Ulcers, Tissue Repair & Healing

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What Happens when a tissue is injured?

• Hemorrhage and clot formation

• Acute Inflammation
  – Resolution
  – Healing by Repair
  – Remodeling
  – Abscess formation

• Chronic inflammation
  – Ulcer – e.g. of persistent chronic inflammation
  – Healing by fibrosis/scaring
Tissue response to injury. Repair after injury can occur by regeneration, which restores normal tissue, or by healing, which leads to scar formation and fibrosis.
Cell Injury

• Cells respond to external stimuli by 3 ways:
  • **Adaption** – response to prolonged stress.
  • **Cell injury** – undergo reversible (hydropic change) or irreversible cellular changes
  • **Cell death** – undergo cell death (necrosis) or apoptosis.
Cell Adaption

- **Atrophy** – reduction in organ size owing to cell loss or reduction in cell size.
- **Hypertrophy** – increase in organ size owing to constitutive cell enlargement.
- **Hyperplasia** – increase in organ size owing to increase in number of cells.
- **Metaplasia** – transformation of one tissue cell type to another.
- **Dysplasia** – premalignant transformation of normal epithelium
Cell Injury

• Causes of cell injury:
  • Oxygen deficiency (hypoxia)
  • Free radicals – superoxide, hydrogen peroxide, hydroxyl radical
  • Chemical or physical agents
  • Biological agents – cytokines, oncogenes
Cell Death

• Necrosis – morphological sign of cell death
• Several forms recognised – end result of inflammation
  – Coagulative necrosis
  – Liquefactive necrosis
  – Caseous necrosis
  – Fat necrosis
  – Fibrinoid necrosis
Types of Necrosis

- **Coagulative necrosis** – typically caused by ischaemia (infarct).
- **Liquefactive necrosis** – typically occur in brain or in an abscess.
- **Caseous necrosis** – typically occur in TB or fungal infections. Characterised by granular material surrounded by epitheloid & multinucleated giant cells.
- **Fat necrosis** – caused by trauma to adipose cells or release of lipolytic enzymes during disease states e.g. Acute pancreatitis.
- **Fibrinoid necrosis** – typically seen in arteries, arterioles or glomerular capillaries damaged by autoimmune diseases. Blood vessels impregnated by fibrin & serum proteins & appear magneta red in histological sections.
Acute Inflammation
Vascular events
Cellular events
Chemical mediators
Pathological types of acute inflammation

ACUTE INFLAMMATION
Inflammation & Repair

• Inflammation is the body’s reaction to injury

• Purpose of reaction is 2 fold:
  – Eliminate cause of injury
  – Initiate repair & healing of injured tissue

• Type of inflammation
  – Acute
  – Chronic
Acute Inflammation

• Classic signs of acute inflammation:
  – Rubor (redness)
  – Tumour (swelling)
  – Calor (heat)
  – Dolor (pain)
  – Functio laesa (impaired function)

• Inflammatory response consists of:
  – Vascular events
  – Cellular events

• Mediated by chemical mediators
Vascular Events in Acute Inflammation

**Active hyperemia**
- Transient arteriolar constriction followed by arteriolar dilation
- Influx of blood under increased pressure

**Oedema**
- Transudation of fluid into perivascular spaces
- Increased intravascular pressure + increased vessel wall permeability

**Stasis of blood in capillaries**
- Dilation of flooded venules
- Slowing of blood outflow
Vascular Events

**NORMAL**
- Extracellular matrix
- Occasional resident lymphocyte or macrophage
- Arteriole
- Venule

**INFLAMED**
- Edema expands extracellular matrix
- Deposition of fibrin and other plasma proteins
- Neutrophil emigration
- Arteriole dilation
- Expansion of capillary bed
- Venule dilation
- Increased blood flow

Ref: Robins Pathological Basis of Diseases, 7th Ed
BP & Plasma Colloid Osmotic Pressure Changes

Increased arteriole pressure, mean capillary pressure increases (due to arteriolar dilation). **Net effect = increased hydrostatic pressure**

