Skin tissue repair: Matrix microenvironmental influences

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Abstract

The process of repair of wounded skin involves intricate orchestration not only between the epidermal and dermal compartments but also between the resident and immigrant cells and the local microenvironment. Only now are we beginning to appreciate the complex roles played by the matrix in directing the outcome of the repair processes, and how this impacts the signals from the various cells. Recent findings speak of dynamic and reciprocal interactions that occurs among the matrix, growth factors, and cells that underlies this integrated process. Further confounding this integration are the physiologic and pathologic situations that directly alter the matrix to impart at least part of the dysrepair that occurs. These topics will be discussed with a call for innovative model systems of direct relevance to the human situation.

1. Introduction

Wound healing is a highly orchestrated process that involves multiple developmental lineages, cell types, and local and systemic effects. Not only do the resident parenchymal cells and their stromal counterparts need to be replaced, but the support structures of the vascular, nervous and immune systems must be re-established. The process has been extensively studied in the skin and mucosal surfaces as these sites are the most often wounded both traumatically and iatrogenically. While most surface wounds heal with near regenerative repair, regaining the vast majority of pre-wound functionality, the ubiquity of such insults, particularly in individuals with comorbidities and advanced age, means that wounds that 'fail to heal' or heal excessively (scarring) remain major medical issues.

It should be noted that the discussion herein focuses on excisional wound repair, i.e. healing that replaces lost tissue. Incisional repair, encompassing surgical wound repair, is both qualitatively and quantitatively distinct in that the major process is a re-integration of the separated tissue sections, rather than a regeneration of tissue mass. Thus, the granulation tissue response that marks excisional repair is largely absent during incisional repair. While some of the processes are common, such as stromal production of a collagen-rich matrix, even in these situations, the extent of these processes is dramatically different to constitute a significant difference. Furthermore, scarring occurs in all tissues, but such a discussion would be excessively extensive. To maintain the focus and comprehensibility, we are limiting our discussion to excisional/regenerative repair of the skin.

Non-healing wounds and pressure ulcers present significant morbidity, and even mortality in the US, with elderly and diabetic and neuropathic patients at the greatest risk. In diabetics alone, non-healing wounds result in over 70,000 amputations annually according to the CDC. At the other end of the spectrum is scarring and keloids. What combines these two different aspects is that these wounds do

