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Wound Healing: A Narrative Review of Cellular Mechanisms, Regulatory Factors, and Clinical Implications

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Abstract: ***Wound healing is a highly regulated and dynamic biological process that restores tissue integrity following injury. It involves a complex interplay of cellular elements, extracellular matrix components, cytokines, and growth factors, progressing through overlapping phases of hemostasis, inflammation, proliferation, and maturation. Disruptions in any phase may result in impaired healing or abnormal scar formation such as hypertrophic scars and keloids. Systemic conditions, including diabetes mellitus and smoking, further compromise wound repair. This narrative review summarizes the current understanding of the biological mechanisms underlying wound healing, highlights factors influencing normal and abnormal repair, and discusses emerging therapeutic approaches.***

Keywords: wound healing process, tissue repair, scar formation, healing disorders, emerging therapies

1. Introduction

Wound healing is a fundamental physiological response to tissue injury and is essential for survival. Rather than a linear process, healing represents a continuum of overlapping biological events involving hemostasis, inflammation, proliferation, and remodeling. These processes are orchestrated by interactions between platelets, inflammatory cells, fibroblasts, endothelial cells, keratinocytes, cytokines, and the extracellular matrix (ECM). Despite advances in molecular biology and tissue engineering, wound healing remains incompletely understood, and aberrations in this process continue to pose significant clinical challenges [1].

2. Phases of Wound Healing

1) Hemostasis

Hemostasis begins immediately following tissue injury and aims to prevent excessive blood loss. Vasoconstriction occurs through the action of vasoactive mediators such as epinephrine, norepinephrine, serotonin, prostaglandins, and thromboxane A2. Platelet aggregation at the site of exposed collagen and tissue factor leads to clot formation, creating a provisional fibrin matrix [2].

Activated platelets release cytokines and growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and vasoactive amines. These mediators initiate chemotaxis of inflammatory cells and provide the scaffold for subsequent cellular migration [3].

2) Inflammatory Phase

The inflammatory phase begins within hours of injury and is marked by vasodilation, increased vascular permeability, and recruitment of inflammatory cells. Thrombin and fibrin degradation products facilitate the extravasation of leukocytes into the wound bed [4].

Neutrophils dominate the early inflammatory response, where they phagocytose bacteria and necrotic debris and release reactive oxygen species. Although important for host defense, neutrophils are not essential for wound closure [5]. Macrophages, however, are critical regulators of healing. They remove debris, secrete collagenases, and release key growth factors such as PDGF, fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF), thereby linking inflammation to tissue regeneration [6].

T lymphocytes migrate into the wound approximately 72 hours post-injury and contribute to immune regulation and collagenase control through cytokine secretion, including interleukin-1 [7].

3) Proliferative Phase

The proliferative phase is characterized by granulation tissue formation, epithelialization, fibroplasia, angiogenesis, and wound contraction. Granulation tissue, appearing within 3–5 days after injury, consists of fibroblasts, inflammatory cells, neovascular structures, and a provisional ECM rich in fibronectin and collagen [8].

4) Epithelialization

Epithelialization involves the migration of keratinocytes from wound edges and adnexal structures to restore epidermal continuity. This process begins within hours of injury and is facilitated by actin cytoskeletal reorganization and interaction with a fibrin–fibronectin matrix. Moist wound environments significantly accelerate epithelialization, supporting the use of occlusive and semi-occlusive dressings [9].

5) Fibroplasia and Collagen Synthesis

Fibroblasts proliferate and migrate into the wound under the influence of PDGF, FGF, TGF-β, and fibronectin. They synthesize collagen, elastin, proteoglycans, and glycosaminoglycans. Early granulation tissue predominantly contains type III collagen, which is later replaced by type I collagen [10]. Collagen hydroxylation requires oxygen, vitamin C, iron, and α-ketoglutarate; deficiencies impair tensile strength and wound stability [11].

6) Angiogenesis

Angiogenesis is essential for supplying oxygen and nutrients to regenerating tissue. Macrophage-derived angiogenic factors, VEGF, and FGF promote endothelial cell proliferation and capillary formation. As metabolic demand decreases, redundant vessels undergo apoptosis [12].

7) Wound Contraction

Wound contraction reduces wound size through centripetal movement of wound edges mediated by myofibroblasts. Contraction peaks between 5 and 15 days post-injury and is independent of collagen synthesis. Excessive contraction may result in pathological contractures [13].

8) Maturation (Remodeling) Phase

The maturation phase begins approximately three weeks after injury and may continue for months to years. During this phase, collagen undergoes continuous synthesis and degradation mediated by matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs). Type III collagen is replaced by type I collagen, fibers become increasingly organized, and cross-linking enhances tensile strength [14].

Despite remodeling, healed wounds achieve only approximately 80% of the tensile strength of uninjured skin. Vascular density decreases, water content is reduced, and the scar becomes flatter and paler over time [15].

9) Cytokines and Growth Factors in Wound Healing

Cytokines act through endocrine, paracrine, autocrine, and intracrine pathways to regulate healing. Epidermal growth factor (EGF) promotes keratinocyte proliferation and angiogenesis. Fibroblast growth factor stimulates fibroplasia, epithelialization, and wound contraction. PDGF enhances fibroblast chemotaxis and collagen synthesis, while TGF-β plays a central role in ECM accumulation and fibrosis. Tumor necrosis factor-α contributes to angiogenesis and collagen turnover [16].

10) Abnormal Wound Healing

Hypertrophic scars and keloids result from excessive collagen deposition and impaired remodeling. Hypertrophic scars remain confined to the original wound margins and often regress, whereas keloids extend beyond the wound and rarely resolve spontaneously. Keloids exhibit disorganized collagen architecture, increased type III collagen, and altered TGF-β signaling, suggesting a failure of normal scar maturation [17]. Risk factors include dark skin pigmentation, wound tension, and anatomical location such as the presternal and deltoid regions [18].

11) Systemic Factors Affecting Wound Healing

Diabetes mellitus adversely affects wound healing through microangiopathy, impaired immune function, reduced collagen synthesis, and diminished angiogenesis. Poor glycemic control (blood glucose >200 mg/dL) is associated with delayed healing and increased wound complications [19].

Smoking impairs healing through nicotine-induced vasoconstriction, reduced oxygen delivery, inhibition of fibroblast function, and decreased collagen synthesis. Smoking cessation for at least 4–6 weeks before surgery significantly improves wound outcomes [20].

3. Future Directions

Fetal wounds demonstrate scarless healing, likely due to altered inflammatory responses, cytokine profiles, and collagen composition. Understanding these mechanisms may lead to therapeutic strategies that mimic fetal wound environments [21]. Emerging modalities such as platelet-rich plasma, laser therapy, electrical stimulation, cytokine modulation, and magnetic field therapy show promise but require further clinical validation [22].

4. Conclusion

Wound healing is a multifaceted biological process governed by tightly regulated cellular and molecular interactions. While the classical phases provide a useful framework, healing is best understood as a dynamic continuum. Advances in understanding cytokine signaling, ECM remodeling, and systemic influences continue to inform novel therapeutic approaches aimed at optimizing healing and minimizing scarring.

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