Introduction to Wound Healing and Tissue Repair

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Restoration of tissue integrity and homeostasis following injury is a fundamental property of all organisms. The repair response is a dynamic, interactive response to tissue damage that involves complex interactions of different classes of resident cells and multiple infiltrating leukocyte subtypes, extracellular matrix molecules, and soluble mediators [1]. The immediate goal in repair is to achieve tissue integrity and homeostasis [2]. To achieve this goal, in most tissues the healing process follows in different organs the principle of sequential phases that overlap in time and space: hemostasis, inflammation, tissue formation, and tissue remodeling (Fig. 5.1).

In humans most organs heal with the end result of a scar that replaces the damaged tissue. Although scar formation is in principle an efficient mechanism to rapidly restore tissue integrity in most organs, it is associated with significant loss of tissue architecture and function. Ideally, wounds would heal by tissue regeneration, a process restoring tissue morphology and function. Fetal wound healing is the paradigm for scarless wound healing; however in most organs this regenerative capacity is lost postnatally. One of the few remarkable examples of postnatal tissue regeneration is the phenomenon of post-injury fingertip regeneration in early childhood [3]. Clinical reports describe that conservatively managed amputation injuries in children restore the digit contour, the fingerprint, normal sensibility, and digit function and heal with minimal scarring [4, 5]. Yet, this regenerative response is restricted to amputation within the terminal phalangeal bone. The underling molecular mechanisms for this process are unresolved.

Cellular responses to injury involve direct cell-cell and cell-matrix interactions, as well as the indirect crosstalk between different tissue resident and recruited 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 [6]. Furthermore, more recent evidence revealed the importance and engagement of the adjacent fat layer in tissue repair and regenerative responses [7]. The sensitive balance between stimulating and inhibitory mediators between neighboring tissue compartments is crucial for achieving tissue homeostasis following injury.

In most organs tissue injury causes immediate leakage of blood constituents into the wound area as well as release of vasoactive factors resulting in the activation of the coagulation cascade. The hemostatic blood clot provides the provisional extracellular matrix (ECM) that facilitates cell adhesion and migration of invading cells. Fibrin, fibronectin, vitronectin, type III collagen, and tenascin among others are important components of the provisional ECM.

Platelets trapped into the initial matrix provide a rich source of cytokines and growth factors (e.g., platelet-derived growth factor, vascular derived growth factor, transforming growth factor-1) which bind to the ECM and together orchestrate the recruitment and activation of immune cells, endothelial cells, and fibroblasts at the wound site [8].

In addition to platelets also polymorphonuclear leukocytes (neutrophils) are entrapped in the clot releasing a wide spectrum of factors and chemoattractants that initiate and amplify the inflammatory phase. Neutrophils are essential effectors of host defense; they initiate the debridement of devitalized tissue and attack infectious agents. To perform this task, they release a variety of highly active antimicrobial substances (reactive oxygen species, eicosanoids) and proteases (elastase, cathepsin G, proteinase 3). Uncontrolled release of these factors can cause severe damage to the tissues of the host [9].

The function of this early inflammatory phase is not limited to combat invading microbes but also to promote the recruit-

