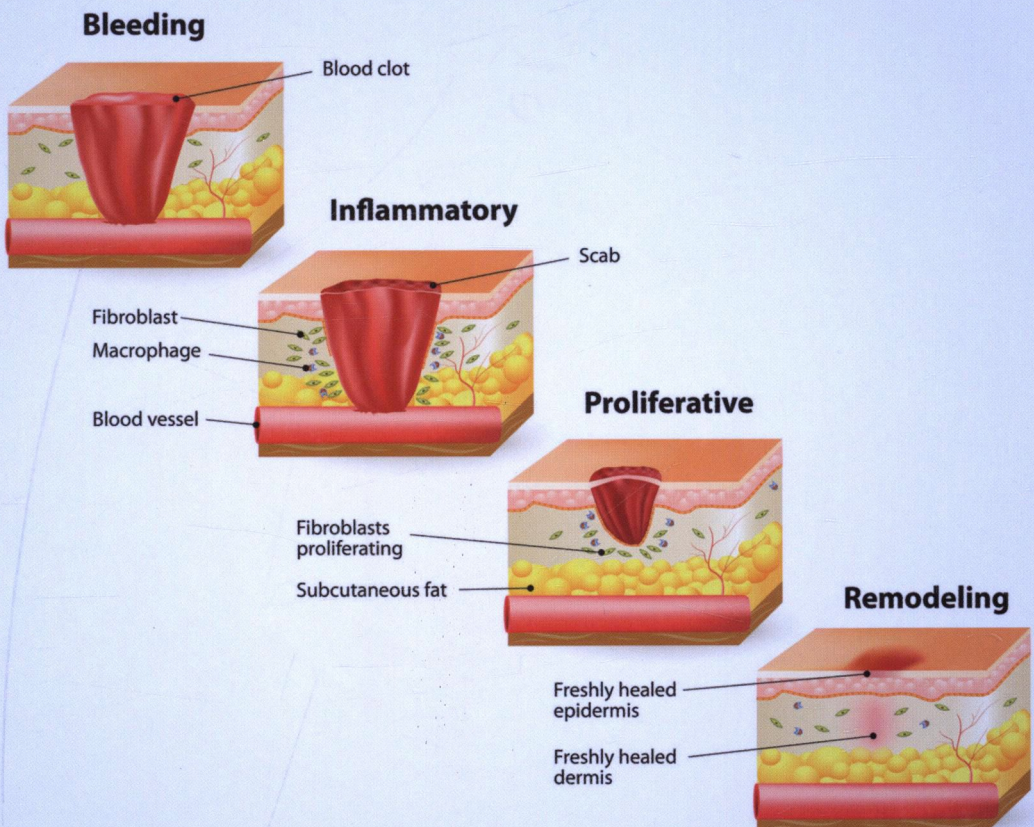


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Wound Healing

Stem Cells Repair and Restorations,
Basic and Clinical Aspects

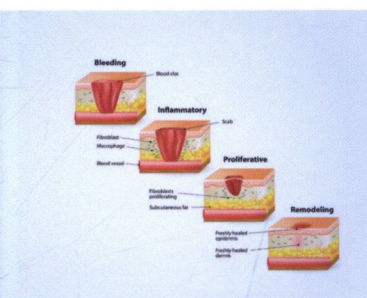


A comprehensive resource on the recent developments of stem cell use in wound healing

With contributions from experts in the field, *Wound Healing* offers a thorough review of the most recent findings on the use of stem cells to heal wounds. This important resource covers both the basic and translational aspects of the field. The contributors reveal the great progress that has been made in recent years and explore a wide range of topics from an overview of the stem cell process in wound repair to inflammation and cancer. They offer a better understanding of the identities of skin stem cells as well as the signals that govern their behavior that contributes to the development of improved therapies for scarring and poorly healing wounds.

