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Review

Transcriptional regulation of wound inflammation

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ABSTRACT

The attraction and activation of immune cells is an important response of the skin to injury and allows an efficient defense against invading pathogens. In addition, immune cells fulfill various functions that are important for the repair process. An exaggerated inflammatory response, however, is a hallmark of chronic, non-healing wounds. Therefore, it is essential to strictly control and coordinate the levels and activities of various immune cells in normal and wounded skin. Recent studies provided insight into the molecular mechanisms underlying the inflammatory response after wounding, and various transcriptional regulators involved in this process have been identified. This review summarizes our current knowledge on the function of different transcription factors in wound repair, with particular emphasis on proteins with a documented role in the control of wound inflammation.

1. Introduction

Wounding of skin in adult mammals initiates a highly regulated series of events that results in repair of the injured body site. The wound healing process comprises three partially overlapping phases – blood clotting and inflammation, formation of new tissue through reepithelialization and granulation tissue formation, and finally tissue remodeling (Fig. 1A–C).

Immediately after generation of a wound that affects the dermis and the epidermis, a platelet plug and a blood clot are formed that terminate the bleeding and provide a provisional sealing of the injured skin. The clot, which fills the wounded area, provides an important barrier against invading pathogens and it protects from excessive loss of water. Furthermore, it serves as a reservoir of cytokines and growth factors and as a provisional matrix for various types of resident cells and immune cells that are attracted to the wound from adjacent non-wounded skin or from the circulation [1,2] (Fig. 1A).

The attraction of inflammatory cells to the wound is a second early event in the healing process. Studies from lower organisms, including *Drosophila* and zebrafish, identified hydrogen peroxide as the first neutrophil chemoattractant that is produced and released at the wound site [3,4]. Additional inflammatory stimuli in early wounds are factors released from degranulating platelets or upon complement activation as well as products of bacterial degradation. At later stages, chemokines/cytokines produced by various cells in the wounded tissue further contribute to the attraction of immune cells. Neutrophils are the first immune cells to arrive at the wound site, followed by monocytes that subsequently differentiate into tissue macrophages (Fig. 1A). At a later stage, recruitment of different types of T lymphocytes occurs [2,5] (Fig. 1B and C). In addition, skin resident mast cells are activated in the dermis at the wound edge and they repopulate the wound tissue at a late stage of the repair process [6,7] (Fig. 1C).

The phase of new tissue formation starts within 1–2 days after wounding by migration of keratinocytes from the injured epidermis and hair follicles (Fig. 1A). This is followed by a wave of proliferation of keratinocytes behind the migrating tongue (Fig. 1B). The combination of keratinocyte migration and proliferation finally leads to the coverage of the wound with a neo-epidermis (Fig. 1C). Redifferentiation of the keratinocytes in the neo-epidermis, which is initiated already prior to complete wound closure, results in efficient reconstitution of the epidermal barrier.

Shortly after the onset of reepithelialization, repair of the injured dermis is initiated. The new tissue, which initially fills the wound bed, is designated as granulation tissue due to its granular appearance upon histological analysis (Fig. 1B and C). It includes fibroblasts, which had been attracted from the wound edge or from the circulation and which rapidly proliferate. A large percentage of these cells differentiate into myofibroblasts, which are important for wound contraction and which are particularly efficient producers of extracellular matrix. In addition, a dense network of mostly

Abbreviations: AP-1, activator protein 1; BMDAC, bone marrow-derived angiogenic cells; Egr, early growth response transcription factor; HIF, hypoxia-inducible factor; HOX, homeobox; IL-1, interleukin 1; iNOS, inducible nitric oxide synthase; KLF, Kruppel-like factor; MIF, macrophage migration inhibitory factor; NFI-C, nuclear factor I-C; NF-κB, nuclear factor κB; Nrf2, nuclear factor erythroid derived 2 like 2 (Nrf2); PPAR, peroxisome proliferator-activated receptor; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.

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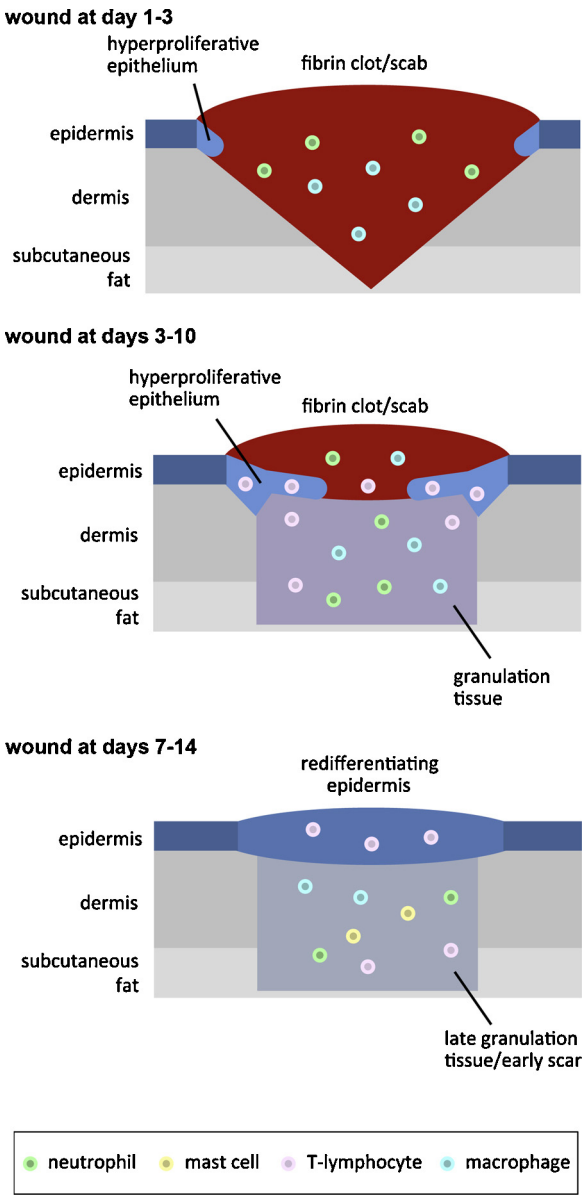