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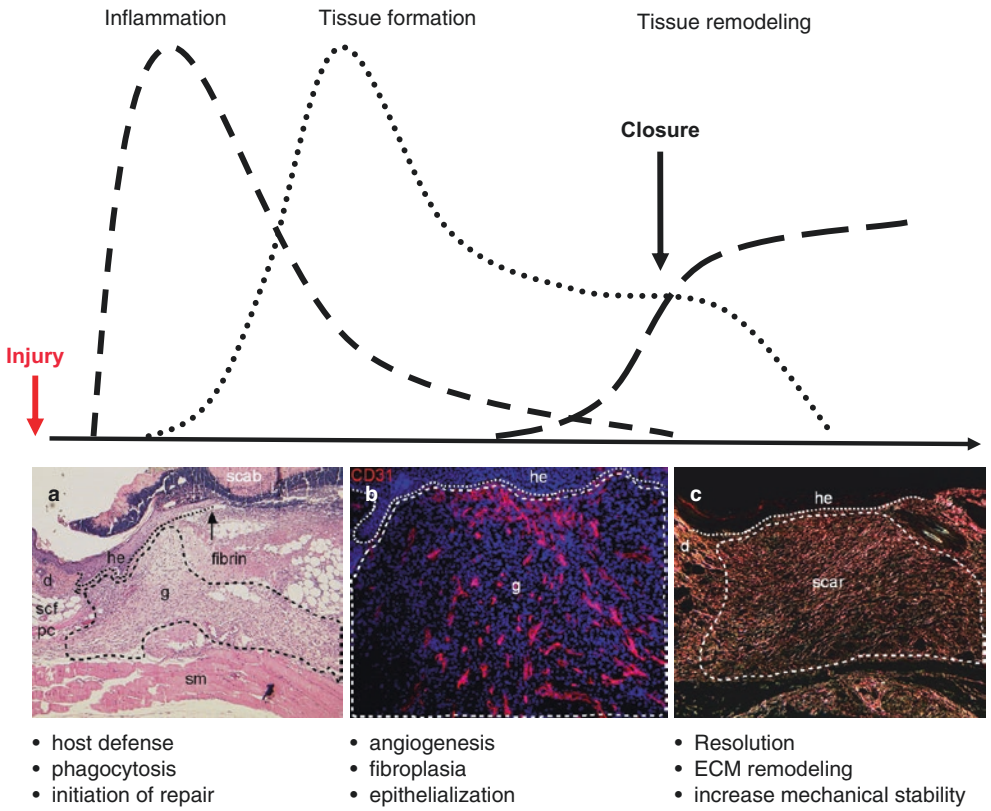

Fig. 5.1 Sequential phases of the healing response: hemostasis, inflammation, tissue formation and tissue remodeling

ment and activation of blood monocytes at the wound site. As monocytes extravasate from the blood vessel, they become activated and differentiate into wound macrophages [10]. This activation process implies major changes in macrophage gene expression which is fundamental to execute multiple functions at the wound site including debridement, induction of tissue growth, and resolution of inflammation [11, 12]. Recent evidence showed that beyond local environmental factors, macrophage functional plasticity is regulated at different levels including ontogeny and epigenetic changes [13].

During the phase of tissue formation, newly formed granulation tissue, consisting of macrophages, endothelial cells, and myofibroblasts, begins to cover and fill the wound area to restore tissue integrity. Fibroblasts differentiate into myofibroblasts, a critical process in the replacement of the provisional ECM in a collagenous matrix [14]. The spatiotemporal regulation of acquisition and maintenance of the myofibroblast phenotype is critical for the balance in ECM homeostasis and the ultimate outcome of the healing response. Biochemical and mechanical factors are fundamental in controlling myofibroblast function [15]. In parallel to granulation tissue maturation, epithelial cells at the wound edge are activated and undergo marked phenotypic and functional alterations, assuring epithelialization of the wound bed [6]. After completion of epithelialization, further remodeling of the ECM is critical for final progression into the healing state.

Phases of repair must occur in a proper sequence for optimal wound healing. Multiple systemic diseases and local factors can inhibit mechanisms of normal wound repair, which may lead to non-healing wounds. The non-healing wound is a result of an impairment in one or more of the healing mechanisms [16].

It is essential to consider which aspect of wound healing biology has been altered when analyzing a chronic non-healing wound. For example, disturbances in inflammation will interfere with all subsequent wound healing processes. Therefore, increased or impaired inflammation may manifest itself as inadequate angiogenesis, mesenchymal cell chemotaxis and proliferation, epithelialization, wound contraction, collagen synthesis, and remodeling.

