**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 | **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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| Maturation (tissue remodeling) |      | 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  PDGF-platelet derived growth factor
ADP-adenosine diphosphate       TGF-α-transforming growth factor alpha
TGF-β-transforming growth factor beta  EGF-epidermal growth factor
FGF-fibroblast growth factor     KGF-keratinocyte growth factor
IGF-1-insulin like growth factor 1  ECM-extracellular matrix
VEGF-vascular endothelial growth factor

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

Wound Healing

Inflammation  →  Proliferation  →  Maturation

6-8 hours  ↓  5-7 days  ↓  3-4 weeks
3-4 days  ↓  1 month  ↓  1 year

Epidermis
Dermis

Wound

- Activated platelet
- Neutrophil
- Macrophage
- Endothelial cell
- Keratinocyte
- Fibroblast
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Inflammation

Persistent  Increased  Resolved  Minimal

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: