The Microstructure and Biochemistry of Chronic Wounds

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Tissue Microstructure

- In Vitro
- In Vivo
  - Animal
  - Human
Pressure

“The perpendicular load or force exerted on a unit of area”

(Collier 1999)
In Vitro Study

- Human foreskin tissue
- Static pressure applied at 50 mm Hg
- Static pressure applied at 170 mm Hg

Static Pressure

- 50 mm Hg
- 4 hour duration
Static Pressure

- 170 mm Hg
- 4 hour duration
Limitations

• Tissue utilized

• In vitro model
Stage I Pressure Ulcer Definition

- A defined area of persistent redness (does not blanche) in lightly pigmented skin
- May appear with persistent red, blue, or purple hues in persons with darker skin tones. (NPUAP 2002)
- Compared to surrounding skin, area may also be
  - Warmer or cooler
  - Firm or boggy
  - Painful or itchy
- There is no open area in the skin
Stage II Pressure Ulcer

Definition

- Partial thickness skin loss involving epidermis and/or portions of dermis

Ulcer is superficial

NPUAP (1989)
Tissue adjacent to pressure ulcers versus normal control tissue

In Vivo Animal Studies

- Tissue subjected to pressures > 60 mm Hg for durations > 1 hour
  - Muscular necrosis, hyaline degeneration, venous thrombosis, etc

- Tissue subjected to pressures > 115 mm Hg for durations > 3 hours
  - More than 10% of the muscle fibers had signs of inflammation

In Vivo Animal Studies

- Tissue subjected to pressures of 100 mm Hg for 2 hours
  - Muscular necrosis, subcutaneous edema, etc

- Tissue subjected to pressures of 100 mm Hg for 6 hours
  - Compressed muscle with large numbers of inflammatory cells

In Vivo Animal Studies

- **Ischemic loading**
  - Changes were reversible

- **Compressive loading**
  - Changes irreversible

Stekelenburg A, Oomens CWJ, Strijkers GJ, Bader DL, Nicolay K. The relative contributions of deformation and ischaemia to deep tissue injury.
• Other Factors???
Wound Healing

- Stages
  - Coagulation
  - Inflammation
  - Proliferation
  - Remodeling
Coagulation Phase

• Clotting process initiated immediately following tissue injury
  – Wounds that extend past the epidermis

• Platelets
  – Aggregation
  – Hemostasis
  – Degranulation
  – Fibrin clot
Inflammation Phase

- Initiated by several growth factors released from platelets
  - PDGF, IGF-I, EGF, TGF-\(\beta\), TNF-\(\alpha\)
  - Migration of Neutrophils and Macrophages

- Secretion of pro-inflammatory cytokines and proteases
  - Elastase and collagenase
  - Degrade and remove damaged ECM components
Elevated Proteases

- **Neutrophil elastase (degrades fibronectin)**
  - Greatly elevated in chronic wounds
    - Yager DR, Chen SM, Ward BS, Olotoye O, Diegelmann RF, Cohen IK. Ability of wound fluid to degrade peptide growth factors is associated with increased levels of elastase activity and diminished levels of proteinase inhibitors. Wound Repair and Regeneration 1997;5:23.

- **MMP-2, 9 Elevated in chronic wounds**
Inflammation Phase

- **Macrophages**
  - Secrete pro-inflammatory cytokines and growth factors
  - Stimulate migration of fibroblasts, vascular endothelial cells, and endothelial cells
Proliferative Phase

• Keratinocytes proliferate, migrate, and differentiate

• Endothelial cells from damaged blood vessels generate capillary buds

• Fibroblasts migrate and proliferate
Fibroblasts

• Synthesis ECM

• Source of matrix metalloproteinases (MMP’s)
  – Matrix degrading enzymes

• Source of tissue inhibitors of metalloproteinases (TIMP’s)
TIMP Changes

• TIMP’s neutralize MMP’s

• TIMP 1,2,3,4
  – decreased levels in chronic wounds


Remodeling Phase

• Initial scar is in the process of synthesizing new components and degrading other components

• Matrix degrading enzymes - MMP’s involved

• May last years
Collagen Synthesis vs. Lysis

• Balance

• Synthesis impeded
  – Decreased tensile strength

• Lysis decreased
  – Hypertrophy or keloid formation may occur
Wound Fluid

• Chronic wound fluid inhibits proliferation of
  • Fibroblasts
  • Keratinocytes
  • Endothelial cells
• Acute wound fluid stimulates

• EGF added to chronic wound fluid had significant degradation (28.6%) versus acute wound fluid (0.6%)
Discussion Points

• Growth factors often enhance healing in acute experimental animal models more than in human trials of chronic wounds

• Single growth factors

• Wound bed preparation
QUESTIONS?