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HISTOLOGICAL BASIS OF SKIN REGENERATION AND WOUND HEALING: FROM CELLULAR MECHANISMS TO TISSUE REPAIR

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Abstract

The skin is the largest organ of the human body and represents a highly specialized biological barrier that protects the organism from mechanical, chemical and biological factors. Its ability to maintain structural integrity depends on continuous cellular renewal and coordinated regenerative mechanisms. Following tissue injury, wound healing occurs through a complex sequence of overlapping processes involving hemostasis, inflammation, proliferation and tissue remodeling. These processes require coordinated interactions among keratinocytes, fibroblasts, endothelial cells, immune cells, extracellular matrix components and tissue-resident stem and progenitor cells. From a histological perspective, successful healing involves restoration of the epidermal barrier, formation of granulation tissue, extracellular matrix deposition, angiogenesis and progressive remodeling of connective tissue. Recent research has emphasized the importance of epidermal stem cells and their interaction with the local microenvironment during re-epithelialization. Advanced approaches, including single-cell analysis, biomaterials, stem-cell-based therapies and tissue engineering, are providing new opportunities for understanding and improving tissue regeneration. This review summarizes the histological organization of the skin, cellular mechanisms of regeneration, major stages of wound healing, the role of stem cells and the current directions of regenerative research.

Keywords: skin, histology, regeneration, wound healing, epidermis, keratinocytes, stem cells, fibroblasts, extracellular matrix, re-epithelialization.

Introduction

The skin is a complex organ consisting primarily of the epidermis, dermis and subcutaneous tissue. It provides mechanical protection, participates in thermoregulation and sensation, prevents excessive water loss, and contributes to immune defense. These functions depend on the structural organization and continuous renewal of its cellular components.

Under normal physiological conditions, the epidermis is continuously renewed as keratinocytes proliferate in the basal layer and progressively differentiate while migrating toward the surface. Epidermal stem cells have an important role in maintaining epidermal homeostasis and responding to tissue injury. Recent studies indicate that these cells are not isolated from their surroundings; instead, their behavior is regulated by interactions with fibroblasts, extracellular matrix, blood vessels and immune cells.

When skin integrity is disrupted, the organism activates a highly coordinated wound-healing response. Classical wound healing is generally described as four overlapping phases: hemostasis,

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inflammation, proliferation and remodeling. Different cell populations and molecular mediators dominate different stages, although the processes overlap considerably.

Understanding these mechanisms from a histological perspective is important because abnormal healing can lead to chronic wounds, excessive fibrosis, hypertrophic scars or keloids. Modern research therefore focuses not only on wound closure but also on restoring tissue architecture and function.

Aim of the Study

The aim of this review is to describe the histological basis of skin regeneration and wound healing, emphasizing the relationships between tissue structure, cellular activity and extracellular matrix remodeling.

Objectives

The objectives are:

1. To describe the normal histological organization of the skin.
2. To characterize the major cellular populations involved in skin regeneration.
3. To explain the histological changes occurring during wound healing.
4. To examine the role of epidermal stem cells in tissue repair.
5. To describe the contribution of fibroblasts, immune cells and endothelial cells.
6. To discuss factors that can interfere with normal regeneration.
7. To summarize recent approaches in regenerative skin research.

Materials and Methods

This article was prepared as a narrative literature review. Scientific literature concerning skin histology, epidermal regeneration, wound healing, epidermal stem cells and tissue repair was reviewed using biomedical literature databases and open-access scientific publications.

Particular attention was given to recent literature published in 2024 and to established studies describing the cellular and histological mechanisms of cutaneous wound healing. Recent reviews concerning molecular mechanisms, epidermal stem cells, wound-healing microenvironments and emerging regenerative technologies were used to identify current research directions.

Normal Histological Organization of the Skin

The skin consists of two principal layers: the **epidermis** and **dermis**. Deep to the dermis lies the subcutaneous tissue, or hypodermis, which is not technically considered part of the skin itself but is closely associated with it.

Epidermis

The epidermis is a keratinized stratified squamous epithelium. Its principal cells are **keratinocytes**, although melanocytes, Langerhans cells and Merkel cells are also present.

In thick skin, five layers can be distinguished:

- stratum basale;
- stratum spinosum;
- stratum granulosum;
- stratum lucidum;
- stratum corneum.

The **stratum basale** contains proliferating keratinocytes and epidermal stem/progenitor cells. These cells generate daughter cells that progressively differentiate as they migrate toward the superficial layers.

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The **stratum spinosum** contains keratinocytes connected by numerous desmosomes. The characteristic "spiny" appearance results from the cytoplasmic bridges associated with these intercellular junctions.

The **stratum granulosum** contains keratinocytes with prominent keratohyalin granules and contributes to the development of the epidermal permeability barrier.

The **stratum lucidum** is present mainly in thick skin such as the palms and soles.

The **stratum corneum** consists predominantly of flattened, keratin-filled corneocytes surrounded by lipid-rich extracellular material. It represents the principal external barrier of the epidermis.

