Cutaneous scarring: Pathophysiology, molecular mechanisms, and scar reduction therapeutics

Part I. The molecular basis of scar formation

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3. Achievement of a 70% or higher on the online Case-based Post Test
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Learning Objectives
After completing this learning activity, participants should be able to describe the 3 pathological stages of cutaneous scarring and delineate the differences between embryonic regenerative healing and adult scar-induced healing.

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Cutaneous scarring is often the epicenter of patient-related concerns, and the question "Will there be a scar?" is one that is all too familiar to the everyday clinician. In approaching this topic, we have reviewed the pathology, the embryology, and the molecular biology of cutaneous scarring. (J Am Acad Dermatol 2012;66:1-10.)

Key words: cutaneous scar; early growth response protein-1; homeobox13; interleukins; mechanisms of scarring; platelet-derived growth factor; transforming growth factor−beta; Wnt pathway.

People with exaggerated skin scarring may face substantial physical and psychosocial consequences.[1] In this first installment of a two-part continuing medical education series, we aim to explore the pathophysiology underlying cutaneous scarring and the molecular mechanisms governing scar formation. Understanding the biology of scarring will allow for a better understanding of the scientific basis of scar-reduction strategies. The latter shall be discussed in Part II of this series.

METHODOLOGY

In preparing this work, we used PubMed to perform literature searches on scar-related research. Key terms used in the search were "scarring," "wound healing," "prevention," and "treatment." Review articles were used as an initial source of information and, where relevant, information from primary research papers was obtained.

PATHOPHYSIOLOGY OF THE CUTANEOUS SCAR

Key points

- **The inflammatory phase of wound healing aims to contain the injury and prevent infection**
- **The proliferative phase is characterized by granulation tissue—composed of macrophages, fibroblasts, and epithelial tissue**
- **The remodeling phase is the lengthy process of extracellar matrix reorganization around the site of injury**
- **Embryonic cutaneous wounds in the first third of gestation heal without a scar**

CAPSULE SUMMARY

- After cutaneous injury, the pathophysiology of wound healing is characterized by an inflammatory phase (days 1-3), a proliferative phase (days 4-21), and a remodeling phase (day 21 to year 1).
- Mammalian cutaneous wounds during the first third of gestation do not scar, because healing occurs via tissue regenerative pathways.
- Scarring is a healing process that has been selected for during evolution because it tackles pathogens quickly, walls off foreign bodies, and seals off an injured area from the environment.
- Transforming growth factor—beta (TGFβ) is pivotal in scar-mediated healing.
- The expression of TGFβ_1 and TGFβ_2 enhances scarring, and the expression of TGFβ_3 reduces scarring.
- The proinflammatory cytokines interleukin-6 (IL-6) and IL-8 augment scarring, but the antiinflammatory cytokine IL-10 has the opposite effects on the scarring response.
- Homeobox b13, the Wnt signaling pathway, early growth response protein-1, and platelet-derived growth factor all propagate a robust fibroblast response in the healing wound, leading to increased scarring.

Disruption of cutaneous epithelial continuity results in a characteristic pathophysiologic response. This response has been traditionally subcategorized into the three phases of normal wound healing. These phases are the inflammatory, proliferative, and remodeling phases (Fig 1). Wound healing, however, is a dynamic process, and at any point in time, processes occurring in one phase overlap with those occurring in another.[2]

Inflammatory phase (days 1-3)

After the disruption of epithelial integrity, the immediate priority is hemostasis. This is achieved by activation of the extrinsic clotting pathway. Ultimately, this results in formation of a fibrin hemostatic plug, which is further solidified by the arrival of platelets from the local microcirculation.[2]

Once the danger of exsanguination subsides, the next priority is the removal of dead tissue and the prevention of infection. Inflammatory cells are crucial to this process. For the first 5 days, neutrophils enter the fibrin-rich zone of injury. Through their actions of phagocytosis and protease secretion, neutrophils kill local bacteria and help degrade dead tissue. On the third day after injury, macrophages also enter the injury zone. In addition to phagocytosing pathogens and tissue debris, these cells secrete a multitude of growth factors, chemokines, and cytokines. These

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