Inflammation Seminar – Fall 2009
Thursdays, 12 – 1 pm
703 Thackeray

WOUND HEALING & CELL MIGRATION

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What is a wound?

- A **wound** is a disruption of normal anatomical **structure** and **function**
- Various types and locations of wounds
  - Trauma – burn, blunt, penetrating
  - Locations – skin, intestine, cornea, lung
- The **healing** process restores anatomical continuity and function
Why model wound healing?

- To distinguish conditions that lead to normal or abnormal wound healing
- To quantify cell migration and predict wound healing rates in adults or embryos
- To suggest new treatment strategies for various pathological wound conditions (e.g., diabetic foot ulcers, NEC)
Four phases of wound healing

1. Hemostasis
2. Inflammation
3. Proliferation
4. Remodeling
1. Hemostasis

- Healing process cannot begin until hemostasis is established
- Vasoconstriction of injured vessels
- Platelet aggregation and formation of fibrin clot
- Release of cytokines – PDGF and TGF-β
2. Inflammation

- **Neutrophils**
  - Remove debris from wound site
  - Engulf bacteria via phagocytosis
- **Mast cells**
  - Cause the surrounding vessels to become leaky
  - Rubor, calor, tumor, dolor
- **Monocytes**
- **Macrophages**
  - Attract fibroblasts and smooth muscle cells to wound
  - Remove remaining bacteria/debris
- **Lymphocytes** (later stage)
3. Proliferation

- TGF-β increases the transcription of matrix proteins
- Epithelialization
- Angiogenesis – new blood vessel formation
- Fibroblasts responsible for producing new cell matrix and collagen
- Cell proliferation
4. Remodeling

- Longest phase of wound healing
- Fibrin and fibrinectin replaced by collagen and proteoglycans
- Remodeling collagen into more organized units and degraded
- Wound contraction
- Scar maturation; establish new equilibrium
Normal and pathogenic responses to injury

Regeneration
- Exact Replacement

Normal Repair
- Reestablished Equilibrium

Deficient Healing
- Chronic Ulcers

Excessive Healing
- Fibrosis and Contractures
Fibrosis

- The replacement of normal tissue by excessive scar tissue
- Typically excessive accumulation of collagen and increased density of mast cells
- Examples of resulting clinical problems: Crohn’s disease, strictures, liver cirrhosis, keloids
Chronic ulcers

- Chronic inflammation due to over abundance of neutrophils
  - Release enzymes that destroy connective tissue
  - Release enzymes that destroy healing factors
- Most common in spinal cord injury patients and in the elderly
- NEC is characterized by defects in the intestinal layer
- Results in bacteria translocation and activated immune response
- Repair process:
  1. Epithelial restitution
  2. Proliferation
- Impaired healing increases the duration and severity of NEC
Cell migration

- Cells adhere to matrix via integrins (optimal level of adhesion)
- Cells spread into flattened shape
- Transmission of contractile forces to generate movement
- Tail end retracts
Migration in two dimensions
Migration in two dimensions

\[ \text{time} = 1 \text{ hr} \]
Migration in two dimensions

time = 2 hrs
Migration in two dimensions

time = 3 hrs
Migration in two dimensions

time = 4 hrs
Migration in two dimensions

time = 5 hrs
Objective of migration model

- To simulate the motion of the epithelial layer in response to a wound
- To determine how different factors (force, elasticity, and adhesion) affect cell migration
- To compare speed of migration with experimental observations of wound closure
Assumptions of migration model

- Cell layer is assumed to be an elastic continuum ($k$)
  - No holes formed in interior
  - Edge and interior cells move in the general direction toward the wound

- Motion of the cell layer is driven by cells at the edge due to formation of lamellipodia ($F$)

- Adhesion between cells and matrix slows cell motion ($b$)
Model development

- \( \rho(x,t) \) = density of cells
- \( v(x,t) \) = velocity of cells
- \( x(t) \) = position of cells at time \( t \)

- Conservation of mass:
  \[
  \frac{\partial \rho(x,t)}{\partial t} + \nabla \cdot (\rho v) = g(x,t)
  \]

- Conservation of momentum:
  \[
  \rho \frac{\partial v}{\partial t} + \rho (v \cdot \nabla) v = f + \nabla \cdot T
  \]

Proliferation
(assume \( g = 0 \))

Friction force:
\( f = -bv \)

External force:
\( T = -k \ln(\rho) I \)
Model equations

- Model with moving boundary:
  \[
  \frac{\partial \rho(x,t)}{\partial t} = \frac{k}{b} \nabla \cdot (\nabla \rho)
  \]

- Initial and boundary conditions:
  \[
  \rho(x,0) = 1 \quad \text{on} \quad \Omega^0
  \]
  Neumann: \( \nabla \rho \cdot n = 0 \) \quad \text{on} \quad \partial \Omega_2 \quad \text{or}
  Dirichlet: \( \rho = 1 \) \quad \text{on} \quad \partial \Omega_2
  \]
  \[
  \rho = e^{-F/k} \quad \text{on} \quad \partial \Omega_1'
  \]
  \[
  \mathbf{v} = -\frac{k}{b}e^{F/k}\nabla \rho \quad \text{on} \quad \partial \Omega_1'
  \]
Evolution of wound edge
Velocity of the wound edge
Time to wound closure

![Graph showing time to closure vs. area (μm²)](image1)

![Bar chart comparing time to wound closure for different shapes)](image2)
Comparison with experiment
The semester ahead

- Reaction-diffusion models (epidermal and dermal wounds); modeling wound contraction
- Mechanistic models – single cell migration, cell sheets
- Agent-based models
- Signaling and biochemical reaction modeling
- Angiogenesis in wound healing
- Disease studies – diabetic foot ulcers, pressure ulcers, tumors
- Tissue engineering