Mechanisms of diabetic wound healing

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Normal Wound Healing

- Body’s natural process of regenerating skin – Complex
  - Inflammatory response
  - Formation of granulation tissue
  - Angiogenesis
  - Collagen deposition
  - Epithelialization
  - Remodeling

- All of these events are impaired during healing in diabetic wounds.
Wound healing is impaired in diabetics

- Significant health problem
- 80,000 amputations per year at $45,000 per amputation.
- Approximately 20.8 million people with diabetes
- 54 million Americans have pre-diabetes.
- ↑ in obesity = ↑ diabetes
Background

- Neuropathy, prevents diabetic patients from feeling discomfort in their lower extremities.
- Thus, a minor abrasion can go unnoticed leading to a very serious chronic wound
Neutrophils

- 1st inflammatory cells to respond to the site of injury within hours
  1. Phagocytose debris and bacteria
  2. Release microbicidal compounds to kill bacteria
  3. Secrete proteases that break down damaged tissue
  4. Produce cytokines to promote inflammatory response
Macrophages

- 2nd cell to migrate into wound.
- Monocytes migrate from bloodstream and become macrophage upon entering the tissue

1. Release microbicidal compounds to kill bacteria
2. Phagocytose debris, bacteria, dead neutrophils
3. Produce cytokines to promote inflammatory response
Macrophages & Wound Healing

• Normal Wound Healing
  – Depletion of macrophages resulted in defective healing

• Diabetic Wound Healing
  – Depletion of macrophages significantly improved healing
Macrophage Activation

**Classically Activated Macs**
- Provide antimicrobial protection by eliminating various pathogens
- Clean the wound by removing dead cells and debris.
- Produce pro-inflammatory cytokines to sustain response
- Helps maintain inflammation

**Alternatively Activated Macs**
- Associated with the resolution of inflammation
- Promotes tissue remodeling and angiogenesis
- Produce anti-inflammatory cytokines

Differentiation depends on proteins in the microenvironment
Hypotheses

• Macrophage activation will be different between normal and diabetic wounds
• Cytokine expression will be different between normal and diabetic wounds
Mice Homozygous for diabetes spontaneous mutation were used as diabetic mice. C57BLCK6 db/db

- Depletion of beta-cells
- Increased blood glucose at 4 weeks

WT mice were C57BLCK6 with the genetic background as diabetic mice
Neutrophil influx is delayed in diabetic wounds
YM1 expression is delayed in diabetic wounds
Ym1 expression is delayed in diabetic wounds
Interleukin-20 is increased in diabetic wounds

![Graph showing the increase of IL-20 in diabetic wounds over PW days 1 to 7.]
Silver and Wound Healing

• Silver wound dressings improve wound healing.
  – Due to reduced bacterial load?
  – Does silver have anti-inflammatory properties?
Delayed wound healing in wounds treated with a gauze dressing compared to wounds treated with a silver nylon dressing across Diabetic and wild type mice.
Silver dressings

- Normal wounds
  - Improved healing
  - Reduced bacterial load

- Diabetic Wounds
  - Improved healing
  - Did NOT reduce bacterial load in diabetic wounds
  - Altered cytokine expression