INFLAMMATION & REPAIR

Lecture 9
Repair, Fibrosis & Healing
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Special thanks to Drs. Hanna and Forzan
• **Definition** = process by which lost or necrotic cells are replaced by vital cells

• involves *regeneration* &/or *fibrosis*.
REPAIR – by Regeneration

- replacement of cells by those of an identical type
- requires:
  - tissue capable of parenchymal regeneration
  - maintenance of the architectural (CT) framework/
    basement membranes

eg, Parvoviral enteritis
- necrosis of intestinal epithelium (crypts)
- regeneration of epithelium = recovery

Note: not all animals survive to see this regeneration!
REPAIR – by Regeneration

- repair starts early in the inflammatory process
- mediators often both pro-inflammation and pro-repair

Fig. 9-11 Normal and injured mucosa, nasal conchae, rats. Normal ciliated epithelium composed of tall columnar cells with numerous cilia. Day 1. Nasal epithelium following exposure to air containing an irritant gas (hydrogen sulfide). Note detachment and exfoliation of ciliated cells, leaving a denuded basement membrane (arrows). This same type of lesion is seen in viral or mechanical injury to the mucosa of the conducting system. Two days after exposure, the basement membrane is lined by rapidly dividing preciliated cells, some of which exhibit mitotic activity (arrow). Ten days after injury, the nasal epithelium is completely repaired. H&E stain.
REPAIR – by Fibrosis

• when replacement by original tissue is impossible
• see increase in fibrous CT within the tissue
  ➢ fibroblasts synthesize collagen & proteoglycans
• new blood vessels are necessary (neovascularization)
• granulation tissue = fibroblasts / collagen & neovascularization
Disorganized, early-stage, granulation tissue

Organized, maturing, granulation tissue

REPAIR – by Fibrosis
Granulation tissue
REPAIR – Regeneration vs Fibrosis

1. ability of the host to eliminate the inciting agent
2. how much tissue damage / necrosis (CT framework, basement membranes)
3. how much of the exudate is removed / resolved
4. nature of injured cells (labile / stable vs permanent)

since so many requirements for a return to normality, some degree of scarring is more common than complete resolution for most significant lesions
Tissue Proliferative Capability

- Labile (continuously dividing)
- Stable (quiescent)
- Permanent (non-dividing)
Labile Cells - usually repairs by regeneration

- Continuously dividing
- after injury (if not severe) see rapid regeneration.
- >1.5% cells in mitoses

Examples:
- Skin / mucosal epithelium
- Lymphoid Cells
- Hematopoietic Cells
Stable Cells – repair by regeneration &/or fibrosis

- low level of replication
  - <1.5% of normal adult cells in mitosis
- can rapid divide in response to injury

Examples:
- Hepatocytes
- Renal tubular epithelium
- Endothelium
- Mesenchymal cells (fibroblasts)
- Smooth muscle cells
Need intact basement membranes for renal tubules or hepatocytes to regenerate.

Glomeruli do not regenerate.
Permanent Cells – repair by fibrosis

- Cells don’t divide
- No regenerative ability
- 0.0% cells are in mitoses

Examples:
- Neurons
- Cardiac myocytes
- Lens epithelium
Repair by Fibrosis

Timeline:
- begins within 24 hours of injury!
- fibroblasts & endothelial cells migrate to the site of injury & proliferate
- 3-5 days see early granulation tissue (fibroblasts / collagen & neovascularization)
- wks to months see $\uparrow$ collagen and $\downarrow$ decreased vessels (scarring)

Figure 3-21 (Robbins)  A, Granulation tissue showing numerous blood vessels, edema, and a loose ECM containing occasional inflammatory cells. Collagen is stained blue by the trichrome stain; minimal mature collagen can be seen at this point. B, Trichrome stain of mature scar, showing dense collagen, with only scattered vascular channels.
Fibrosis
Repair by Connective Tissue Replacement

4 components

1) Angiogenesis (neovascularization)
2) Migration & proliferation of fibroblasts
3) Deposition of extracellular matrix
4) Maturation and reorganization of fibrous tissue
1) Angiogenesis

Figure 3-15A  In angiogenesis from preexisting vessels, endothelial cells from these vessels become motile and proliferate to form capillary sprouts. Regardless of the initiating mechanism, vessel maturation (stabilization) involves the recruitment of pericytes and smooth muscle cells to form the periendothelial layer.
2) Migration/Proliferation of Fibroblasts

- due to growth factors: PDGF, TGF-β, FGF

3) Deposition of ECM (mainly collagen)

- starts within 3-5 days; esp due to TGF-β & PDGF
4) Maturation and reorganization of fibrous tissue

- development of granulation tissue and subsequent scar tissue formation
Wound Healing

- process of **fibrous replacement** and **regeneration** (varying amounts of each)
- results in restoration of tissue continuity, with or without function.
Wound Healing

1. Injury → inflammation (necrosis)

2. Parenchymal cells regenerate (if possible)

3. Migration/proliferation
   - fibroblasts & endothelial cells
   - parenchymal cells

4. Synthesis of ECM (collagen / proteoglycans)

5. Remodeling of parenchymal cells (restore function)

6. Remodeling of connective tissue (wound strength)
What might impair Wound Healing?

- infection
- nutrition
- glucocorticoids
- mechanical factors
- poor perfusion
- foreign bodies
- type & amount of tissue injured
- location of injury
Cutaneous Wound Healing by First Intention

- possible when tissue elements in close proximity (eg surgical wound).