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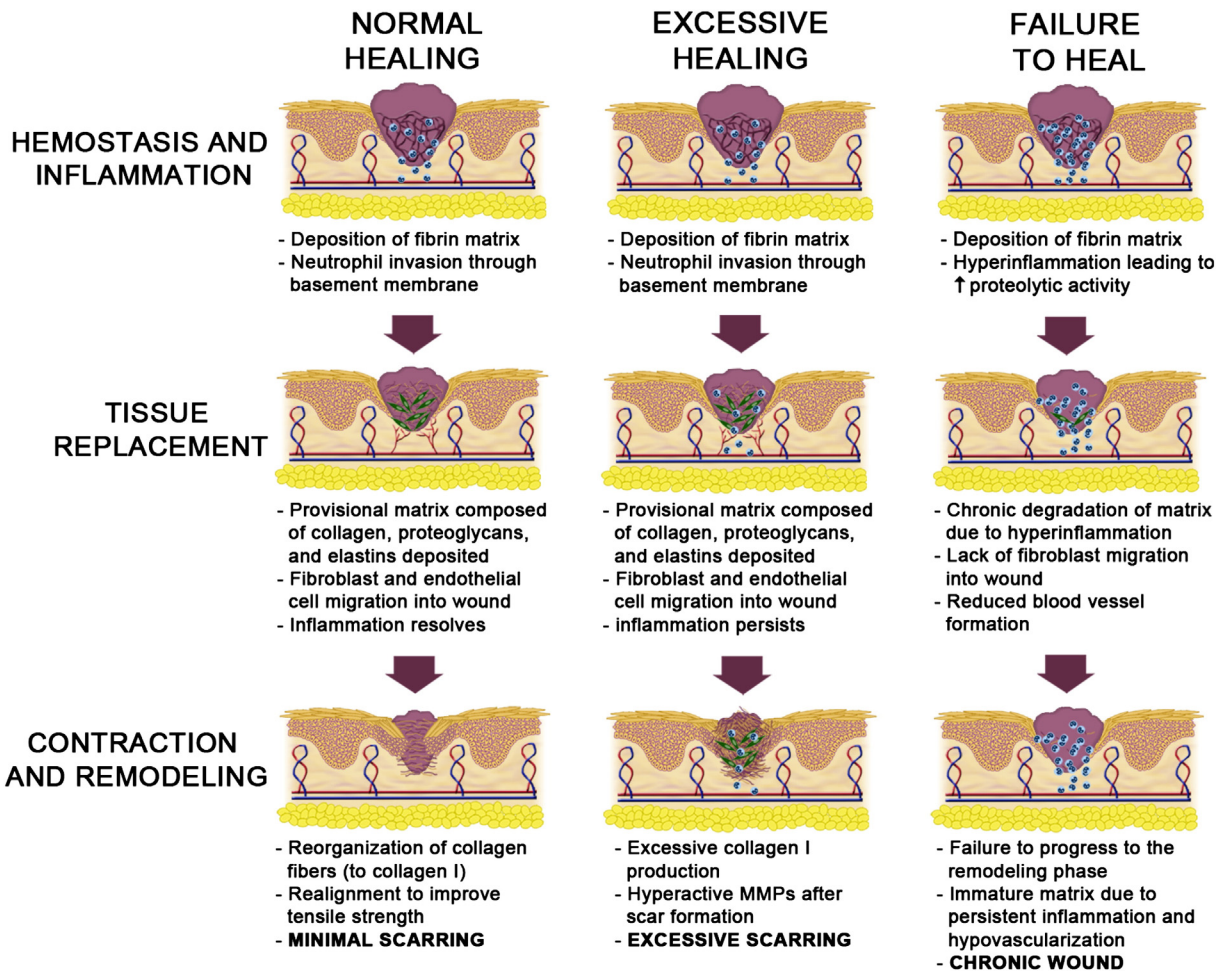

Fig. 1. Phase transitions in excisional wound healing and dysrepair. Wound healing proceeds from the initial homeostatic phase through tissue regeneration and into resolution. While these phases overlap both temporally and spatially within a wound, the orchestrated progression leads to re-established functioning with minimal scarring (left sequence). If the resolution phase has excessive cellularity and matrix from an over exuberant tissue replacement phase that lacks stop signals, this is not a stable phenotype. The renewal of an active immature matrix in the resolution phase results in excessive tissue and hypertrophic scars or even keloids (middle sequence). When the homeostatic phase does not transition towards regeneration, the healing is stalled and the initial, tissue-destructive inflammation persists. This situation leads to a chronic wound or ulcer (right sequence).

not progress from the tissue replacement phase to a competent resolving phase and thus remain in an immature state of cellular proliferation and matrix deposition/remodeling. Immature wounds are significantly weaker and prone to dehiscence. Hypervascular wound beds are also at increased risk of re-ulceration. Both events predispose to infection and chronic wounding, and ultimately failure to heal such wounds is the major cause of amputation in the US today [1,2].

Repair of this tissue system is also the best-described as the skin is readily accessible for both wounding and longitudinal observation with easy, repeated sampling. As most wounds heal with little to no complication, such studies have been undertaken in human volunteers. What has emerged is a process that has been parsed into overlapping stages: initial hemostasis to quickly seal the breach and prevent desiccation and infection (hemostatic phase), tissue regeneration to replace the lost cells (tissue replacement phase), and finally wound resolution to restore the diverse functions of the skin and remodel the new matrix (resolving phase) (Fig. 1) [3].

These phases, which occur at different rates across the wound, have been considered from multiple angles (Fig. 2). Many conceptions of wound healing focus on either the cell types, soluble signals, or structures that predominate during each phase. However, the reality is that each of these not only are present but impact each other. For instance, the hemostatic stage includes both the initial platelet

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