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Wound healing biology

By Samantha Gardeen, MD, Anna Kozlowski, MD, and Lina Rodriguez, MD, FAAD

Primary intention healing: Approximation of wound edges
-Primary closure
-Flaps
-Grafts

Secondary intention healing: Wound heals without intervention
-Contraction by myofibroblasts

Phase	Time	Cell type	Description
Inflammation	Starts within 6-8 **hours**, lasts 3-4 days Chronic Inflammation: Inflammatory phase lasting >2 weeks. Can occur due to wound contamination with pathogens, foreign material, necrotic tissue	Platelets: **First cell** to arrive **Neutrophils: First major WBC to arrive** Macrophages: 2nd major WBC to arrive	Extrinsic and intrinsic coagulation pathways activated. **Platelets: Fibrin clot formation and coagulation**. Release of ADP, clotting factors, PDGF, EGF, fibrinogen (first ECM component), fibronectin, TGF-α, and TGF-β, helping to create a matrix for fibroblast migration. Vasodilatory elements released: histamine, prostaglandins, complement, kinins. **Neutrophils: Tissue debridement, bacterial clearance**. Attracted by chemotactic factors, fibrinogen/fibrin products, C5a, leukotrienes. **Macrophages: Critical** for transition from inflammatory to proliferative phase. Secrete growth factors for **fibroblast stimulation** and ECM development- PDGF, TGF-α, TGF-β, FGF. Predominate over neutrophils as wound healing progresses. Phagocytose and debride wound.
Proliferation (tissue formation)	Starts within 5-7 **days**, lasts up to 1 month	**Macrophages: Essential** to initiate proliferative phase through secreted growth factors Keratinocytes: Re-epithelialization Fibroblasts: Make ECM Endothelial cells: Angiogenesis	Re-epithelialization, angiogenesis, and fibroplasia (**granulation tissue**). **Initiated by growth** factors released by macrophages- PDGF, TGF-α, TGF-β, FGF, EGF, KGF, IGF-1, and other growth factors released by platelets, fibroblasts, and keratinocytes. **Keratinocytes 'leap frog'** over each other from **wound edges and adnexal structures**. Occurs through desmosome breakdown and lateral mobilization (mediated by EGF, KGF, TGF-β, MMPs). Fibroblasts migrate via fibronectin matrix to deposit collagen, proteoglycans, elastin. Fibronectin matrix replaced by type III collagen. **Myofibroblasts contract wound**. Endothelial cells migrate to form new blood vessels through angiogenesis. Provide nutrition and oxygen to healing wound. Stimulated by VEGF, TGF-β, angiogenin, low oxygen tension, lactic acidosis. VEGF upregulates endothelial cell integrin receptors to help facilitate endothelial cell migration.

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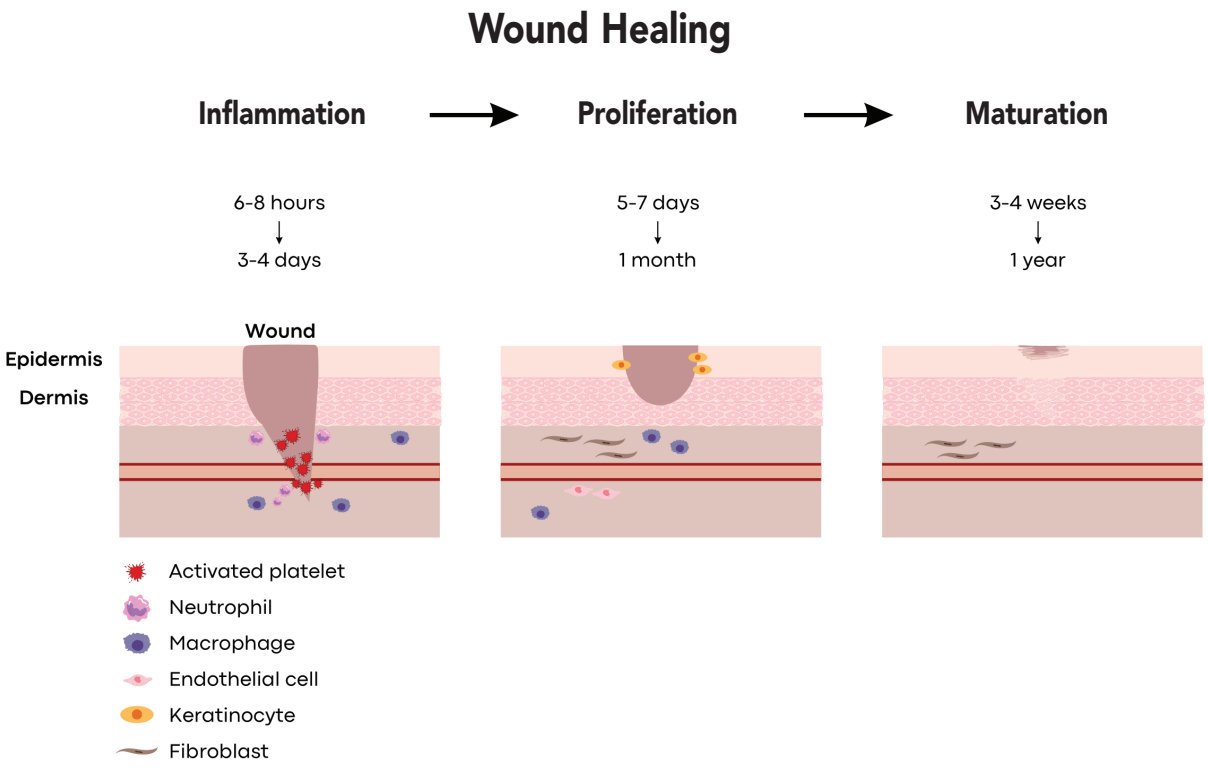
Phase	Time	Cell type	Description
Maturation (tissue remodeling)	Starts within 3-4 **weeks**, lasts about 1 year	Fibroblasts: Major cell in scar formation	Granulation tissue regression, scar matrix formation. Fibroblasts release collagen (**type III collagen replaced by type I collagen**) and hyaluronic acid. Initial clot must be cleared (by plasminogen/plasmin and MMPs) for appropriate scar healing. **Vitamin C required for collagen hydroxylation**. MMPs produce collagenases to modulate ECM turnover, keratinocyte migration, and wound contraction. **Myofibroblasts** continue to **contract** wound through actin microfilaments. Scar strength **1 week: 5%** **3 weeks: 20%** **6 weeks: 40-50%** **1 year: 80%**

