Introduction to Wound Healing Physiology

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Learning Objectives

1. Describe the various Wound Healing Models

2. Describe the three phases of wound healing:
   • Inflammatory
   • Proliferative
   • Remodeling

3. Understand the various factors that may impact wound healing:
   • Intrinsic
   • Extrinsic
   • Iatrogenic
Photographs and Illustrations

• Most images/illustrations obtained via Google Images

• Some images obtained from the CAWC slide series
What is ‘Wound Healing’?

- Cascade of immunologic and biologic events resulting in a closed wound
- Acute wounds proceed through the processes involved in wound healing in an orderly and timely manner
- Chronic wounds fail to heal in a timely and orderly manner
- Viability of tissues will determine the course and quality of healing
WOUND HEALING MODELS
Wound Healing Models

• Superficial wound healing
• Primary intention wound healing
• Delayed primary intention wound healing
• Partial thickness wound healing
• Full thickness/secondary intention healing
Superficial Wound Healing

- Ulcerations in the superficial skin

- Soft tissues heal themselves over time via inflammatory repair process

- I.e. stage I pressure ulcer, superficial burn, or contusion
Primary Intention Wound Healing

• A.k.a. Surgical wound healing

• Connective tissue deposition and epithelialization

• No granulation tissue formation or wound contraction
Delayed Primary Intention

- Wound left open to:
  - Promote drainage
  - Reduce bacterial burden

- Later (often within seven days) surgically closed
Partial Thickness Wound Healing

- Wounds with loss of the epidermis or partial thickness skin loss of the dermis
- Heal by epithelialization/regeneration
  - Wound edges
  - Dermal appendages
- Normal appearance and function
- I.e. abrasions, skin tears, stage II pressure ulcers, blisters, and partial thickness burns
Full Thickness/Secondary Intention Healing

• Most effective method when:
  • The wound extends through all layers of skin
  • High microorganism count
  • Debris or non-viable tissue present

• Involves inflammation, epithelialization, proliferation, and remodeling

• Scar tissue formation and contraction

• Replacement tissue will have less elasticity/tensile strength
What Healing Model do These Wounds Represent?
Chronic Wound Healing

- Associated with secondary intention

- A chronic wound is one that has “failed to proceed though an orderly and timely process to produce anatomic and functional integrity, or proceeded through the repair process without establishing a sustained anatomic and functional result” \(^6\)
PHASES OF WOUND HEALING
Phases of Wound Healing

- Every wound is unique, “with a unique set of physiologic and social circumstances preventing or retarding wound healing”.

- The normal wound repair process consists of three phases that occur in a predictable sequence:
  - Inflammation
  - Proliferation
  - Remodeling
Phases of Wound Healing

• “The end result of uncomplicated healing is a fine scar with little fibrosis, minimal if any wound contraction, and a return to near normal tissue architecture and organ function”\textsuperscript{1}

• If a wound does not heal in an timely and/or orderly fashion or if there is a lack of structural integrity, then the wound is considered chronic\textsuperscript{1,2}
The Inflammatory Phase

Cutaneous trauma
- Haemostasis (adhesion/platelet aggregation)
- Release of pro-inflammatory cytokines

- Red blood cell
- Fibrin-platelet clot
- Release of cytokines and growth factors
- Fibroblast
- Collagen

Elastin
Monocyte polymorphonuclear
Matrix Metalloproteases
Growth factors
NOSF
Inflammatory Phase

• Immediately initiated by tissue injury

• Body’s immune system reaction:
  • Redness, heat, swelling, pain, loss of function

• Typically lasts 3-7 days

• Goals:
  • Hemostasis (coagulation cascade – stops bleeding and prevents bacterial infiltration)
  • Breakdown and removal of debris (natural autolysis)

• Major cell types: platelets and white blood cells
Inflammatory Phase Continued

• Key processes:
  • Coagulation cascade (platelet activation and hemostasis)
  • Mitogenesis and chemotaxis of growth factors
  • Controlled tissue degradation
  • Perfusion
  • Hypoxia and regulatory function of oxygen-tension gradient
  • Complement system activation to control infection
  • Neutrophil, macrophage, mast, fibroblast cell functions
  • Keratinocyte activation
  • Current of injury stimulus
Inflammatory Phase Continued