Fig. 1. Different stages of the wound healing process. Full-thickness excisional mouse wounds are shown at day 1–3 (inflammatory phase), day 3–10 (phase of new tissue formation), and day 7–14 (phase of tissue remodeling). The different types of immune cells present in the wounds at these stages are indicated.

immature vessels is formed that subsequently undergoes vascular remodeling, involving regression of most vessels and stabilization of the remaining ones. Finally, the granulation tissue includes a large number of immune cells, in particular macrophages and at later stages also T lymphocytes and mast cells.

The late stage of new tissue formation overlaps with the final phase of the healing process, the phase of tissue remodeling. The latter involves the reduction in keratinocyte proliferation and their redifferentiation and a long period of granulation tissue remodeling involving apoptosis of (myo)fibroblasts, endothelial cells and of excess immune cells. As a consequence, the resulting dermal tissue has only a low cell density and is mainly composed of extracellular matrix. The latter undergoes significant remodeling, including a switch from production of collagen type III to collagen type I, reorganization of the deposited collagen and alterations in its cross-linking. As a consequence, the tensile strength of the new tissue increases, although it never reaches the strength of non-wounded skin. Importantly, the resulting scar tissue lacks hair follicles and sebaceous and sweat glands, which cannot regenerate [2].

Remarkably, wounds generated in mammalian embryos up to the end of the second trimester heal without scar formation. This is thought to result, at least in part, from the much milder and more transient inflammatory response that occurs in embryonic compared to adult wounds [8]. Given these crucial functions of inflammation in wound healing and scar formation, it is important to understand the control of immune cell function at the molecular level. In this review we summarize data on the role of transcriptional regulators in mammalian wound healing, with particular emphasis on factors for which a functional role in wound inflammation has been demonstrated. Transcriptional control of other aspects of wound repair has previously been reviewed [9,10].

2. Transcription factors with a role in wound inflammation

2.1. PU.1

In contrast to embryos, which have the capability to heal without scar formation, wounds in adult mammals heal with a scar, and this is accompanied by a massive inflammatory response [11]. To study the role of macrophages and neutrophils for the wound healing process, wound healing studies were performed in neonatal mice deficient in PU.1, a member of the Ets family of transcription factors. These mice are completely deficient in macrophages and functional neutrophils [12]. Although it had previously been thought that at least macrophages are essential for wound healing [13], normal closure of small incisional wounds was observed in *Pu.1* knockout mice. Most interestingly, these wounds even healed without obvious scarring [14]. Therefore, at least small wounds in young mice do not require an inflammatory response for efficient healing, and the latter even promotes the scarring response.

2.2. Glucocorticoid receptor

The results obtained with *Pu.1* knockout mice raised the intriguing possibility that a limited reduction of the inflammatory response after wounding is beneficial, in particular with regard to scar formation. On the other hand, it has been demonstrated in various experimental and clinical studies that treatment with anti-inflammatory steroids (glucocorticoids) strongly inhibits the wound healing process, an effect that is thought to result from the anti-inflammatory, but also from the anti-mitotic effect of glucocorticoids for various cell types and from the regulation of several key genes involved in wound repair by glucocorticoids [15]. By contrast, the role of endogenous glucocorticoids in wound healing is less well understood. This is an interesting question with regard to the known deleterious effects of stress on wound healing, which is thought to result at least in part from an increase in glucocorticoid serum levels [16]. In addition, it has been shown that keratinocytes at the wound site produce cortisol, in particular in response to an increase in the pro-inflammatory cytokine interleukin-1 (IL-1) [17].

Glucocorticoids exert their functions through binding to and activation of glucocorticoid receptors, which are members of the nuclear hormone receptor family. They regulate transcription via direct binding as dimers to glucocorticoid response elements in the promoter/enhancer regions of their target genes or by interference of glucocorticoid receptor monomers with members of the activating protein 1 (AP-1) or nuclear factor κB (NF-κB) transcription factor families. The role of endogenous glucocorticoids in wound healing was first addressed using mice expressing a DNA-binding-defective mutant of the glucocorticoid receptor. These mice lack the capacity to induce gene expression via direct binding to glucocorticoid receptor elements, since the receptor is not able to dimerize.

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