Comprehensive in scope, this authoritative resource covers a wealth of topics such as: an overview of stem cell regeneration and repair, wound healing and cutaneous wound healing, the role of bone marrow derived stem cells, inflammation in wound repair, role and function of inflammation in wound repair, and much more. This vital resource:

- Provides a comprehensive overview of stem cell use in wound healing, including both the basic and translational aspects of the field
- Covers recent developments and emerging subtopics within the field
- Offers an invaluable resource to clinical and basic researchers who are interested in wound healing, stem cells, and regenerative medicine
- Contains contributions from leading experts in the field of wound healing and care



Wound Healing offers clinical researchers and academics a much-needed resource written by noted experts in the field that explores the role of stem cells in the repair and restoration of healing wounds.

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Wound Healing

Stem Cells Repair and Restorations, Basic and Clinical Aspects

Edited by

Kursad Turksen

WILEY Blackwell

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Contents

<i>List of Contributors</i>	vii
1 Stem Cell Regeneration and Repair – Overview	1
<i>Clement D. Marshall, Alessandra A. Moore, Michael T. Longaker, and H. Peter Lorenz</i>	
2 Cadherins as Central Modulators of Wound Repair	15
<i>Melissa Crawford and Lina Dagnino</i>	
3 Tight Junctions and Cutaneous Wound Healing	31
<i>Thomas Vollsdorf and Johanna M. Brandner</i>	
4 The Role of Microvesicles in Cutaneous Wound Healing	43
<i>Alexandra Laberge and Véronique J. Moulin</i>	
5 Wound Healing and Microenvironment	67
<i>Elgin Türköz Uluer, Hafize Seda Vatansever, and Feyzan Özdal Kurt</i>	
6 Wound Healing and the Non-cellular Microenvironment	79
<i>Hayley S. Ramshaw, Jasreen Kular, and Michael S. Samuel</i>	
7 Contribution of Adipose-Derived Cells to Skin Wound Healing	89
<i>Barbara Gawronska-Kozak, Joanna Bukowska, Xiying Wu, Amy Lin Strong, Trivia Frazier, Bruce A. Bunnell, and Jeffrey M. Gimble</i>	
8 Role of Bone Marrow-Derived Stem Cells in Wound Healing	103
<i>Feyzan Özdal Kurt, Hafize Seda Vatansever, and Elgin Türköz Uluer</i>	
9 Role of Vitamin D and Calcium in Epidermal Wound Repair	113
<i>Daniel D. Bikle, Chia-ling Tu, and Yuko Oda</i>	
10 Oral Mucosal Healing	125
<i>Luisa A. DiPietro and Megan Schrementi</i>	
11 Role of Adipose-Derived Stem Cells in Wound Healing: An Update from Isolation to Transplantation	133
<i>Selami Demirci, Ayşegül Doğan, and Fikrettin Şahin</i>	
12 The Hair Follicle as a Wound Healing Promoter and Its Application in Clinical Practice	149
<i>Francisco Jimenez, María Luisa Martínez, Eduardo Escario, and Ander Izeta</i>	
13 Impaired Wound Healing in Diabetic Ulcers: Accelerated Healing Through Depletion of Ganglioside	167
<i>Duncan Hieu M. Dam, Sophia A. Jelsma, and Amy S. Paller</i>	

14	Inflammation in Wound Repair: Role and Function of Inflammation in Wound Repair	177
	<i>Amanda S. MacLeod and Jeffery T. Kwock</i>	
15	Inflammation, Wound Healing, and Fibrosis	195
	<i>Shibnath Ghatak, Vincent C. Hascall, Ricardo Moreno Rodriguez, Roger R. Markwald, and Suniti Misra</i>	
16	The Potential Role of Photobiomodulation and Polysaccharide-Based Biomaterials in Wound Healing Applications	211
	<i>Heidi Abrahamse, Sathish Sundar Dhilip Kumar, and Nicolette Nadene Houreld</i>	
17	Is Understanding Fetal Wound Repair the Holy Grail to Preventing Scarring?	225
	<i>Olivier A. Branford and Kerstin J. Rolfe</i>	
18	Inflammation and Cancer	239
	<i>Suniti Misra, Vincent C. Hascall, Roger R. Markwald, Paul E. O'Brien, and Shibnath Ghatak</i>	
	<i>Index</i>	275

