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Wound Care 2019 & Epidemiology 2019: The synergistic effect of tumor endothelial marker 1 and platelet-derived growth factor in wound healing - Yi-Kai Hong, Guey-Yueh Shi and Hua-Lin Wu - National Cheng Kung University, Taiwan

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Tumor endothelial marker 1 (TEM1), also known as endosialin or CD248, is a type I transmembrane glycoprotein containing a C-type lectin-like domain. It is specifically expressed in smooth muscle cells, pericytes, and fibroblasts. Dermal fibroblasts play a pivotal role in cutaneous wound healing, especially in the proliferative and remodeling phases. However, the mechanism by which TEM1 physiologically regulate wound healing remains to be unexplored. In the process of wound healing, both TEM1 and platelet-derived growth factor (PDGF) receptor α (PDGFRα) expressions were significantly up-regulated in myofibroblasts in the granulation tissues. A delayed wound healing was observed in TEM1 deficiency mice. Fibroblast activation, collagen deposition, and proliferation of fibroblasts were decreased in granulation tissues in the wounds of TEM1 deleted mice. The migration, adhesion, and proliferation activities in NIH3T3 cells were attenuated when TEM1 expression was knockdown by short hairpin RNA. The signal transduction, mitogenic and chemoattractive effects induced by PDGF-BB were inhibited by TEM1 silencing. Furthermore, TEM1 and PDGFRα were co-localized in sub-cellular organelles in dermal fibroblasts. The association of TEM1 and PDGFRαwas also demonstrated by co-immunoprecipitation. In conclusion, we demonstrated that TEM1, in cooperation with PDGFRα, plays a critical role in wound healing by enhancing the mitogenic and chemoattractive effects of PDGF-BB and collagen deposition in myofibroblasts.

Recombinant platelet-derived growth factor (BB homodimer, rPDGF-BB), transforming growth factor beta 1 (rTGF-beta 1), and basic fibroblast growth factor (rbFGF) can accelerate healing of soft tissues. However, little information is available characterizing the components of wound matrix induced by these growth factors and the molecular mechanisms underlying accelerated repair and wound maturation. In this study, the composition, quantity, and rate of extracellular matrix deposition within growth factor-treated lapine ear excisional wounds were analyzed at different stages of healing using specific histochemical and immunohistochemical stains, coupled with image analysis techniques. Single application of optimal concentrations of each growth factor accelerated normal healing by 30% (P less than 0.0003); rPDGF-BB markedly augmented early glycosaminoglycan (GAG) and fibronectin deposition, but induced significantly greater levels of collagen later in the repair process, compared with untreated wounds rTGF-beta 1 treatment led to rapidly enhanced collagen synthesis and maturation, without increased GAG deposition. In contrast, rbFGF treatment induced a predominantly angiogenic response in wounds, with a marked increase in endothelia and neovessels (P less than 0.0001), and increased wound collagenolytic activity (P less than 0.03). rbFGF-treated wounds did not evolve into collagen-containing scars and continued to accumulate only provisional matrix well past wound closure. These results provide new evidence that growth factors influence wound repair via different mechanisms: 1) rPDGF-BB accelerates deposition of provisional wound matrix; 2) rTGF-beta 1 accelerates deposition and maturation of collagen; and 3) rbFGF induces a profound monocellular angiogenic response which may lead to a marked delay in wound maturation, and the possible loss of the normal signal(s) required to stop repair. These results suggest that specific growth factors may selectively regulate components of the repair response by differing mechanisms, offering the potential for targeted therapeutic intervention.

Cytokines such as the platelet-derived growth factor (PDGF) have the potential to initiate and mediate many if not all of the complex biological responses

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associated with inflammation and wound healing. PDGF is a potent cytokine that may be used to illustrate the diverse activities initiated by the interactions ofPDGF with its receptor relevant to the inflammatory response and subsequent wound repair. Because PDGF can chemotactically attract, activate, and initiate new expression of quiescent genes (e.g. the small inducible gene, SIG, family), it fulfills the predictions anticipated of a candidate wound hormone. PDGF added directly to experimental wounds in animals enhances wound healing, which suggests that cytokines will become increasingly important as therapeutic agents in the treatment of wounds in humans. Adequate inflammatory response and tissue repair are essential for maintenance and survival of multicellular species. Abundant histological evidence details the sequences of cellular events involved in inflammation and tissue repair; however, little is known about the mechanisms or mediators that initiate and sustain these essential processes. This review focuses primarily on platelet-derived growth factor (PDGF) and suggests that this potent growth factor may be used as a model to indicate how a cytokine may not only initiate mesenchymal tissue repair processes but also may regulate the orderly progression of inflammation, repair, and remodeling. In addition to being mitogenic toward cells with appropriate receptors (perhaps through both autocrine and paracrine mechanisms), growth factors direct cell migration, activate various cell types, and initiate new gene expression. An increasing number of these properties are now recognized as playing important roles necessary for the wound healing process. Evidence has established that direct application of growth factors to wounds accelerates the normal healing process. Nevertheless, there is still insufficient information to establish precisely the relative contributions of growth factors in vivo to the healing of normal wounds. This chapter examines properties of PDGF and of several other cytokines and suggests general and perhaps unique roles for each in directing inflammation and repair. Many excellent reviews of other growth factors and of related areas (such as the roles of growth factors in the immune response) have recently been published (Normal wound healing is thought to occur in three stages: (a) a directed and sequential migration of neutrophils, monocytes, and fibroblasts into the wound over the first several days; (b) the activation of wound macrophages and fibroblasts, resulting in de novo synthesis of growth factors and other cytokines, synthesis of extracellular matrix proteins, and proliferation of fibroblasts during the next 2-3 weeks; and (c) remodeling with active collagen turnover and crosslinking from two weeks to one year postwounding. Factors that direct cell migration into wounds and that activate the fibroblast have been postulated for over 60 years. It was thought that these factors are derived from cells within the wounds, specifically from the platelets and macrophages. Because platelets are invariably associated with wounds and release factors that attract inflammatory cells such as the neutrophil and the macrophage, they are likely important in both the initiation and progression of wound repair, from inflammation to resolution through collagen remodeling. The stages of inflammation and tissue repair involve a series of highly regulated and coordinated cellular responses. Molecules ordinarily within intracellular compartments such as the platelet ex-granule are released and appear to interact with target cells to initiate cell migration, activation, and division. The very early synthesis of other potent molecules such as the prostaglandins and leukotrienes also affects both intracellular responses and extracellular activities of striking complexity. The release of some of these factors triggers a second wave of events via the transcriptional activation of genes that encode proteins with signaling roles. Inflammatory cells are found in close proximity to platelets in models of inflammation and immune complex disease and in lesions of atherosclerosis. These findings support the critical early role of the platelet and suggest close interactions and an exchange of signals between platelets and inflammatory cells. Such a relationship may mutually stimulate the release of signaling molecules, which then initiate attraction of additional inflammatory cells and subsequent transcriptional events initiating the synthesis of additional mediators of inflammation and wound repair.

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