Venous pressure increases, osmotic pressure reduced (due to protein leakage). **Net effect = decreased colloid osmotic pressure**
5 mechanisms of increased vascular permeability

Gaps due to endothelial contraction
- Venules
- Vasoactive mediators (histamine, leukotrienes, etc.)
- Most common
- Fast and short-lived (minutes)

Increased transcytosis
- Venules
- Vascular endothelium—derived growth factor

Direct injury
- Arterioles, capillaries, and venules
- Toxins, burns, chemicals
- Fast and may be long-lived (hours to days)

New blood vessel formation
- Sites of angiogenesis
- Persists until intercellular junctions form

Leukocyte-dependent injury
- Mostly venules
- Pulmonary capillaries
- Late response
- Long-lived (hours)
Cellular Events in Acute Inflammation

**Margination**
PMNs settle at side of vessel wall as blood flow slows

**Activation**
Inflammatory mediators trigger selectins & intergrins to appear on endothelial & PMN surfaces respectively

**Adhesion**
PMNs adhere to endothelial cells mediated by selectins & intergrins

**Transmigration** (diapedesis)
PMNs cross vessel wall & move into interstitial space

**Chemotaxis** (movement within ECM)
PMNs move toward infection in response to chemotactic factors (bacteria, compliment, chemokines, AA derivatives)

**Phagocytosis**
PMNs ingest bacteria & kill them.

**Repair & healing**
Macrophages move in to remove necrotic material. Initiate repair & healing process
Cellular Events

Ref: Robins Pathological Basis of Diseases, 7th Ed
Chemical Mediators

• Chemical mediators account for vascular & cellular events

• **Cell derived mediators**
  – Histamine
  – AA derivatives
    • Cyclooxygenase pathway
    • Lipoxygenase pathway

• **Plasma derived mediators**
  – Kinins
  – Coagulation proteins
  – Fibrinolytic proteins
  – Compliment components
Arachidonic Acid Derivatives - Eicosanoids

Cell membrane phospholipids

Phospholipases

Steroids inhibit

ARACHIDONIC ACID

HETEs

HPETEs

Other lipooxygenases

5-Lipoxygenase

5-HPETE

5-HETE

Leukotriene B₄

Chemotaxis

Vasoconstriction
Bronchospasm
Increased permeability

Leukotriene A₄ (LTA₄)

Leukotriene C₄ (LTC₄)

Leukotriene D₄ (LTD₄)

Leukotriene E₄ (LTE₄)

12-Lipoxygenase

Prostaglandin G₂ (PGG₂)

Prostaglandin H₂ (PGH₂)

Cyclooxygenase

COX-1 and COX-2 inhibitors,
aspirin, indomethacin inhibit

Prostacyclin
PGI₂

Causes vasodilation,
inhibits platelet aggregation

Thromboxane A₂
TXA₂

Causes vasoconstriction,
promotes platelet aggregation

Lipoxin A₄ (LXA₄)

Lipoxin B₄ (LXB₄)

Vasodilation
Inhibit neutrophil chemotaxis
Stimulate monocyte adhesion

PGD₂

Vasodilation
Potentiate edema

PGE₂

PGF₂α
Plasma Derived Mediators

- Kinins e.g. bradykinin
- Coagulation proteins e.g. fibrin, fibrin split products
- Fibrinolytic proteins e.g. plasmin
- Compliment

- These mediators are typically activated by \textbf{XIIa} (Hageman factor)
Plasma Derived Mediators

Cofactor = high-molecular-weight kininogen (HMWK)

Factor XII (Hageman factor)
Collagen, basement membrane, activated platelets

Factor XIIa

Kinin cascade
XIIa
Kallikrein
Prekallikrein

Bradykinin

Fibrinolytic system
Kallikrein

Plasminogen → Plasmin

Complement cascade
Plasmin

Fibrin
Fibrin-split products
Fibrinopeptides

Fibrinogen

Prothrombin (Factor II) → Thrombin (IIa)

