Inflammation in Wound Repair: Molecular and Cellular Mechanisms

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In post-natal life the inflammatory response is an inevitable consequence of tissue injury. Experimental studies established the dogma that inflammation is essential to the establishment of cutaneous homeostasis following injury, and in recent years information about specific subsets of inflammatory cell lineages and the cytokine network orchestrating inflammation associated with tissue repair has increased. Recently, this dogma has been challenged, and reports have raised questions on the validity of the essential prerequisite of inflammation for efficient tissue repair. Indeed, in experimental models of repair, inflammation has been shown to delay healing and to result in increased scarring. Furthermore, chronic inflammation, a hallmark of the non-healing wound, predisposes tissue to cancer development. Thus, a more detailed understanding in mechanisms controlling the inflammatory response during repair and how inflammation directs the outcome of the healing process will serve as a significant milestone in the therapy of pathological tissue repair. In this paper, we review cellular and molecular mechanisms controlling inflammation in cutaneous tissue repair and provide a rationale for targeting the inflammatory phase in order to modulate the outcome of the healing response.

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Introduction

Wound healing is a highly dynamic process and involves complex interactions of extracellular matrix molecules, soluble mediators, various resident cells, and infiltrating leukocyte subtypes. The immediate goal in repair is to achieve tissue integrity and homeostasis (Martin 1997; Singer and Clark, 1999). To achieve this goal, the healing process involves three phases that overlap in time and space: inflammation, tissue formation, and tissue remodeling. During the inflammatory phase, platelet aggregation is followed by

Editor's Note

Wound healing has been recognized as important to health since the time of Hammurabi. A Sumerian clay tablet (c 2150 BC) described early wound care that included washing the wound in beer and hot water, using poultices from substances such as wine dregs and lizard dung and bandaging the wound. Hippocrates (c 400 BC) detailed the importance of draining pus from the wound, and Galen (c 130–200 AD) described the principle of first and second intention healing (Broughton G *et al.* (2006) A Brief history of wound care. *Plast Reconstr Surg* 117:6s). Wound healing advanced slowly over the centuries, with major advances in the 19th century in the importance of controlling infection, hemostasis and necrotic tissue. The discovery of cytokines and growth factors in the 1950s opened a new age in wound healing research and led to many important breakthroughs concerning the basic biology of healing wounds in the skin. In this issue of the JID, a new Perspective series focused on wound healing begins. These articles detail the role of inflammation in wound healing and fibrosis, the key involvement of fibroblasts, myofibroblasts, and keratinocytes in the healing wound, and the great opportunities that tissue engineering provides to improve wound healing. Hippocrates recognized that ''Healing is a matter of time, but it is sometimes also a matter of opportunity.'' These Perspectives show the great new opportunities that we now have for understanding and improving the process of healing wounds of the skin.

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Abbreviations: MCP, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; PMN, polymorphonuclear leukocyte; ROS, reactive oxygen species; SCC, squamous cell carcinoma; TGF, transforming growth factor; TNF, tumor necrosis factor

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infiltration of leukocytes into the wound site. In tissue formation, epithelialization and newly formed granulation tissue, consisting of endothelial cells, macrophages and fibroblasts, begin to cover and fill the wound area to restore tissue integrity. Synthesis, remodeling, and deposition of structural extracellular matrix molecules, are indispensable for initiating repair and progression into the healing state. Cellular responses to injury involve direct cell–cell and cell–matrix interactions, as well as the indirect crosstalk between different cell populations by soluble mediators. Indeed, complex interactions between the epidermal and dermal compartment are essential. During the past decade numerous factors have been identified that are engaged in a complex reciprocal dialogue between epidermal and dermal cells to facilitate wound repair (Werner and Grose, 2003). The sensitive balance between stimulating and inhibitory mediators during diverse stages of repair is crucial to achieving tissue homeostasis following injury.

The inflammatory response is regarded as the first of a number of overlapping processes that constitute wound healing. In skin repair, the infiltrating leukocytes are the principal cellular components of the inflammatory response. They are not only effector cells combating invading pathogens but are also involved in tissue degradation and tissue formation. As such, an excessive or reduced influx or activation of infiltrating leukocytes into the damaged tissue may have profound effects on downstream cell migration, proliferation, differentiation, and ultimately the quality of the healing response. Continuing progress in understanding the essential and complex role of the inflammatory response in wound repair will provide strategies to modulate diseases with pathologic tissue remodeling, such as healing disorders, various chronic inflammatory disease states, and cancer.

