promoting human keratinocytes (epidermal cells) first to multiply and then to differentiate to replicate the architecture of the human epidermis. Unlike human skin, Apligraf does not contain melanocytes, Langerhans' cells, macrophages, and lymphocytes, or other structures such as blood vessels, hair follicles or sweat glands.[42]

Indeed, the topical application of growth factors in an attempt to heal human chronic wounds has been reported with mixed reviews, highlighting the complexities of the chronic wound pathology. The drug Regranex, a recombinant human platelet-derived growth factor-BB (rhPDGF-BB), is currently the only growth factor with U.S. Food and Drug Administration (FDA) approval for treatment of DFUs, as it has been shown to improve healing in DFUs in randomized clinical trials.[43]

Stem cells have proven to be a useful tool in cell-based therapies for a wide collection of diseases. For ASCs, the development of detailed and differentiation protocols for various cell types, optimization of *in vivo* delivery methods, and mitigation of immune response in allogeneic transplantations are some of the challenges that need to be overcome. Many of these challenges have been considered and investigated of late, but additional work is necessary in order to bridge the gap between ndings in basic science and the clinical treatment of diseases with stem cell-based regenerative medicine.[44]

Conclusion

In view of these studies, MSCs offer the potential to be used in wound healing. Despite the fact that resources of MSCs are very different, BMSCs and ASCs can be isolated easily from the adults; embryonic sources are proved troublesome in terms of ethics. In addition to their abilities of self-renewal and proliferation, MSCs can promote the cells *in vivo* for migration, angiogenesis, immunomodulation, so these facilities enhance their reliability and allow for their clinical use in dermatology.

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