*Abbreviations

MMPs-matrix metalloproteinases
ADP-adenosine diphosphate
TGF-β-transforming growth factor beta
FGF-fibroblast growth factor
IGF-1-insulin like growth factor 1
VEGF-vascular endothelial growth factor
PDGF-platelet derived growth factor
TGF-α-transforming growth factor alpha
EGF-epidermal growth factor
KGF-keratinocyte growth factor
ECM-extracellular matrix

Optimal wound healing
-Occlusive wound environment: Effective in accelerating wound healing
-Up to 40% faster healing than when exposed to air
-Enhances keratinocyte migration



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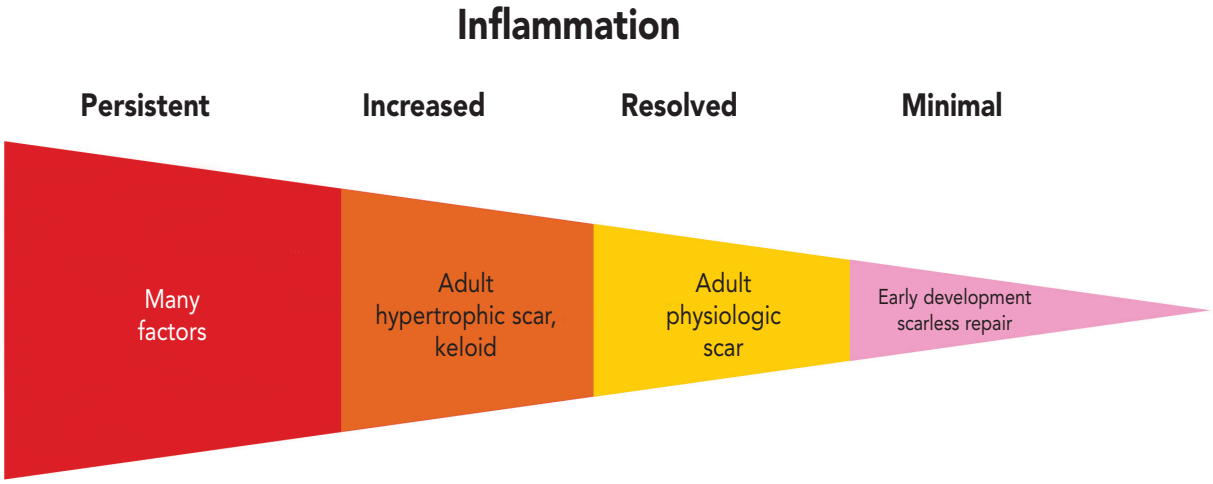

Many factors:

- Malnutrition
- Diabetes or vascular disease
- Connective tissue diseases
- Hypercoagulability
- Medications: corticosteroids, penicillamine, nicotine, NSAIDs, antineoplastic agents
- Advancing age
- Excessive tension, devitalized tissues, tissue ischemia
- Infections
- Hemostatic agents
- Foreign body reaction
- Adverse wound microenvironment: dry, biofilms
- Neuropathy
- Chronic radiation

References:

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