The Science of Wound Healing

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Defining Wounds

- **Superficial**
  - loss of epidermis only

- **Partial thickness**
  - involve the epidermis and dermis

- **Full thickness**
  - involve the dermis, subcutaneous fat and sometimes bone
Wound Healing Phases

Four distinct, overlapping phases:

Hemostasis
Inflammation
Proliferation
Remodeling

Distinct biologic markers characterize healing in each phase and conversely, are responsible for non healing.
Successful Wound Healing

- Cell senescence
- Impaired ECM production and maintenance
- Impaired migration and proliferation
- Decreased response
- Abnormal levels

CELLS
Keratinocytes fibroblasts

MATRIX

SIGNALING MOLECULES
Growth Factors Cytokines
Role of Extracellular Matrix (ECM)

- The structural and functional complex that physically supports and orients cells
- Creates an environment that allows regulation of the cell’s ability to divide, move, and function
- Helps maintain moisture balance
- Provides a structure that supports modulation of MMP and growth factor activity
Matrix Metalloproteinases (MMP)


**Enzymes which act on proteins**
Protein breakdown to allow new tissue formation

**Produced by:**
Inflammatory Cells
Wound Cells (fibroblasts, epithelial cells, endothelial cells, etc.)

**Inhibited by:**
TIMP (Tissue Inhibitors of Metalloproteinases)
MMPs in Wound Healing


**Positive Role**

**Inflammatory Phase**
- Removal of damaged ECM
- Removal of bacteria

**Proliferative Phase**
- Capillary basement membrane degradation for angiogenesis
- Epidermal cell migration

**Remodeling**
- Contraction and remodeling of ECM scar

**Negative Role**

**Excess MMPs results in breakdown of non-substrate proteins**

- Excess due to:
  - Continuous neutrophil recruitment
  - MMP-8 (neutrophil collagenase) = *ECM Degradation*

**Impaired healing**
- Decrease TIMP in chronic wounds
- “Off-Target” destruction of cells/tissue
Wound Healing Phases


**Cytokines** – cell to cell signaling molecules. Control gene activation responsible for cellular migration and proliferation. *Key sources: platelets and macrophages.*

**Chemokines** – regulate trafficking of leukocyte populations. Direct the recruitment and activation of neutrophils, lymphocytes, macrophages, eosinophils, and basophils during inflammation.
Inflammatory Phase

Cellular Events

- **Platelets**
  - Growth Factors
    - PDGF, TGF-B, EGF, IGF

- **Macrophage**
  - Oxygen Radicals
  - Nitric Oxide
  - Phagocytosis
  - Antimicrobial Function
  - Collagenase, Elastase

- **Epithelial Cell**
  - Angiogenesis
    - Growth Factors
      - bFGF, VEGF
    - Cytokines
      - TNF-alpha

- **Fibroblast**
  - Matrix Component Synthesis
    - Collagen, Elastin, GAGs, Adhesive Glycoproteins

- **Growth Factors**
  - PDGF, TGF-B, EGF, IGF

- **Cytokines**
  - TNF-alpha

- **Enzymes**
  - Phagocytosis
    - Enzymes
      - Collagenase, Elastase
  - Prostoglandins

- **Matrix Synthesis Regulation**
  - Cell Recruitment and Activation

- **Phagocytosis**
  - Antimicrobial Function

- **Wound Debridement**

- **T-Cell**
  - With permission
  - Suhad Hadi, DPM

- **B-Cell**

With permission
Suhad Hadi, DPM
Hemostasis

- Injury
- Platelets release clotting factors, growth factors and cytokines
- Vasoconstriction

Up to 2 days
Wound Healing
Home Rebuilding Analogy

**Inflammation**
Leukocytes, Macrophages and Mast Cells migrate to the wound
- Anti-infectious defense
- Phagocytosis
- Immune system response
- Vasodilation

2-5 days
Wound Healing
Home Rebuilding Analogy

**Proliferation**
- Fibroblasts are the contractors
- Extracellular matrix is deposited
- Collagen is the largest part of the ECM
- Vascular proliferation occurs
- Granulation tissue is produced
- Epidermal cells grow into the wound from the margin

5 – 21 days
Wound Healing

Home Rebuilding Analogy

**Remodeling**
Collagen matures / becomes organized
Epithelialization with scar at 80% tensile strength

21 days – 1 year
Home Building Analogy

Acute vs. Chronic Wounds

**Acute Wounds**

Proceed through the phases in an organized fashion with ease

**Chronic Wounds**

There is a delay in progress because of a system problem
Chronic Wounds

**Chronic Wound** – wound healing processes last for longer than 4 weeks and no tendency to healing is apparent

- **Necrotic burden**
  - Normal cellular migration over the wound bed is impaired – apoptosis of fibroblasts and keratinocytes is inhibited

- **Intensely inflammatory**
  - Chronic wound fluid inhibits proliferation of keratinocytes, fibroblasts and endothelial cells
  - Key resident cells are senescent - phenotypically altered and no longer responsive; cytokine and protease levels remain elevated
  - Exudate competes with healing or effectiveness of therapeutic products
Wound Bed Preparation

Wound bed preparation is an approach that takes into account the overall health status of the patient and converts the molecular and cellular environment of a chronic wound bed into that of an acute, healing wound. Ultimately, the process will promote formation of good quality granulation tissue leading to complete wound closure, either naturally or through skin products or grafting procedures.

- Debridement
- Bacterial Balance - Biofilms
- Management of exudate
- Dressing Selection
Clinical Factors Affecting Wound Healing

Age
Infection
Perfusion
Nutrition
Senescent cells
Metabolic disorders
Bacterial bioburden
Sustained inflammation
Deficient growth factor response

General Wound appearance
Periwound skin integrity
Wound evolution
Wound etiology
Drainage
Strategies for Successful Wound Healing

- Is the wound infected?
- Is the wound ischemic?
- Is there pressure?
- Is the wound hypoxic?
- How is edema managed?
- Are there nutritional issues?
- Is the patient adherent?
- What is happening at the cellular level?
Conclusion

**FIGURE 4.** The molecular environment of healing and nonhealing chronic wounds.
Understanding the bridge between what is happening at the basic science level and what we see clinically will yield the best outcomes.