Trauma to skin

Intense vasoconstriction (5-10 minutes)

Active vasodilation and increased capillary permeability (within 10-30 minutes) = blood, O2, nutrients

Platelet adhesion at the site of injury and clot formation/hemostasis
Inflammatory Phase Continued

Neutrophils appear, followed by macrophages (kill bacteria and emulsify necrotic tissue)

Influx of polymorphonuclear leukocytes and mononuclear leukocytes, which mature to macrophages, and later to lymphocytes

Protein rich serum enters the interstitial space

Fibronectin is deposited, which creates a scaffolding on which fibroblasts can migrate into
Activated neutrophils release free O2 radicals and lysosomal enzymes (proteases, collagenases, elastases) which fight infection and clean the wound\textsuperscript{1,3}

Lymphocytes appear in greater numbers, which attract fibroblasts and clear the wound of old neutrophils\textsuperscript{1,4}
The Proliferative Phase
Proliferation Phase\textsuperscript{1,5}

- Occurs 2-10 days after injury

- Goal:
  - Formation of granulation tissue (fills in the wound)
  - Angiogenesis
  - Contraction (pulling edges together)
  - Epithelialization (covering of wound)

- Major cell types:
  - Fibroblasts (scar formation)
  - Endothelial cells (angiogenesis)
  - Epithelial cells (re-epithelization)
Proliferation Continued

Fibroblasts produce GAGS and collagen (increases wound tensile strength)

↓

Angiogenesis

↓

Collagen fibers cross-link to increase their strength
The Maturation Phase

- Remodelling
  - Orientation of Collagen Fibres
    - Reabsorption of Type III Collagen
    - Replacement with more Type I Collagen
      - Structure of final scar as similar as possible to parent tissue
Maturation Phase

- Starts by 3 weeks after injury
- Homeostasis between collagen synthesis and degradation, and wound remodeling begins
- Process continues for up to 2 years – collagen structurally re-organized to increase tensile strength
- A plateau is reached – healed wound will never exceed 80% strength

- Major cell types:
  - Growth factors
  - Collagenases
Maturation Phase Continued\(^1\)

- Wound re-epithelialization:
  - Mobilization
  - Migration
  - Mitosis
  - Cellular differentiation

Of epithelial cells
Schematic of Epithelialization

With injury basal cells detach from the basement membrane.

The cells migrate while holding on to their "parent" cells and pull them into the center to close the wound.

When the two sides meet, movement ceases.

Basal cells differentiate and proliferate...

...to become multilayered and restore the epidermis.
Maturation Continued

- Wound contraction:
  - Starts one week after wounding
  - Some fibroblasts will transform to smooth muscle actin (myofibroblasts)
  - Secure attachments, drawing the wound edges closer
  - At the same time, collagen is synthesized, deposited, and cross linked, holding the wound in place
PHASES OF WOUND HEALING

INJURY
1

CLOSURE
?? DAYS

HAEMOSTASIS
- Damaged vessels constrict to slow blood flow
- Platelets aggregate to stop
- Bleeding
- Leucocytes migrate into tissue to initiate inflammatory process

INFLAMMATION
- Neutrophils secrete chemicals to kill bacteria
- Macrophages engulf and digest foreign particles and necrotic debris
- Macrophages release angiogenic substances to stimulate capillary growth and the granulation process

PROLIFERATION
- Fibroblasts proliferate in the wound and secrete glycoproteins and collagen
- Epidermal cells migrate from the wound edge
- Granulation tissue is formed from macrophages, fibroblasts and new capillaries

REMODELLING
- Fibroblasts secrete collagen to strengthen wound
- Wound remodelling occurs to reorganise fibres
- Wound contracts increasing tissue integrity
- Epidermal cells grow over connective tissue to close wound
FACTORS AFFECTING WOUND HEALING
Impediments to Wound Healing

