Fibrocytes: A potential therapeutic cell population in chronic wounds

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Chronic wounds, such as venous stasis ulcerations, pressure sores, and diabetic foot ulcers, are challenging medical issues that physicians are increasingly facing. With the growing incidence of this problem, a great amount of research into possible treatments, such as topical application of growth factors, has been funded with the goal of helping augment the healing of chronic wounds; but these treatments have provided unsatisfactory outcomes in clinical trials. Insufficient inflammation, cellular proliferation, and migration, as well as extracellular matrix (ECM) deposition and angiogenesis are common to all complex tissue defects.

Numerous studies have indicated that bone-marrow-derived stem cells may contribute to tissue repair or regeneration,1,2 which provides us with a new perspective in wound healing. In the early 1990s, a distinct population of fibroblast-like cells was discovered by their rapid and specific recruitment from the circulation to implanted wound chambers in mice.3 These cells, which are now called fibrocytes, comprise 0.1–0.5% of nonerythrocytic cells in the peripheral blood.3 Fibrocytes are bone marrow-derived cells that appear to differentiate from the circulating CD14+ cell population and exhibit hematopoietic stem cell and stromal cell characteristics. It has been revealed that fibrocytes can migrate to wound sites via several chemokine receptors, including chemokine receptor 3 (CCR3), CCR5, CCR7, and C-X-C chemokine receptor type 4.4 Fibrocytes appear to be precursor stem cells of myofibroblasts, which are essential in wound contraction and healing. Dermal regeneration during wound healing may depend on the recruitment of fibrocytes.

Fibrocytes are able to enter wound sites and participate in local inflammatory and wound-healing responses. Fibrocytes purified from wound chambers were found to secrete inflammatory cytokines including interleukin (IL)-1β, IL-10, and tumor necrosis factor (TNF)-α.5 IL-1β and TNF-α, two important mediators of the wound-healing response, can stimulate chemokine and hemopoietic growth factor secretion in vitro. Compared with the coexistent monocytes and T cells isolated from the wound chamber, fibrocytes expressed a higher level of macrophage inflammatory protein (MIP)-1, 2, platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β, and macrophage colony stimulating factor (M-CSF).5 These cytokines and growth factors play an essential role in inflammatory response, cellular proliferation and migration, ECM deposition, and angiogenesis during wound healing.

Wounds or tissue injuries result in a loss of integrity of the skin. Damage to this critical immune defense barrier allows pathogenic bacteria to invade and infection to occur. Chesney et al revealed that fibrocytes were involved in the initiation of immunity to defend the body during tissue injury and repair. Fibrocytes can initiate antigen-specific immunity through antigen-presenting cells (APCs) and have a proliferative activity between monocytes (low) and dendritic cells (high) in vitro.6 Furthermore, human fibrocytes secrete MIP-1α and MIP-1β, which are potent chemoattractant molecules for CD4+ T cells. These CD4+ T cells, which are essential for the generation of antigen-
specific responses in vivo, are major immunoregulators in wound healing. Thus, fibrocytes contribute to wound healing by regulating the host defense response during tissue injury.

The ECM contributes to wound healing by regulating cell proliferation, survival, shape, migration, and differentiation. Ex-vivo cultured fibrocytes express numerous ECM molecules, including vimentin, fibronectin, collagen I, and collagen III, demonstrating the ability to produce ECM proteins. Moreover, treatment of ex-vivo cultured fibrocytes isolated from peripheral blood with TGF-β enhanced both collagen production and α-SMA (smooth muscle actin) expression by these cells. Fibrocytes can differentiate into mature myofibroblasts and serve as a contractile force via α-SMA expression in response to TGF-β. Myofibroblasts are known to exert a critical contractile force to pull the wound edges together. In addition, these cells exhibit increased levels of α-SMA, enhanced collagen production, and other ECM proteins that accelerate wound contracture and healing in response to TGF-β in vitro. Therefore, fibrocytes can facilitate wound closure by producing ECM proteins and accelerating wound contracture in the presence of TGF-β.

It has also been revealed that fibrocytes play a critical role in angiogenesis. Angiogenesis is a key phase in wound closure, which includes proteolytic degradation of the matrix as well as migration, proliferation, and tube formation by vascular endothelial cells. Ex-vivo cultured fibrocytes secrete high levels of active matrix metalloproteinase, which can mediate the dissolution of the basement membrane during early tissue repair and initiate endothelial cell invasion, and may further facilitate angiogenesis. Fibrocytes promote endothelial cell proliferation by producing several proangiogenic factors, including vascular endothelial growth factor, PDGF, IL-8, IL-1β, M-CSF, hepatocyte growth factor, granulocyte-macrophage-CSF, basic fibroblast growth factor, and connective tissue growth factor. In addition to the role of fibrocytes in accelerating endothelial cell proliferation in vivo, culture supernatants from fibrocytes were found to have the ability to promote endothelial cell migration and differentiation (tube formation) in vitro. Moreover, an in-vivo Matrigel implant model of angiogenesis demonstrated that fibrocytes and fibrocyte culture supernatants promoted blood vessel formation. Thus, fibrocytes are postulated to have an important role in blood vessel formation during wound healing due to their ability to promote endothelial cell proliferation, migration, and differentiation in vivo.

In summary, fibrocytes play an essential role in wound healing by initiating antigen-specific immunity as APCs; secreting cytokines, growth factors, and ECM proteins; accelerating wound contraction; and promoting angiogenesis. Fibrocytes participate in the phases of wound healing and demonstrate the ability to accelerate wound healing. Furthermore, fibrocytes can easily be obtained through peripheral blood and can further be propagated into a larger numbers with high purity ex vivo before being applied back into wounds. Therefore, it is reasonable to believe that fibrocytes can hopefully provide us with a promising therapeutic strategy for chronic wounds.

References