- a primary union where regeneration predominates over fibrosis
Cutaneous Wound Healing by First Intention

24 hours
- neutrophils migrate into fibrin clot
- basal epidermal cells at edges increase mitotic activity
Cutaneous Wound Healing by First Intention

24-48 hours
- epithelial cells migrate and proliferate
- deposition of basement membrane
Cutaneous Wound Healing by First Intention

**Day 3**
- macrophages replace neutrophils
- fibroblasts & collagen fibers at margins (vertical)
- epithelial cells continue to proliferate

**Day 5**
- neovascularization peaks
- collagen fibers bridge wound (horizontal)
Cutaneous Wound Healing by First Intention

Day 14

- fibroblasts and collagen accumulation continue
- decreased leukocytes & edema
- vascular channels regress
Cutaneous Wound Healing by First Intention

4 weeks
- scar (fibroblasts and collagen)
- few inflammatory cells
- tensile strength increases with time
Cutaneous Wound Healing by Second Intention

- where there is poor apposition (e.g., ragged cuts)
- more complex repair process
  - more inflammation (fibrin & leukocytes)
  - more granulation tissue
  - contraction due to myofibroblasts
  - often an irregular scar
Figure 3-20 (Robbins) Healing of skin ulcers.
The histologic slides show: B, a skin ulcer with a large gap between the edges of the lesion; C, a thin layer of epidermal re-epithelialization and extensive granulation tissue formation in the dermis; and D, continuing re-epithelialization of the epidermis and wound contraction.
Wound Strength

- immediate (if sutured) → ~70%
- if not sutured:
  - 1 week → ~10%
  - 3 months → ~70-80%
Granulation tissue

• pink, soft, granular tissue on wound surface
• histologically see proliferation of new small blood vessels and fibroblasts
Granulation tissue

Red fox with snare injury, 3 weeks duration
Granulation Tissue (4 zones)

1) Necrotic debris and fibrin

2) Zone of macrophages and in-growing capillaries

3) Zone of capillary and fibroblast proliferation

4) Zone of fibrous connective tissue
Exuberant Granulation Tissue
“Proud Flesh”

- due to:
  - severe and prolonged tissue injury
  - loss of tissue framework (BM’s)
  - large amounts of exudate
- hypertrophic scar – precludes epithelization
Exuberant granulation tissue

- humans can also get exuberant granulation tissue
- one type is called keloid = excessive amount of scar tissue that grows beyond the boundaries of the original wound and does not regress.
Fibrosis and/or Exuberant Granulation Tissue
Consequences

- loss of functional parenchymal tissue
- alteration of physical properties of tissue
  - skin with scar more prone to tearing
  - pulmonary fibrosis decreases compliance requiring more respiratory effort.
Repair in Specific Tissues
HEALING - LIVER

- healing can vary from complete parenchymal regeneration to extensive scar formation
- depends on how much damage to the CT framework
• healing can vary from complete parenchymal regeneration to extensive scar formation
• depends on how much damage to the CT framework

Nodules of proliferating / regenerating hepatocytes (ie nodular hyperplasia, red areas); these nodules representing hepatocytes trying to regenerate in liver with damaged CT framework

Fibrosis (blue areas)
HEALING - KIDNEY

- variable regenerative capacity
  - cortical tubules – good
  - medullary tubules – minimal
  - glomeruli - none

- note, tubular regeneration requires intact BM’s
HEALING - KIDNEY

Normal

Chronic interstitial nephritis with fibrosis
HEALING - LUNG

- Alveoli with intact BM’s
  - regenerate by type 2 pneumocyte
- Unresolved exudate
  - organized by fibrosis
- Alveoli with damaged BM’s
  - fibrosis / scarring

Normal alveoli

Chronic inflammation in the lung:
1) chronic inflammatory cells (*)
2) Destruction of parenchyma, ie normal type 1 pneumocytes replaced by type 2 pneumocytes (arrowheads)
3) Replacement by fibrous connective tissue (black arrows)
Heart, cougar. Myocardial abscesses (mycotic infection)

Q: If cougar had lived, how would repair occur?

A: by fibrosis (myocardial scarring)
HEALING - BRAIN

- Fibroblasts and glial cells proliferate along vasculature
  - neurons are permanent cells – can’t proliferate / regenerate
  - astrocytes & fibroblasts proliferate – form fibrous network
  - microglial cells are phagocytic - clean up debris

Pig brain: Cerebellar abscess with associated cerebellar atrophy
BONE REPAIR - STAGES

Hematoma – 1-2 days
Inflammatory phase – up to 7 days
Reparative phase – wk 1 to many wks
Remodeling phase – several wks to months

soft callus = organizing fibrocellular tissue before calcification.

hard callus = hard bony tissue that develops around the ends of fractured bone during healing
BONE REPAIR - Callus
The End!

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