Chapter 1

Stem Cell Regeneration and Repair – Overview

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Introduction

While at first glance the skin appears to be no more than a static unchanging surface, it is in fact a complex, dynamic organ that continuously replenishes its cellular and molecular content. In addition to this homeostatic maintenance, skin has evolved the remarkable ability to rapidly repair itself after injury. For our most distant ancestors, there was presumably evolutionary pressure to rapidly restore the barrier function of skin before infection could set in. The result of this evolutionary necessity is scar tissue, which serves as a protective barrier, but falls short in several ways compared with uninjured skin. In humans, the end point of healing all but the smallest injuries is the formation of scar [1]. For most people, scars are a cosmetic concern, but many patients are affected by major scars that result in debilitating contractures as well as disfigurement in aesthetically sensitive areas such as the face. Children with major scars in visible areas such as the face often suffer from long-term psychological stress and impaired self-esteem [2]. If excessive scar formation represents one end of the human wound healing spectrum, the other end consists of chronic and non-healing wounds. Often arising in patients with diabetes, peripheral arterial disease, impaired mobility, and other comorbidities, chronic wounds typically require months of intensive treatment and consume substantial healthcare resources [3].

Stem cells are a key cellular player in the repair of skin after injury and during normal homeostasis. Tremendous progress has been made in recent years toward delineating the role of stem cells in these processes. An improved understanding of the identities of skin stem cells as well as the signals that govern their behavior will hopefully allow for the development of improved therapies for scarring and poorly healing wounds. This chapter will begin with an overview of the events of normal wound healing and stem cell biology and will then review our current understanding of the role of stem cells in skin regeneration and repair.

Overview of Skin Wound Healing

The major function of skin is to provide a barrier that excludes noxious and infectious agents of the outside world while protecting underlying structures from trauma and preventing the loss of valuable body fluid. Wound repair appears to have evolved in a way that rapidly restores these functions while simultaneously preventing infection of the wound (Figure 1.1).