Dermis

The dermis is connective tissue located beneath the epidermis and consists of two major regions:

Papillary dermis – a superficial layer composed of relatively loose connective tissue containing capillaries, sensory structures and fine collagen fibers.

Reticular dermis – a deeper layer composed of denser irregular connective tissue containing thicker bundles of collagen and elastic fibers.

Fibroblasts are particularly important in the dermis because they synthesize extracellular matrix components including collagen and other structural molecules.

The dermis also contains blood vessels, nerves, sensory receptors and skin appendages such as hair follicles and glands.

Cellular Basis of Skin Regeneration

Skin regeneration depends on the coordinated activity of multiple cell populations rather than a single cell type.

Keratinocytes

Keratinocytes are the predominant cells of the epidermis. Following injury, they become activated, proliferate and migrate toward the wound area. Their migration is essential for **re-epithelialization**, which restores the epidermal barrier. Keratinocytes also produce signaling molecules that influence other cells involved in healing.

Fibroblasts

Fibroblasts are major connective-tissue cells involved in repair. They synthesize extracellular matrix components, particularly collagen, and contribute to the formation and remodeling of granulation tissue.

Endothelial cells

Endothelial cells participate in the formation of new blood vessels during **angiogenesis**. Newly formed vessels supply oxygen and nutrients to regenerating tissue and facilitate the recruitment of cells involved in repair.

Immune cells

Neutrophils, macrophages and other immune cells participate in the inflammatory phase and help remove damaged tissue and microorganisms. Macrophages also contribute to the transition from inflammation toward tissue repair.

Epidermal stem cells

Epidermal stem cells possess self-renewal capacity and contribute to epidermal maintenance and repair. Current research emphasizes their interaction with the local microenvironment, including extracellular matrix, fibroblasts, endothelial cells and immune cells.

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Histological Stages of Wound Healing

Hemostasis

Hemostasis begins immediately after tissue injury.

Damage to blood vessels results in vasoconstriction and activation of platelets and the coagulation system. A fibrin-rich clot develops and temporarily seals the damaged area.

Histologically, the wound contains a provisional matrix consisting of fibrin and other extracellular components. This structure provides an initial scaffold for subsequent cellular migration.

Platelets also release signaling molecules that participate in the recruitment and activation of cells involved in later stages of repair.

Inflammation

The inflammatory phase follows hemostasis and involves recruitment of immune cells.

Neutrophils are among the early cells entering the injured tissue. They participate in the removal of microorganisms and damaged cellular material.

Macrophages subsequently become particularly important. They remove cellular debris and produce signaling molecules that influence fibroblasts, endothelial cells and keratinocytes.

Inflammation is therefore not simply a destructive process. Properly regulated inflammation is necessary for progression toward tissue repair. Excessive or prolonged inflammation, however, can interfere with normal healing.

Proliferative Phase

The proliferative phase is characterized by several simultaneous histological events.

Re-epithelialization

Keratinocytes at the wound margins proliferate and migrate across the wound surface. This process progressively restores the epithelial barrier.

Fibroblast proliferation

Fibroblasts migrate into the wound and produce extracellular matrix components. Collagen deposition increases as the provisional matrix is replaced by more organized connective tissue.

Granulation tissue formation

Granulation tissue consists of newly formed capillaries, proliferating fibroblasts, inflammatory cells and extracellular matrix.

Angiogenesis

New blood vessels develop from existing vascular structures. Angiogenesis provides the metabolic support required by actively regenerating tissue.

Together, these processes progressively replace the provisional wound environment with newly formed tissue.

Tissue Remodeling

Remodeling represents the later phase of wound healing.

During this stage, extracellular matrix components are continuously degraded and reorganized. Collagen fibers become increasingly organized, and the vascularity and cellularity of the newly formed tissue gradually decrease.

Matrix metalloproteinases and their inhibitors participate in extracellular matrix turnover. The balance between matrix synthesis and degradation is important for determining the final organization of repaired tissue.

Complete restoration of the original tissue architecture is not always possible. Depending on the depth and nature of injury, healing may result in scar formation.

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Role of Epidermal Stem Cells in Regeneration

Epidermal stem cells are particularly important for maintaining epidermal homeostasis and responding to injury.

These cells have two fundamental characteristics:

- **self-renewal**, allowing maintenance of the stem-cell population;
- **differentiation**, allowing production of cells that contribute to the epidermis.

Recent research has demonstrated that epidermal stem-cell behavior is strongly influenced by the tissue microenvironment. Interactions with extracellular matrix components, fibroblasts, blood vessels and immune cells can influence proliferation, migration and differentiation.

An important emerging concept is that differentiated epidermal cells can also exhibit considerable plasticity following injury. Research published in 2024 has contributed to a more detailed understanding of the relationship between epidermal stem cells, differentiated cells and wound repair.

This suggests that regeneration should not be viewed simply as replacement of cells from a fixed stem-cell population. Instead, tissue repair involves dynamic changes in cellular states and interactions within the wound microenvironment.

