Wound Healing in Patients with Diabetes

Javier La Fontaine, DPM, MS
UT Southwestern Medical Center
Department of Plastic Surgery
Dallas, Texas
# The Chronic Wound

## Systemic factors
- Infection
- Nutrition
- Glycemic Control
- Edema (MMP’s)
- Oxygen/Vascular?
- Functional microvascular disease

## Local factors
- Inadequate off-loading
- Lifestyle
- Abnormal Plantar Pressure
- Osseous Deformity/Instability
- Dysfunctional biology
Microenvironment imbalance of chronic wounds

HEALING WOUNDS
- Apoptotic clearing (without necrosis)
- Mitotically competent cells
- Low Inflammatory cytokines
- Low Proteases
- Increase growth factors
- High cellular activity

CHRONIC WOUNDS
- Senescent cells
- Increased Inflammatory cytokines
- Increased Proteases
- Bioburden
- Reduced growth factors
- Reduced cells functioning

ROS = Reactive oxygen species.
ECM = Extracellular matrix.

Components of Wound Healing

- Coagulation Process
  - Platelets

- Inflammatory Process
  - Platelets
  - Macrophages
  - Neutrophils

- Migratory/Proliferative Process
  - Macrophages
  - Lymphocytes
  - Fibroblasts
  - Epithelial cells
  - Endothelial cells

- Remodeling Process
  - Fibroblasts

Cell Types Involved

Phases of Wound Healing in Diabetes

Response to Diabetes

- Inflammation
- Regeneration
- Fibrosis
Cellular Dysfunction
Perspective on MSCs

Embryonic

Blastocyst

Blood Elements
- Red Blood Cells
- White Blood Cells
- Platelets

Adult

Hematopoietic

Connective Tissues
- Stroma
- Bone
- Muscle
- Cartilage
- Ligaments and Tendons
- Fat

Mesenchymal (MSC)
Diabetes impairs adipose tissue derived stem cell (ASC) function and efficiency in promoting wound healing.

MSCs Decline With Age

Estimates Obtained by CFU-f assay

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>MSCs per Marrow Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>1,000,000</td>
</tr>
<tr>
<td>Teen</td>
<td>100,000</td>
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<tr>
<td>30</td>
<td>250,000</td>
</tr>
<tr>
<td>50</td>
<td>400,000</td>
</tr>
<tr>
<td>80</td>
<td>2,000,000</td>
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</tbody>
</table>

Caplan, Al. 2007. Adult Mesenchymal Stem Cells for Tissue Engineering Versus Regenerative Medicine; Journal of Cellular Physiology
Diabetes Alters the Regenerative Potential of Mesenchymal Stem Cells

<table>
<thead>
<tr>
<th>Characteristics of Diabetic MSCs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td>Altered</td>
</tr>
<tr>
<td>Growth</td>
<td>Decreased</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Decreased</td>
</tr>
<tr>
<td>Senescence and Apoptosis</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Role of Fibroblasts in Wound Healing

- Migration/Proliferation
  - From surrounding tissues influenced by growth factors/cytokines
    - PDGF
    - EGF
    - FGF-7
    - CTGF
    - Activin

- ECM production
  - Linkage between actin bundles and ECM
  - Serves as scaffold
  - Tensile strength

- Growth factor/cytokine production
  - PDGF
  - EGF
  - FGF-7
  - CTGF
  - Activin

- Angiogenesis
  - ECM remodeling
    - Dissolves
      - Nonviable tissue
      - Fibrin barrier
  - Growth Factors/cytokines
    - FGF-7
    - EGF
    - Activin

- Protease release
  - From surrounding tissues influenced by growth factors/cytokines
    - PDGF
    - EGF
    - FGF-7
    - CTGF
    - Activin
Role of Keratinocytes in Wound Healing

Migration/Proliferation

- Epiboly
- Integrins

Migration/Proliferation

- ECM production
- Growth factor/cytokine production
- Matrix formation
- Basement membrane formation
- VEGF
- TGF-α
- PDGF
- PD-ECGF