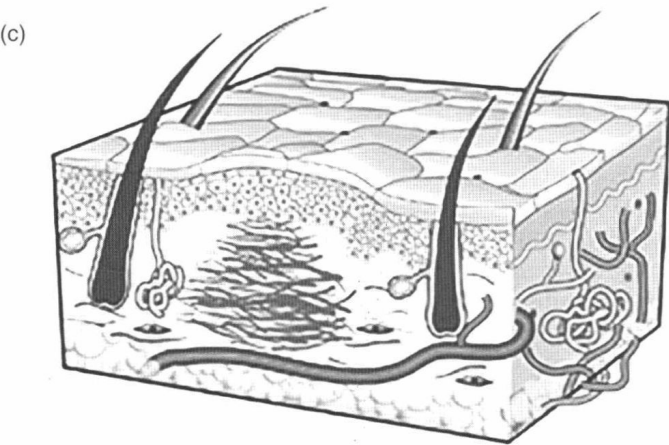
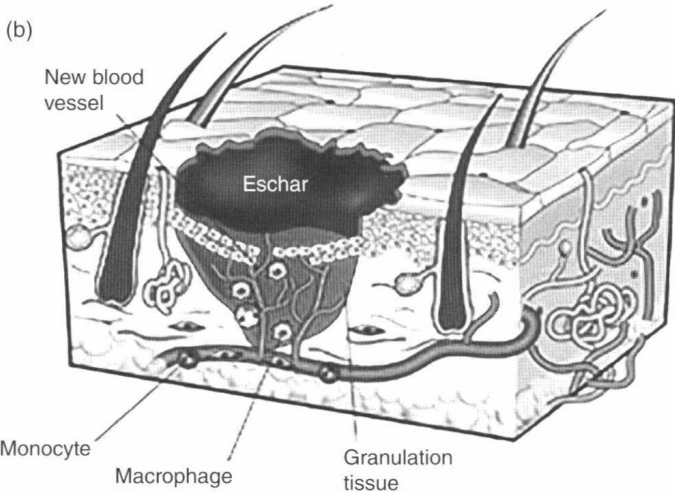
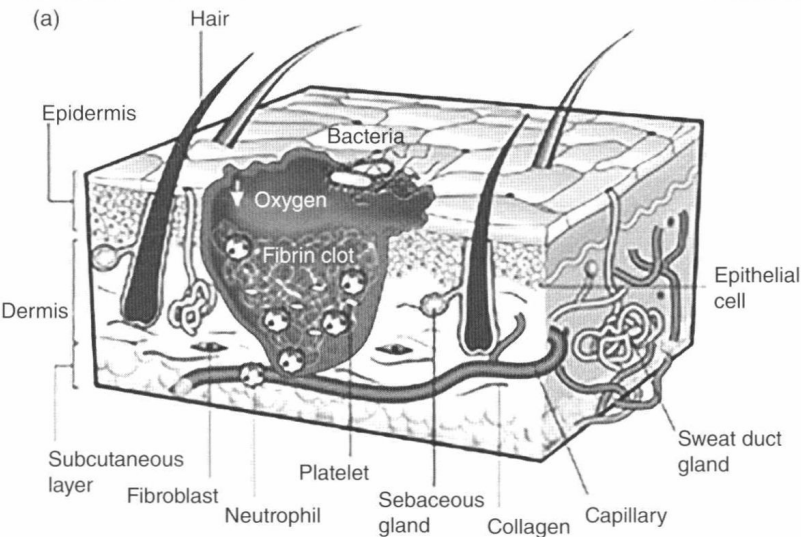
The first events after a skin injury has occurred relate to the restoration of hemostasis. A fibrin and platelet plug prevents ongoing bleeding from blood vessels. The fibrin matrix that composes the plug provides a scaffold for wound healing cells that will migrate in later. Activated platelets in the injury provide early chemical signals that activate other cells and potentiate further wound healing events [4].

The first phase of a true wound repair is known as the inflammatory phase. Immune cells such as macrophages, neutrophils, and lymphocytes enter the wound tissue and begin the process of removing bacteria, dead cells, and other debris [5]. Cytokines released during wounding and hemostasis are critical for the recruitment of these immune cells to the wound [4]. Immune cell influx is accompanied by a local inflammatory reaction characterized by increased blood flow and capillary leaking, causing the typical symptoms of redness, swelling, and increased warmth. In addition to cleaning the wound area and removing infectious agents, immune cells release a host of cytokines and other chemical mediators that encourage other cells to engage in healing behaviors [4].

Inflammation is followed by the proliferative phase of wound healing. This refers to the migration of cells into the wound, particularly fibroblasts and keratinocytes, that are responsible for building new tissue to reconstruct the wound. These cells are highly responsive to chemical mediators released by immune cells during the inflammatory phase [6]. New epidermis and dermis are constructed to replace the empty space left by the wound during this phase. In almost all wounds, the new skin is built in the form of scar [1]. Compared with normal skin, scar lacks hair follicles and sweat glands, is stiffer, and is often raised and hyperpigmented. The basement membrane of the epidermis in scar is flat and does not contain the rete pegs that normally project down into the dermis [7] (Figure 1.2). Large scars, particularly those located over a joint, often contract as a result of myofibroblast action. This contraction occurs in the remodeling phase of wound healing, during which scar extracellular matrix, including collagen, is extensively remodeled [4]. Contractures can be painful and cause severe physical impairment, particularly in patients with large burn scars [8].

Figure 1.1. There are three classic stages of wound repair: (a) inflammation, (b) new tissue formation, and (c) remodeling.