Factor X → Xa

Factor XI → XIa

Factor VIII

Acute inflammation

Protease-activated receptors
Outcomes of Acute Inflammation

• **Resolution** – repair, regeneration, healing and remodeling
• **Abscess** - cavity filled with pus and walled off by fibrous tissue
• **Ulcer** – loss of surface epithelium & break in mucuosa
• **Fistula** – abnormal communication between two organs or between an organ and a surface
• **Scar formation** – distortion of structure and sometimes function
• **Conversion to chronic inflammation** – marked by replacement of neutrophils & monocytes with lymphocytes, plasma cells & macrophages.
CHRONIC INFLAMMATION

Inflammatory response
Vascular events
Cellular events
Pathological types of chronic inflammation
Outcome of Acute Inflammation

**ACUTE INFLAMMATION**
- Vascular changes
- Neutrophil recruitment
- Mediators

**RESOLUTION**
- Clearance of injurious stimuli
- Clearance of mediators and acute inflammatory cells
- Replacement of injured cells
- Normal function

**FIBROSIS**
- Loss of function

**INJURY**
- Infarction
- Bacterial infections
- Toxins
- Trauma

**CHRONIC INFLAMMATION**
- Angiogenesis
- Mononuclear cell infiltrate
- Fibrosis (scar)

**Progression**

**Healing**

**Pus formation (abscess)**

**Healing**
Chronic Inflammation

- Prolonged inflammation & mediated by cells that have longer lifespan than PMNs
  - Involves tissue destruction & repair

- Vascular response – similar to acute inflammation but include angiogenesis
  - Cellular events – mediated by macrophages, lymphocytes & plasma cells.
  - Eosinophils – respond to parasitic infections or allergic rxns (immune-mediated)
Factors affecting healing
Normal wound healing
Healing by primary intention
Healing by secondary intention
Abnormal wound healing
Overview of Repair

• Repair: the process to restore the destroyed cells and tissue by regenerating the same cell type and connective tissue

• Involves restoration of normal structure: ECM & connective tissue is intact.
  – Surviving parenchymal cells have ability to regenerate

• Requires cellular proliferation: mediated by growth factors
Overview of Repair

• Repair process involves:
  – Removal of debris
  – Granulation tissue formation
  – Scaring

• A complete restore or incomplete restore of injured tissue depends on
  – degree of injury (the original framework remains or not)
  – ability of regeneration of injured parenchymal cells
Outcome of Repair

• Regeneration of injured tissue by parenchymal cells of the same type
• Replacement by connective tissue (fibrosis), resulting in a scar
• In most cases tissue repair involves both of these two processes.
Type of cell & Wound Healing

- Continuously cycling labile cells (e.g., epidermis, GI tract epithelium)
- Chromosome duplication
- Check for DNA damage (G₁/S checkpoint)
- Restriction point
- Centrosome duplication
- Growth in mass
- Quiescent, stable cells (e.g., hepatocytes)
- G₀
- Permanent cells (e.g., neurons, cardiac myocytes)
- G₁
- G₂
- Check for damaged or unduplicated DNA (G₂/M checkpoint)
- Mitosis
- Cell division
- Cell cycle
Cell Type & Wound Healing

• **Cell types – according to cell cycle**
• **Labile cells**
  – Divide continuously
  – Organs derived from these cells heal completely
  – Skin, GIT mucosa
• **Quiescent Stable cells (facultative mitotic)**
  – Replaced by regeneration from remaining cells stimulated to enter cell cycle
  – Liver & kidneys
• **Permanent (post-mitotic) cells**
  – Cannot be replaced
  – Scar tissue laid down in their stead
  – Neurones, cardiac myocytes
Mechanisms regulating cell populations.