The factors that lead to impaired healing can be classified as systemic and local factors. Local factors include necrotic tissue, senescent cells, bacterial components, local toxins, mechanical irritation, growth factor deficiency, increased proteolytic activity, and inadequate blood supply [16]. Systemic or constitutional factors are characterized by underlying internal conditions and/or diseases, including connective tissue diseases, vasculitis, age, and therapeutic interventions such as immunosuppressant drugs [17, 18]. When a therapeutic regime is discussed, each of these factors has to be critically considered, and an accurate diagnosis of the factors impairing healing is a prerequisite for the successful treatment of a non-healing wound (Fig. 5.2).

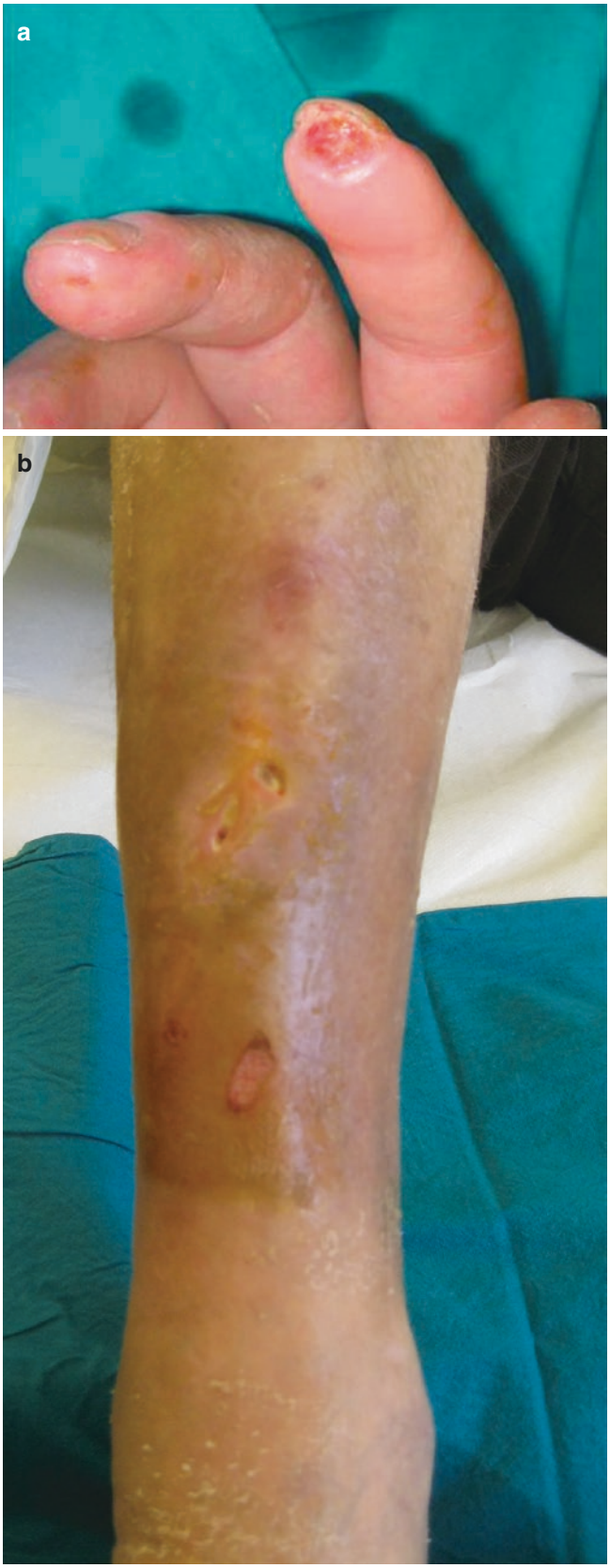

Fig. 5.2 Patient with systemic scleroderma representing (**a**) digital ulcer and (**b**) leg ulcer

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