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REVIEW ARTICLE

Stem Cell Therapy for Dermal Wound Healing

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The use of cellular therapy in the treatment of dermal wounds is currently an active area of investigation. Multipotent adult stem cells are an attractive choice for cell therapy because they have a large proliferative potential, the ability to differentiate into different cell types and produce a variety cytokines and growth factors important to wound healing. This review focused on the roles of adult stem cells such as endothelial progenitor cells, bone marrow and adipose-derived mesenchymal stem cells, during dermal wound healing process and their therapeutic potentials for the treatment of chronic wounds, which remain a major clinical problem, especially in diabetic patients.

Keywords: Stem cell, Transplantation, Wound healing

Wound healing

Cutaneous wound healing is a complex procedure involving the interaction between different cells in the injured tissue, including inflammatory cells, fibroblasts, keratinocytes, and endothelial cells (1, 2). These cells contribute to healing process by releasing various chemo-cytokines and growth factors in a cell type specific manner to stimulate inflammation, angiogenesis, wound contraction and remodeling. In the first inflammation phase, monocytes/macrophages start phagocytosis in order to remove debris and secret a large number of potent tissue growth factors, thereby activating keratinocytes, fibroblasts, endothelial cells. Their functional importance has been shown in monocyte/macrophage-deficient animals, which exhibit delayed angiogenesis and re-epithelialization (3). In the next angiogenesis phase, the production of angiogenic growth factors and various cytokines by macrophages promotes the formation of new blood vessels. Newly formed vessels not only allow leukocyte migration into the wound, but also provide the nutrients and oxygen required to develop the granulation tissues. In the final tissue remodeling phase, wound contraction and extracellular matrix reorganization occurs over several months, transiting granulation tissues into mature scar. Overall, efficient wound healing results from a sufficient supply of growth factors and adequate circulation of oxygenated blood.

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Stem cell therapy for cutaneous wound healing

The use of cellular therapy in the treatment of dermal wounds is currently an active area of investigation. Multipotent adult stem cells are an attractive choice for cell therapy because they have a large proliferative potential, the ability to differentiate into different cell types and produce a variety cytokines and growth factors important to wound healing. This review focused on the contribution of adult stem cell populations during dermal wound healing process and their therapeutic potentials as cell therapy.

Endothelial progenitor cells

Endothelial progenitor cells (EPCs) are endothelial precursors involved in the revascularization of injured tissue and tissue repair (4). Their vascular repairing potentials have been reported in a variety of preclinical and clinical studies with ischemic diseases, including myocardial in-

faction, stroke and peripheral arterial disease (5). In addition, several publications including ours reported that EPC transplantation accelerated wound healing by enhancing neovascularization in granulation tissue. Suh et al. reported that the intradermally injected EPCs secreted a variety of wound healing-related growth factors and cytokines, thereby promoting the recruitment of monocyte/macrophage and stimulating endogenous angiogenesis during the wound healing process (6). Barcelos et al. reported that the transplantation of human $CD133^+$ progenitor cells into streptozotocin-induced diabetic mice, increased the wound closure rate and the capillary density in the granulation tissues (7). Another study showed that the treatment of ischemic hindlimb with EPC-conditioned medium (EPC-CM) leaded to a substantial increase in blood flow in the presence of enhanced neovascularuzation, vascular maturation and muscle function. Recently, Di Santo et al. reported that the regenerative potential of EPC-CM was equivalent to that achieved by EPC transplantation, suggesting that EPC-CM might serve as another therapeutic option that is free from allograft-associated immune rejection concern (8). These results suggested that EPC transplantation could be beneficial for the treatment of cutaneous wounds, especially chronic wounds that are often associated with decreased peripheral blood flow and remain difficult to heal using current therapeutic approaches.

Bone marrow-derived mesenchymal stem cells

Bone marrow-derived mesenchymal stem cell (BM-MSCs), also referred to as stromal progenitor cell, is another promising candidate to repair or replace damaged tissues (9). They have been known to have ability to differentiate into multiple lineages, such as endothelial cells (10, 11), neural cells (12), hepatocytes (13) and others. In addition, Mikako et al. recently show that BM-MSCs contributed to wound repair by differentiating into multiple skin cell types (14). In this study, BM-MSCs were able to differentiate into keratinocytes, endothelial cells, pericytes and monocytes. In 2007, Wu et al. reported that BM-MSCs significantly enhanced wound healing in both diabetic and nondiabetic mice, in that BM-MSC-treated wounds exhibited accelerated wound closure by releasing proangiogenic factors such as VEGF and angiopoietin-1 (15). Analysis of paracrine factors released from BM-MSCs with real-time PCR and of BM-MSC-CM by ELISA showed that BM-SMCs secreted VEGF, IGF-1, EGF, KGF, angiopoietin-1, and stromal derived factor-1. These paracrine factors from MSC-CM made a great contribution in recruiting $CD14^+$ monocytes, keratinocytes and endothelial cells into wounded tissues, thereby promoting the wound healing process (16).

Adipose tissue-derived stem cells

Adipose tissue-derived stem cells (ADSCs) are located within the stromal vascular fraction of adipose tissue. ADSCs have the potential to differentiate into adipogenic, osteogenic, chondrogenic, and myogenic cells when they are cultured in specific culture conditions. Recent reports described the potential impact of ADSCs on neovascularization in ischemic disease animal models. ADSCs have been shown to release many potent angiogenic factors and also to be incorporated into blood vessels through differentiating into endothelial cells in *in vivo* study (17-19). In 2009, Ebrahimian et al. reported the transplantation of ADSCs promoted wound closure and improved the blood perfusion in the wounded skin (20). When ADSCs were cultured in hypoxic conditions, they secreted VEGF 5-fold more than in normoxic condition. Conditioned media obtained from hypoxic ADSCs significantly increased endothelial cell growth and reduced endothelial cell apoptosis (21).

Conclusion

Stem cell-assisted wound healing is potentially a therapeutic approach for the treatment of healing-impaired wounds, in which natural wound-healing processes are not enough to prevent tissue necrosis and ischemia, partially because of an inadequate supply of growth factors and insufficient blood circulation. Although many efforts have been made to enhance chronic wounds by provding wound healing-related growth factors, clinical results have been discouraging, with only modest improvements in the length of time to closure, in breaking strength, and in neuropathy. However, stem cell therapy has several theoretical advantages over growth-factor-mediated approaches, in that transplanted stem cells not only differentiate into multiple cell types composing the skin, but also provide cytokines and growth factors required for wound healing. Therefore, stem cell transplantation may be regarded as an attractive therapeutic option for the treatment of chronic wounds, which remain a major clinical problem, especially in diabetic patients.

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Potential Conflict of Interest

The authors have no conflicting financial interest.

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