Cell numbers can be altered by increased or decreased rates of stem cell input, by cell death due to apoptosis, or by changes in the rates of proliferation or differentiation.
Differentiation pathways for pluripotent bone marrow stromal cells. Activation of key regulatory proteins by growth factors, cytokines, or matrix components leads to commitment of stem cells to differentiate into specific cellular lineages. Differentiation of myotubes requires the combined action of several factors (e.g., myoD, myogenin); fat cells require PPARγ, the osteogenic lineage requires CBFA1 (also known as RUNX2), cartilage formation requires Sox9, and endothelial cells require VEGF and FGF-2.
Differentiation of embryonic cells and generation of tissue cells by bone marrow precursors. During embryonic development the three germ layers-endoderm, mesoderm, and ectoderm-are formed, generating all tissues of the body. Adult stem cells localized in organs derived from these layers produce cells that are specific for the organs at which they reside. However, some adult bone marrow stem cells, in addition to producing the blood lineages (mesodermal derived), can also generate cells for tissues that originated from the endoderm and ectoderm (indicated by the red lines).
The Extracellular Matrix

• A dynamic, constantly, remodeling, macromolecular complex
  – Interstitial matrix
  – Basement membrane (BM)

• Major components
  – Collagens
  – Elastic fibers
  – Fibronectin
  – Laminin
  – Proteoglycans
Major components of the extracellular matrix (ECM), including collagens, proteoglycans, and adhesive glycoproteins. Both epithelial and mesenchymal cells (e.g., fibroblasts) interact with ECM via integrins. To simplify the diagram, many ECM components (e.g., elastin, fibrillin, hyaluronan, syndecan) are not included.
Steps in collagen synthesis
The Extracellular Matrix

• Roles of ECM
  – mechanical support for cell anchorage
  – determination of cell orientation (polarity)
  – control cell growth
  – maintenance of cell differentiation
  – scaffolding for tissue renewal
  – establishment of tissue microenvironments, storage and presentation of regulatory molecules
Definition - Healing

• Healing is a response to tissue injury, and represents an attempt by the organism to restore integrity to an injured tissue.

• It overlaps the inflammatory process, and it is only for didactic purposes that the two are discussed separately.
Wound Healing

• The orderly process by which a wound is eventually replaced by a scar

• Destruction of epithelium only is termed an erosion, and heals exclusively by regeneration

• If destruction of the basement membrane occurs (extracellular matrix), then a scar will form
Steps in Wound Healing

• Induction of an acute inflammatory response
• Regeneration of parenchymal cells
• Migration and proliferation of both parenchymal and connective tissue cells
• Synthesis of extracellular matrix proteins (collagen III)
• Remodeling
• Collagenization and maturation of wound
Wound Healing

• Contraction
  – Accounts for a reduction in size of the defect primarily by the action of myofibroblasts
  – This process produces faster healing, since only one-third to one-half of the original defect must be repaired
  – Myofibroblasts account for contraction, and represent an intermediate type of cell, between a fibroblast and a myocyte
Normal Wound Healing Process

• Skin wound healing can occur via 2 ways:
  • Healing by primary intention
    – Clean surgical wounds
  • Healing by secondary intention
    – Large gaping wounds
    – Infected wounds
Healing by Primary Intention

**Scab Formation**
Blood fills defect, coagulates forming meshwork of fibrin & fibronectin. PMNs infiltrate scab

**Formation of granulation tissue**
Macrophages remove debris & secrete GF stimulating angiogenesis, myofibroblasts, fibroblasts ingrowth

**Re-epithelisation**
Epithelium regenerates covering surface defect

**Collagen deposition**
ECM deposition. Initially collagen type III & later type I

**Normal tissue**
After 12 months

**Scar maturation**
Cross-linking of collagen. 80% normal tensile strength after 3 months

**Scar formation**
10% preoperative strength regained first week. Sutures can be removed
## Selected Growth Factors

<table>
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<tr>
<th>Growth Factor</th>
<th>Function</th>
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| PDGF. Synthesized by plts & other cells| Promote proliferative reposes of fibroblasts, smooth muscle cells. Requires other growth factors for effective function.  
• Chemotactic for fibroblasts & smooth muscle cells  
• Chemotactic for monocytes               |
| Epidermal growth factor                | Promote growth of endothelial cells, fibroblasts & epithelial cells      |
| Fibroblast growth factor               | Promote synthesize of ECM proteins by fibroblasts, endothelial cells, monocytes |
| Fibronectin                            | Chemotactic for fibroblasts & endothelial cells, links ECM components to cell-surface intergrins (intergrins mediate interactions between cells & ECM) |
| Transforming growth factors            | Growth inhibitor. Aid in modulation                                       |
Wound Healing by Secondary Intention

