Wound healing in the 21st century

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Delayed wound healing is one of the major therapeutic and economic issues in medicine today. Cutaneous wound healing is an extremely well-regulated and complex process basically divided into 3 phases: inflammation, proliferation, and tissue remodeling. Unfortunately, we still do not understand this process precisely enough to give direction effectively to impaired healing processes. There have been many new developments in wound healing that provide fascinating insights and may improve our ability to manage clinical problems. Our goal is to acquaint the reader with selected major novel findings about cutaneous wound healing that have been published since the beginning of the new millennium. We discuss advances in areas such as genetics, proteases, cytokines, chemokines, and regulatory peptides, as well as therapeutic strategies, all set in the framework of the different phases of wound healing. (J Am Acad Dermatol 2010;63:866-81.)

Key words: cellular; molecular; novel findings; signal transduction; pH value; skin wound.

Cutaneous wounds are the result of disrupted skin integrity. The healing process depends on local wound factors, systemic mediators, the underlying disease, and the type of injury. These factors combine to determine if physiologic or acute wound healing occurs, or if there is an abnormal healing process, also called chronic wound healing. Chronic wounds are the result of an inadequate repair process that is unable to restore anatomic and functional integrity in an appropriate length of time. Chronic wounds affect about 1% of the European population and are frequently a management challenge, even with an interdisciplinary approach. In addition to having an adverse effect on the quality of life of the affected individuals, chronic wounds also create a significant economic burden: nearly 2% of health budgets are devoted to the care of chronic wounds.[1]

Our understanding of the mechanisms involved in cutaneous wound healing has dramatically increased in the past few years. Keeping up to date with the current literature is sometimes difficult. Our aim is to provide researchers and clinicians working in the field of wound healing with selected new insights into wound pathogenesis and cutaneous repair

Abbreviations used:

AGE:	advanced glycation end product
Cyr61:	cysteine-rich angiogenic inducer-61
ECM:	extracellular matrix
EGF:	epidermal growth factor
ERK:	extracellular regulated kinase
FGF:	fibroblast growth factor
HGF:	hepatocyte growth factor
HSP:	heat shock protein
IL:	interleukin
IL-1ra:	interleukin-1 receptor antagonist
KGF:	keratinocyte growth factor
LacZ:	lactose operon Z
LL-37:	C-terminal fragment of human cathelicidin antimicrobial peptide-18
MMP:	matrix metalloproteinase
mTOR:	mammalian target of rapamycin
NF:	nuclear factor
NPY:	neuropeptide Y
Nramp1:	natural resistance—associated macrophage protein-1
Nrf:	nuclear factor-E2-related factor
PI3K:	phosphatidyl inositol-3 kinase
RE:	response element
Shh:	sonic hedgehog
SPARC:	secreted protein acidic and rich in cysteine
TF:	tissue factor
TGF:	transforming growth factor
TIMP:	tissue inhibitor of matrix metalloproteinase
TLR:	toll-like receptor
VEGF:	vascular endothelial growth factor

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Supported by grants of the German Research Foundation (Deutsche Forschungsgemeinschaft DFG, BA 3410/3-1) and the Novartis Foundation (S.S., Novartis Graduate Scholarship).

Conflicts of interest: None declared.

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Published online June 24, 2010.
0190-9622/$36.00

doi:10.1016/j.jaad.2009.10.048

mechanisms. We consider topics such as genetics, proteases, cytokines, chemokines, and regulatory peptides, as well as therapeutic strategies. All are viewed in the context of the intertwined phases of wound healing: (1) inflammatory phase, (2) proliferative phase (neoangiogenesis, granulation, re-epithelialization), and (3) remodeling phase (extracellular matrix [ECM] remodeling). Detailed figures are provided to facilitate the understanding of the rather complex pathogenetic mechanisms.

Chronic wounds are defined as wounds that do not follow the well-defined stepwise process of physiologic healing. Instead, they are trapped in an uncoordinated and self-sustaining phase of inflammation that impairs the restoration of anatomic and functional integrity in the normal period of time. Many of the pathophysiologic factors (hypoxia, pH changes, and bacterial colonization) that contribute to delayed wound healing are well known. However, the exact pathogenesis of chronic wounds remains unclear.

Rather than giving a comprehensive overview on wound healing, the following sections will focus on newly discovered molecular mechanisms and their importance in wound healing.

CAPSULE SUMMARY

- Since the beginning of the new millennium a large number of articles have been published dealing with cutaneous wound healing.
- This article reviews novel findings related to the major phases of cutaneous wound healing: inflammation, proliferation, and tissue remodeling.
- Newly discovered molecular targets and pathways provide the basis for further research and future clinical studies.

THE INFLAMMATORY PHASE

The initial phase after cutaneous injury is dominated by inflammatory reactions mediated by cytokines, chemokines, growth factors, and their actions on cellular receptors (Fig 1). Intracellular signaling cascades are activated, contributing to cell proliferation, migration, and differentiation. In addition, chemoattractant factors recruit different cell types, such as granulocytes and macrophages, to the wound site, thus initiating wound repair. The wound milieu—consisting of various proteinases, cytokines, chemokines, pH gradients, and pO_2 gradients—has a major impact on cellular functions. The importance of wound fluid in regulating the responsiveness of fibroblasts to proliferation signals mediated by cytokines has been shown by Nedelec et al.[2]

During the inflammatory phase of wound healing, a variety of membrane-bound receptors play a role in recruiting leukocytes and other cells. One receptor mediating leukocyte-endothelial cell interaction[3] is intercellular adhesion molecule-1 (CD54). Intercellular adhesion molecule-1 interacts with leukocytes via CD11a (together with CD18 = lymphocyte function-associated antigen-1). Nagaoka et al[4] found that intercellular adhesion molecule-1—deficient mice showed impaired wound healing because of a lack of leukocyte and macrophage infiltration into the wound site. These cells are required to establish an inflammatory reaction, which is a major milestone on the way to organized wound repair.

Coordinated inflammatory phases require a subtle balance of proinflammatory cytokines and chemokines and their antagonists. Although interleukin (IL)-1 is known as a key factor, little is known about the functions of the IL-1 receptor antagonist (IL-1ra). Ishida et al[5] found that IL-1ra −/− mice showed an interruption in transforming growth factor (TGF)-β1 signaling, which resulted in reduced collagen deposition and vascular endothelial growth factor (VEGF) expression. IL-1ra is only temporarily up-regulated until 10 days after skin injury. IL-1ra deficiency induces prolonged nuclear factor (NF)-κB p65 nuclear translocation. The prolonged inflammatory phase leads to delayed wound healing in these mice.

Ishida et al[6] further studied the role of chemokine receptors in wound pathogenesis in a full-thickness excisional skin mouse model. The chemokine chemokine C-X3-C motif ligand-1 (CX3CL1) (nomenclature according to patterns of conserved cysteines: chemokine C-X3-C motif ligand-1; fractalkine) and its receptor chemokine C-X3-C motif receptor-1 (CX3CR1) are up-regulated at wound sites. Their role in wound healing was elucidated in an excisional wound CX3CR1 −/− mouse model that showed reduced macrophage infiltration and then reduced TGF-β1 and VEGF signaling (because both are released by macrophages), which in turn led to decreased collagen deposition and neoangiogenesis, inevitably resulting in delayed wound healing. When IL-1ra is knocked out, different chemokines are also up-regulated.

Furthermore, the shift in balance between proinflammatory and anti-inflammatory factors is one of the central reasons for persistent inflammation in chronic wound healing. An anti-inflammatory factor involved in regulating the balance is secretory leukocyte protein inhibitor-1. Its gene expression is