- Intrinsic factors (underlying pathology)
- Extrinsic factors (environmental influences)
- Iatrogenic factors (inappropriate management)
A. Intrinsic Factors

- Age
- Chronic disease and immunosuppression
- Perfusion and oxygenation
- Neurologically impaired skin
Effects of Aging on Skin

- 20% decrease in dermal thickness leads to thinning of the skin

- Epidermal-dermal papillae become flattened, increasing susceptibility to friction and shear

- Loss of penetrability to substances, irritants more readily absorbed

- Elasin fibers are lost – skin less elastic
Effects of Aging on Skin

• Dermis atrophies:
  • Slows wound contraction
  • Increases risk of dehiscence

• Diminished dermis vascularity

• Subcutaneous fat atrophies
  (most noticeable in face, backs of hands and shins)

• Collagen in the skin reduces (collagen fibers become compressed)
Effects of Aging on Skin

- Blood vessels become thinner and more fragile causing small hemorrhages called senile purpura
- Reduction in sweat glands and sebum resulting in decreased skin hydration (dry, itchy, inelastic skin)
Chronic Disease

• Affect cardiopulmonary system and oxygen transport pathway

• Diabetes are at risk for poor healing due to
  • Hyperglycemia (increases risk of infection)
  • Microvascular/neuropathic components

• Immunosuppression (diabetes, cancer, HIV, AIDS) results in lack of ability to promote immune response
Perfusion and Oxygenation

• Anemia:
  • Reduced hemoglobin
  • Reduced oxygen carrying capacity of blood

• Hypovolemia:
  • Insufficient volume to transport oxygen and nutrients to tissue and to remove waste
  • Diminishes leukocyte activity

• Diabetes:
  • Increased peripheral arterial disease
  • Results in stenosis and occlusion – ischemia and ulceration
Neurologically Impaired Skin

• Peripheral neuropathy result of chronic diabetes and alcoholism

• Types of neuropathy:
  • Sensory
  • Autonomic
  • Motor

• CNS neuropathy (spinal cord injury)
B. Extrinsic Factors

- Medications
- Nutrition
- Irradiation/chemo
- Stress
- Bioburden
Medications

• Anticoagulation, antiplatelet aggregation, and NSAIDS:
  • Impair platelet activations
  • Results in decreased collagen production

• Steroids:
  • Topically or systemically
  • Inhibit macrophage levels
  • Reduce immunocompetent lymphocytes
  • Decrease antibody production
  • Diminish antigen processing

• Vitamin E
Nutrition

• Protein malnutrition

• Insufficient calories

• Lack of vitamin A and C, zinc, iron

• Dehydration
Irradiation and Chemo

• Irradiation:
  • Disrupts cell mitosis
  • Injures fibroblasts and endothelial cells (repair cells)
  • Poor vasculature

• Chemo:
  • Damages DNA and/or prevents DNA repair
  • Induced peripheral neuropathy
Stress

- Induces release of cortisol that can:
  - Up or down regulate proinflammatory cytokine production
  - Suppress migration of neutrophils and synthesis of proinflammatory mediators, which leads to decreased macrophage function and suppression of fibroblast proliferation and matrix degradation that affects the duration and strength of the wound
Bioburden

- Presence of devitalized tissue or foreign material in wound:
  - Prevents epithelialization
  - Contributes to proliferation of bacteria
C. Iatrogenic Factors

• Local ischemia:
  • Inappropriate application of compression
  • Smoking

• Inappropriate wound care:
  • Misuse of antiseptics
  • Skin tears and blisters from tape
  • Wound desiccation or over hydration
  • Frequent dressing changes

• Trauma:
  • Retards healing
  • Alters tensions of respiratory gasses in wounds
  • Increases risk of infection

• Wound extent and duration
Review

1. Wound Healing Models

2. Phases of wound healing:
   - Inflammatory
   - Proliferative
   - Remodeling

3. Factors that may impact wound healing:
   - Intrinsic
   - Extrinsic
   - Iatrogenic
For more information visit: woundcare.thehealthline.ca
References