(a) Inflammation. This stage lasts until about 48 h after injury. Depicted is a skin wound at about 24–48 h after injury. The wound is characterized by a hypoxic (ischaemic) environment in which a fibrin clot has formed. Bacteria, neutrophils, and platelets are abundant in the wound. Normal skin appendages (such as hair follicles and sweat duct glands) are still present in the skin outside the wound. (b) New tissue formation. This stage occurs about 2–10 days after injury. Depicted is a skin wound at about 5–10 days after injury. An eschar (scab) has formed on the surface of the wound. Most cells from the previous stage of repair have migrated from the wound, and new blood vessels now populate the area. The migration of epithelial cells can be observed under the eschar. (c) Remodeling. This stage lasts for a year or longer. Depicted is a skin wound about 1–12 months after repair. Disorganized collagen has been laid down by fibroblasts that have migrated into the wound. The wound has contracted near its surface and the widest portion is now the deepest. The re-epithelialized wound is slightly higher than the surrounding surface and the healed region does not contain normal skin appendages. (Reproduced from Gurtner et al. [1], with permission from Nature Publishing Group.) For a color version of this figure, see the color plate section.



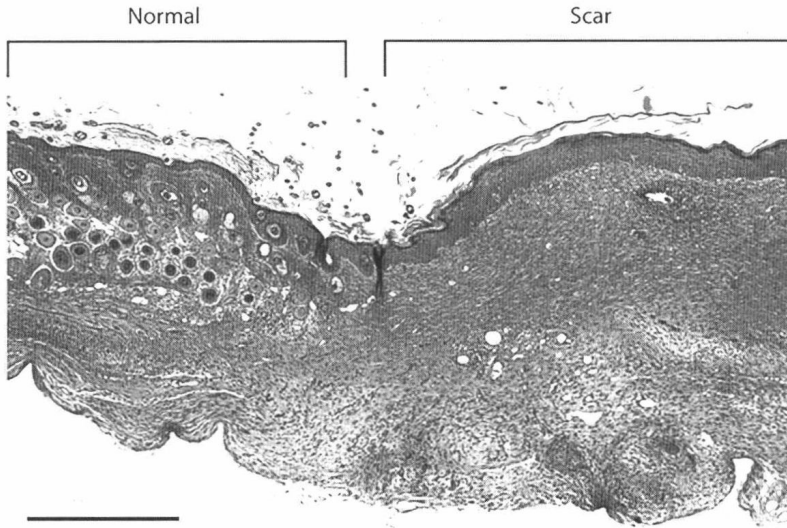


Figure 1.2. Masson's trichrome staining of the interface between normal (left) and scarred (right) dorsal skin in the adult mouse.

Normal skin contains hair follicles and other dermal appendages. Scarred skin does not contain these appendages and the epidermis is flattened. Note that that scarred dermis is thicker than the normal dermis. Scale bar, 500 μm . For a color version of this figure, see the color plate section.

While stem cells are normally active at a low level in uninjured skin to maintain homeostasis, they are recruited during the proliferative phase of wound healing to provide large numbers of new cells to populate the healing wound [9].

Stem Cell Definition: History

Most cells have short life spans and are not capable of indefinite self-renewal. In the 1970s, the concept of the stem cell was developed to describe a special population of cells that divide in order to replenish a population of differentiated cells but do not themselves differentiate. Over time the definition of the stem cell has evolved [10]. Today, stem cells are generally considered to be undifferentiated cells that self-renew and that produce differentiated cells as progeny [11]. Within this broad definition there are many types of stem cells that differ based on their capacity for long- or short-term self-renewal and the number of different cell types that they produce [11].

The presence of stem cells has been verified in most tissues of the body, although certain tissues such as the pancreas may not contain stem cells [10, 12]. The precise manner in which a stem cell behaves and produces differentiated progeny differs depending on the tissue involved. Cell surface markers and genes expressed by stem cells also differ markedly between tissues, making identification and isolation of stem cells sources challenging. Many stem cells express regulatory genes that are switched off in their progeny, making the identification of the progeny cells *in vivo* more difficult. Furthermore, a stem cell's progeny may change its morphology, cell surface marker expression, or migrate to a new location.

A *lineage* can be defined as a particular population of cells and all subsequent cells descended from them, regardless of location or phenotype. The concept of lineage tracing