• More pronounced & prolonged inflammatory phase in which PMNs may persists for days
• More abundant granulation tissue
• Wound contraction by myofibroblasts to help draw margins of wound closer to one another
Healing

Skin ulcer
Acute inflammatory exudate at base
Mature epithelium
Re-epithelialization & granulation
Wound contraction
Chronic Ulcer

Example of ulcer: peptic ulcer
Factors that Influence Wound Healing

• Type, size, and location of the wound
• Vascular supply (diabetics heal poorly)
• Infection - delays wound healing and leads to more granulation tissue and scarring
• Movement - wounds over joints do not heal well due to traction
• Radiation - ionizing radiation is bad, UV is good
Factors that Influence Wound Healing

• Overall nutrition: vitamin and protein deficiencies lead to poor wound healing, especially vitamin C, which is involved in collagen synthesis

• Age: younger is definitely better!

• Hormones - corticosteroids drastically impair wound healing, because of their profound effect on inflammatory cells
Complications of Wound Healing

• Defective scar formation
• Contraction
• Poor healing and defective or weak scar formation
  – Dehiscence (separation of margins) or ulceration is usually due to:
    • Wound infection (common)
    • Malnutrition (scurvy - rare)
    • Hypoxia with ulceration, usually due to inadequate vascularity in a skin flap (common).
• Tension
Abnormal Wound Healing

- Excessive scar formation (keloid)
- Delayed wound healing
  - Infection
  - Mechanical factors (trauma, tension, foreign bodies)
  - Malnutrition, poor circulation or old age
  - Drugs e.g. corticosteroids, cytotoxic drugs
Excessive Scar Formation

• **Keloids** (hypertrophic scars) are the result of over-exuberant production of scar tissue, which is primarily composed of type III collagen.

• The cause is thought to be due to genetic factors, perhaps due to lack of the proper *metalloproteinases (collagenases)* to degrade type III collagen.
Contraction

• Excessive contraction of a wound is known as a **contracture**. They are a special problem in the treatment of extensive burns

• Several diseases of unknown cause are characterized by the formation of contractures — Peyronie disease of the penis
Tissue response to injury. Repair after injury can occur by regeneration, which restores normal tissue, or by healing, which leads to scar formation and fibrosis.
Repair response after injury

INJURY

Cellular and vascular response

Stimulus removed (acute injury)

- Parenchymal cell death (intact tissue framework)
- Superficial wounds
- Some inflammatory processes

REGENERATION
Restitution of normal structure
- Examples:
  - Liver regeneration after partial hepatectomy
  - Superficial skin wounds
  - Resorption of exudate in lobar pneumonia

HEALING
Scar formation; organization of exudate
- Examples:
  - Deep excisional wounds
  - Myocardium infarction

FIBROSIS
Tissue scar
- Examples:
  - Chronic inflammatory diseases (cirrhosis, chronic pancreatitis, pulmonary fibrosis)

Persistent tissue damage
Fibrosis in chronic inflammation

- Persistent stimulus (chronic inflammation)
  - Activation of macrophages and lymphocytes
    - Growth factors (PDGF, FGF, TGFβ)
      - Proliferation of fibroblasts, endothelial cells, and specialized fibrogenic cells
    - Cytokines (TNF, IL-1, IL-4, IL-13)
      - Increased collagen synthesis
    - Decreased metalloproteinase activity
      - Decreased collagen degradation

Fibrosis
REFERENCES
Robins Pathological Basis of Diseases 7th Ed.

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