The Biology Of Healing

I. Wound Healing - Mystery & Magic
   • The Historical Struggle to Understand and Control

II. The Common Pathway for Tissue Healing
   • Wound - a disruption of normal anatomical structure and function (open & closed)
   • Healing - a dynamic process resulting in the restoration of anatomical continuity & prior function
   • The basic processes of healing, present in all tissues, varies as each tissue modifies the process to
     maintain unique organ-specific functions.
     1. Regeneration = regrowth of normal host tissue [bone, nerve, muscle, skin wounds]
     2. Repair = replacement of injured tissue with a collagenous gel, called scar tissue

III. Stages of Wound Healing
   1. INFLAMMATORY PHASE = "Cleanup Crew"
   2. FIBROPLASIA PHASE = "Building Crew"
   3. REMODELING PHASE = "Decorating Crew"

IV. INFLAMMATORY PHASE – Days "Inflammatory Soup"
   • Hemostasis "Clean & Close"
     i. Blood vessel damage - bleeding to flush out wound contaminants
     ii. Platelets
        - form fibrin clot: seals off the wound; temporary matrix for cell migration & wound strength
        - platelet degranulation: releases a cocktail of growth factors that initiates healing response
     iii. Mast cells "The Fire Alarm"
        - release histamine - causes non-injured vessels to dilate
        - release histamine & tryptase - attract inflammatory cells

   Signs of Inflammation = rubor (redness), calor (heat), tumor (swelling), dolor (pain)

Effects of tissue effusion
• Intra-articular effusion causes predictable joint positions to accommodate the swelling and decrease pain
• Nociceptors respond to effusion with selective inhibitory and facilitatory actions on muscles

• Cytokines (Growth Factors) "Secrete"
  - chemicals released by inflammatory cells that exert both stimulatory +/- inhibitory effects
  - net result of all signals is vigorous response to ensure rapid connective tissue deposition
  - during healing, the release & concentration of of cytokines changes markedly
  1. Platelet derived growth factor (PDGF) - initiates activation & chemotaxis cells into wound
  2. Transforming growth factor beta (TGF- β) - promotes migration & differentiation of cells
  3. Fibroblast activating factor (FAF) - recruits fibroblasts to wound
  4. Epidermal growth factor (EGF) - activates epithelial cell division & migration
  5. Vascular endothelial growth factor (VEGF) - activates vessel endothelial cell growth
  6. Interferon (IFN-y) - decreased college content

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7. Tumor necrosis factor (TNF-a) +/- modulates endothelial & fibroblast cells

- Phagocytosis: “Eat” leukocytes that ingest foreign materials, bacteria and damaged tissue
  i. Neutrophils: engorge themselves with bacteria forming “pus”
  ii. Macrophages: “Director Cells” due to their role in recruiting appropriate cells
  iii. T Lymphocytes: lesser role in phagocytosis; functions more as a signal cell

**Inflammatory Active Cells:** platelets, mast, cytokines, leukocytes, macrophages

V. **FIBROPLASIA PHASE** - weeks  “One Wound Concept”

- Epithelialization - “Raise The Roof”
  - resurface the wound: protective barrier & prevent fluid loss
    1. Epithelial cells at edge of wound, in hair follicles, in sweat glands, begin to migrate out, moving along under the scab and on the surface of wound
    2. Bridge is complete when one side meets another (contact inhibition): enzymes released to dissolve attachments at base of scab - gradual removal of scab

- Neovascularization (Angiogenesis)  “Feed the troops”
  i. High metabolic activity at wound site demands greater oxygen and nutrients
  ii. Low ph, reduced oxygen tension, increased lactate, cytokines - stimulates endothelial cells
  iii. As new blood vessels grow into wound area, O2 tension returns to normal (better for healing)
  iv. Extra blood vessels contribute to bulk and redness of early scar; as healing matures, the need for extra capillaries diminishes, and they recede leaving a flatter and paler scar