Inflammation in physiological wound repair: cell lineages, functions, and mediators

Tissue injury causes the immediate onset of acute inflammation. It has long been considered that the inflammatory response is instrumental to supplying growth factor and cytokine signals that orchestrate the cell and tissue movements necessary for repair (Simpson and Ross, 1972; Leibovich and Ross, 1975). In various experimental animal models and human skin wounds, it has been demonstrated that the inflammatory response during normal healing is characterized by spatially and temporally changing patterns of various leukocyte subsets (Martin 1997; Singer and Clark, 1999). The well-defined chronology of these events is essential for optimal repair.

PMNs. Immediately after injury extravasated blood constituents form a hemostatic plug. Platelets and polymorphonuclear leukocytes (neutrophils, PMN) entrapped and aggregated in the blood clot release a wide variety of factors that amplify the aggregation response, initiate a coagulation cascade, and/or act as chemoattractants for cells involved in the inflammatory phase (Szpaderska *et al.*, 2003). Within a few hours post-injury the bulk of neutrophils in the wound transmigrate across the endothelial cell wall of blood capillaries, which have been activated by proinflammatory cytokines IL-1β, tumor necrosis factor-α (TNF-α), and IFN-γ at the wound site, leading to expression of various classes of adhesion molecules essential for leukocyte adhesion and diapedesis. Adhesion molecules which are crucial for neutrophil diapedesis include endothelial P- and E-selectins as well as the ICAM-1, -2. These adhesins interact with integrins present at the cells surface of neutrophils including CD11a/CD18 (LFA-1), CD11b/CD18 (MAC-1), CD11c/CD18 (gp150, 95), and CD11d/CD18 (Kulidjian *et al.*, 1999). Chemokines and their receptors are most likely crucial mediators for neutrophil recruitment during repair (Gillitzer and Goebeler 2001; Esche *et al.*, 2005). These include IL-8, growth-related oncogene-α, and monocyte chemoattractant protein-1 (MCP-1) (Engelhardt *et al.*, 1998). In addition, bacterial products, such as lipopolysaccharides and formyl-methionyl peptides, which accumulate in the bacterially infected wound, can accelerate the directed neutrophil locomotion.

Recruited neutrophils begin the debridement of devitalized tissue and phagocytosis of infectious agents. To perform this task, neutrophils release a large variety of highly active antimicrobial substances (reactive oxygen species (ROS), cationic peptides, eicosanoids) and proteases (elastase, cathepsin G, proteinase 3, urokinase-type plasminogen activator) (Weiss 1989) (Table 1). Microarray technology has recently revealed that migration of PMNs to skin lesions induces a large transcriptional activation program, which may regulate cellular fate and function and promote wound healing (Theilgaard-Mönch *et al.*, 2004). Despite detailed knowledge on the synthesis of mediators released by PMNs and mechanisms involved in their recruitment and their role in host defense, these cells can be beneficial or detrimental to healing. Experiments in the 1970s showed that depletion of neutrophils by antiserum from guinea pigs did not significantly perturb tissue repair of incisional wounds under sterile conditions (Simpson and Ross, 1972). A recent study by Dovi *et al.* (2003), using a similar approach of neutrophil depletion, partially confirmed these early studies. Although dermal repair parameters were not affected by neutropenia, reepithelialization was significantly accelerated (Dovi *et al.*, 2003). However, in this study it remains unclear whether the lack of PMNs has a direct, beneficial effect on reepithelialization or whether the relative increase in other subsets of inflammatory cells, such as the macrophages, might be responsible for accelerated epithelialization. Recent *in vitro* studies demonstrated that neutrophils isolated from sites of repair can modulate the phenotype and cytokine profile expression of macrophages, thereby regulating the innate immune response during healing (Daley *et al.*, 2005). In addition, a recent report shows that closure of excisional wounds in CD18-depleted mice was significantly delayed, most likely due to impaired myofibroblast differentiation and reduced wound contraction (Peters *et al.*, 2005). The authors speculated