Extracellular Matrix and Fibroblasts

The extracellular matrix is an essential component of tissue regeneration.

It provides:

- structural support;
- sites for cellular adhesion;
- biochemical signals;
- a framework for cell migration;
- regulation of tissue organization.

Fibroblasts are central to extracellular matrix production and remodeling. During wound healing, they synthesize collagen and other matrix components and participate in wound contraction.

However, excessive fibroblast activity or abnormal matrix deposition can contribute to pathological scarring. Recent research emphasizes the importance of fibroblast heterogeneity and their interactions with immune and epithelial cells in determining healing outcomes.

Factors Affecting Skin Regeneration

The rate and quality of wound healing depend on multiple factors.

Age

Aging is associated with alterations in cellular function, extracellular matrix organization and inflammatory responses. These changes can contribute to delayed cutaneous repair.

Nutrition

Adequate availability of proteins, vitamins, minerals and energy substrates is necessary for cellular proliferation, collagen synthesis and tissue remodeling.

Oxygen and blood supply

Adequate vascularization is important because regenerating tissues have increased metabolic requirements.

Infection

Persistent microbial contamination can prolong inflammation and interfere with normal progression through the stages of healing.

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Metabolic conditions

Metabolic abnormalities can alter cellular metabolism and inflammatory signaling. Recent research has shown that glucose, lipid and amino-acid metabolism are closely connected with skin wound repair.

Inflammation

A controlled inflammatory response is necessary, whereas persistent inflammation may contribute to delayed or pathological healing.

Pathological Wound Healing

Wound healing does not always proceed normally.

Two major pathological outcomes are **chronic non-healing wounds** and **excessive scar formation**.

Chronic wounds may remain in a prolonged inflammatory state and fail to progress efficiently toward tissue regeneration. Diabetes, aging, infection and disturbances of the local tissue environment can contribute to impaired healing.

In contrast, excessive extracellular matrix deposition can produce abnormal scars such as hypertrophic scars and keloids. Fibroblast behavior and dysregulated collagen remodeling are important mechanisms in pathological scar formation.

Therefore, successful wound healing requires a balance between inflammation, proliferation, matrix deposition and matrix degradation.

Current Research and Regenerative Medicine

Modern histological research increasingly combines traditional microscopy with molecular and computational approaches.

One important development is **single-cell sequencing**. Instead of analyzing tissue as a single population, single-cell technologies can characterize gene-expression patterns in individual cells. This has helped researchers identify cellular heterogeneity and investigate how different populations behave during wound healing.

Another important research direction is the development of **stem-cell-based therapies**. Various stem-cell approaches are being investigated for difficult-to-heal wounds, although challenges such as cell survival, delivery and control of the inflammatory environment remain.

3D bioprinting, engineered scaffolds and biomaterials are also being investigated as methods for constructing tissue environments that support regeneration. These approaches aim not simply to close wounds but to promote more functional tissue restoration.

Research into signaling pathways, metabolic regulation and the wound microenvironment may also provide new opportunities for developing individualized regenerative therapies.

Discussion

Histologically, skin regeneration is a highly coordinated process in which epithelial and connective tissues interact continuously. The epidermis cannot be considered independently from the dermis because signals from fibroblasts, extracellular matrix and vascular structures influence epithelial behavior.

The classical four-stage model of wound healing remains useful for understanding the general sequence of events. However, modern research demonstrates that these phases overlap and involve complex cellular interactions rather than completely separate stages.

Epidermal stem cells are particularly important because they contribute to tissue homeostasis and repair while responding to signals from their microenvironment. Recent studies have expanded the

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traditional view of regeneration by demonstrating cellular plasticity and complex communication among epithelial, immune, vascular and stromal populations.

From a clinical perspective, understanding these mechanisms may help researchers develop treatments that promote regeneration while limiting chronic inflammation and excessive fibrosis.

Conclusion

Skin regeneration and wound healing are complex histological processes involving coordinated changes in epithelial cells, connective tissue, blood vessels, immune cells and extracellular matrix.

The four classical stages—hemostasis, inflammation, proliferation and remodeling—provide a useful framework for understanding tissue repair. Keratinocyte proliferation and migration restore the epidermal barrier, fibroblasts produce and remodel extracellular matrix, endothelial cells contribute to angiogenesis, and immune cells coordinate inflammatory and reparative responses.

Epidermal stem cells have an important role in maintaining tissue homeostasis and responding to injury. Their activity is strongly influenced by interactions with the surrounding microenvironment, including fibroblasts, extracellular matrix, vascular cells and immune cells.

Recent developments in single-cell sequencing, stem-cell research, biomaterials and tissue engineering are expanding understanding of skin regeneration. Future research may increasingly focus on restoring functional tissue architecture rather than simply achieving wound closure.

Thus, the histological study of skin regeneration provides an important bridge between basic tissue biology and modern regenerative medicine.

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