Angiogenesis

- VEGF
- KGF (FGF-7)

Angiogenesis

- Chemoattractants

Matrix synthesis regulation

- Dissolves
  - Nonviable tissue
  - Fibrin barrier

Matrix synthesis regulation
Cell Therapies

- New Cells with high proliferative and healing capacity
- Cells that produce an array of cytokines
- Cells that produce matrix proteins
- Cells that produce antimicrobial peptides
- Cells that differentiate to produce a complex epidermis similar to human skin in function and barrier activity
- Cells that persist in and can respond to the wound
Microvascular Disease
Anatomy

- Abnormal blood flow is due to defective C-fiber function
- DM patients shunt blood away from skin
- Loss of Autoregulation

Vascular Endothelial Cells

Basement Membrane

Basement Membrane
Factors that affect endothelial dysfunction (ED)

• Hypercholesterolemia
• Smoking
• Diabetes
• Hypertension
• Hyperlipidemia
The healthy endothelium not only mediates endothelium-dependent vasodilation, but also actively suppresses thrombosis, vascular inflammation, and hypertrophy.

Anti-inflammatory (Inhibition of leukocyte adhesion and migration) → Healthy endothelium → Antithrombotic (Inhibition of platelet adhesion and aggregation) → Anticoagulant and Profibrinolytic

Healthy endothelium → Endothelium-dependent vasodilation

Healthy endothelium → Antihypertrophic (Inhibition of vascular smooth muscle cell proliferation and migration)

Microvascular Changes in Type 1 Diabetes

Stage 1
- Increased microvascular pressure and flow (A-V shunting)
- Endothelial injury
- “Functional Change”
- Increased hydrostatic pressure

Stage 2
- Capillary basement membrane thickening
- Arteriolar hyalinosis
- Inability to vasodilate
- Autoregulatory dysfunction
- Increase permeability

Parving, Metabolism 32, 1983; Tooke, Clin Sci 70, 1986
Early Microvascular Changes in Type 2 Diabetes

Reduced insulin sensitivity

Endothelium-dependent vasodilation

Endothelium-independent vasodilation

Nitric Oxide

C-fiber mediated axon

Morris SJ, Tooke JE, Diabetologia 39, 1995
Vascular Endothelial Cells

Nitric Oxide

L-Alginine
O2
L-Citrulline

NOS

NO
Nitric Oxide: Vascular Endothelial Mediator

- Regulation of wound healing
- NO enhances:
  - Wound O2 availability
  - Infection control
  - Mediator of wound repair
Future Treatments

• Thiazolidinediones
  – Troglitazone*, Actos, Avandia, Avandamet
• Statins- promote repair of endothelium
• ACE inhibitors
• Ca++ Channel blockers
• Fibrates

*Caballero et.al.: Metabolism 52, 2003
How does it apply to the foot?

- Transient pressure-induced vasodilation
- ED does not resolve completely after revascularization
- Autonomic neuropathy and reduction of neurogenic vascular response

Koitka et al.: Diabetes 53, 2004
Microvascular Disease

No Occlusion, but

Functional Deficiency

Malfunction of Endothelial Cells
Infection
Bacterial biofilm is a major barrier to wound healing

- Bacteria protected from topical agents
- Bacteria protected from systemic antibiotics
- Impaired migration and proliferation of keratinocytes
- Low oxygen in biofilm niches
- Host defenses unable to clear infection
Biochemical Impairment of Chronic Wounds

- Elevated proinflammatory cytokines
- Elevated proteinase activity – MMPs
- Diminished activity of growth factors
- Degraded receptor sites
- Decrease TIMP 2,9
Acute vs. Chronic wound
Biofilm Steps approach

• Debridement
• Biocides
  – Silver
  – Iodosorb
• Anti biofilms agents
  – Super-oxidized water
• Antibiotics
  – Adjunct
  – Long term
• Advanced therapies
Thank You!

Javier.lafontaine@utsouthwestern.edu
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