- Produce Scar-  “Fiber Makers Build”
  i. Fibroblasts activated to move into all areas of wound along fibrin matrix
  ii. Fibroblasts produce procollagen chains and ground substance (GAGS + water)
  iii. Procollagen chains twist into triple helix and are excreted from fibroblast
  iv. Procollagen + hydroxyproline (nutritional dependent) = becomes stronger tropocollagen
  v. Tropocollagen + Ground Substance = Granulation Tissue (Scar)

- Wound Contraction-  “Shrink The Wound”
  - wound closure is facilitated by contraction forces
  i. Fibroblasts, in response to cytokines and loss of normal tissue tension, change into contractile fibroblasts with smooth muscle features
  ii. Myofibroblast contract - process in which granulation tissue is pulled toward center of wound
    GOOD: faster healing, less scar formation
    BAD: contraction can lead to soft tissue & joint contractures
    Skin grafts partially decrease contraction (31% with STG; 77% with FTG)
  iii. Apoptosis = “Cell Suicide” -programmed cell death
    Normal - myofibroblast population disappears as tissue is repaired
Pathology – myofibroblast activity persists (hypertrophic, keloid, DD, scleroderma)
*chronic inflammation via Mast Cells results in increased numbers of myofibroblasts: fibrosis

Fibroplasia Active Cells: epithelial cell, endothelial cells, fibroblast, myofibroblast

VI. REMODELLING PHASE – months “Strength & Function”

• Tensile Strength
  i. Scar has 15% of its ultimate tensile strength at 3 weeks
  ii. Crosslinking bonds (microscopic welding) improves tensile strength of collagen
     *Intramolecular Bonds: weak, form between helical chains in one filament
     *Intermolecular Bonds: strong, form from one collagen filament to another
  iii. Maximum tensile strength of a healed tissue is 80% compared to normal

• Decrease bulk of scar “Synthesis -Lysis Balance”
  i. Wound has greatest amount of scar at beginning of this phase
  ii. Collagenase enzyme [fib. & macroph] cleaves crosslinks, breaks down collagen
  iii. Collagen turnover is higher in active wounds as both synthesis & lysis rates are accelerated,
     but in balance with each other in normally healing wounds.
  iv. Result of higher turnover is a flatter but stronger scar

• Alignment of collagen fibers for form & function “Form Follows Function”
  i. Early disorganized, non-stressed collagen deposition contributes to scar weakness
  ii. All tissues have a characteristic weave or orientation of their collagen fibers related to their tissue function (skin: random; ligaments, tendon: parallel and crimped)

  iii. Induction Theory: scar is induced by tissue type in immediate proximity to “mimick” characteristics of this tissue (dense or soft connective tissue)
     • Silastic Joint Implants: dense implant/dense capsule
     • Interpositional fat or aerolar tissue: soft tissue interposition/soft scar
     • Sequencing of surgical repairs: repair dense tissues first/later soft tissues

  iv. Tension Theory: newly formed scar orientation is affected by stress/tension
     • Wolf’s Law for soft tissue: tissue develops the structure most suited to resist the forces acting upon it, “form follows function”
     • Motion prevents unwanted crosslink development between mobile and stable tissues

Remodeling Active Processes: crosslinks, synthesis/lysis, alignment to tension

Regenerative Medicine & Rehab “Regeneration is in our DNA”

• Present Possibilities to improve; tissues heal with a combination of regeneration and scar
  Skin – thickness dependent
  Tendon – motion dependent
  Cartilage – motion dependent
  Nerve – gap and distance from anterior horn cells dependent
Bone – rigid fixation dependent

- Future Possibilities
  - Materials induced regeneration – bio-inert, temporary scaffolding
  - Cellular seeding – embryonic, adipose, periosteal derived stem cells

"Rehab training programs must incorporate research that refines our intervention strategies to maximize the benefits of these new biological therapies.” Ambrosio 2010, PT

REFERENCES

Ambrosio F, Wolf S et al. The emerging relationship between regenerative medicine and physical therapeutics. PT 2010;90:12:1807-1814


Gailit J, Marchese M et al. The differentiation and function of myofibroblasts is regulated by mast cell mediators. JInvest Derm 2001;117:1113-1119


Hinz B. Formation and function of the myofibroblast during tissue repair. JInvestDerm 2007;127;526-537


