Cellular and Molecular Basis of Diseases

Banchob Sripa
Professor, Department of Pathology
Faculty of Medicine, Khon Kaen University
Outlines

- Diseases and cause of diseases
- Acute Inflammation
  - Vascular changes and cellular events
  - Chemical mediators of inflammation
  - Systemic effects of inflammation
  - Outcome of acute inflammation
- Chronic inflammation
- Tissue repair & Angiogenesis
Disease – damage done by injury and host responses
Tissue Injury
- Trauma
- Ischemia
- Neoplasm
- Infectious agent (bacterium, virus, fungus, parasite)
- Foreign particle (e.g., asbestos)

Vasoactive Mediators
- Histamine
- Serotonin
- Bradykinin
- Anaphylatoxins
- Leukotrienes/prostaglandins
- Platelet activating factor

Increased vascular permeability

EDEMA

Production of Inflammatory Mediators

Chemotactic Factors
- C5a
- Lipoxygenase products: LTB₄
- Formylated peptides
- Lymphokines
- Monokines

Recruitment and stimulation of inflammatory cells

Acute Inflammation
- PMNs
- Platelets

Chronic Inflammation
- Macrophages
- Lymphocytes
- Plasma cells

Repair
Inflammation

- **3000 BC** - Signs of inflammation were described in Egyptian papyrus
- **Celsius** - a Roman writer listed 4 cardinal signs; *dolor* (pain), *tumor* (swelling), *rubor* (redness) and *calor* (heat)
- **Virchow** - add the 5th clinical sign- *lost of function* (*functio laesa*)
- **Several scientists** later described components of inflammation
Acute inflammation
**Inflammation**

- **Inflammation** - The reaction of blood vessels, leading to the accumulation of fluid and leukocytes in vascularized tissue.

- **Inflammation** is closely intertwined with the process of **repair**.

- **Inflammation** is fundamentally a **protective response**.

- **Inflammatory response** include plasma, circulating cells, blood vessels, cellular and extracellular connective tissue.
Acute inflammation is the immediate and early response to an injurious agent

- Alterations of vascular caliber → blood flow↑
- Structural changes in microvasculature leading to plasma proteins leakage
- Emigration of WBC from the vessels and their accumulation in the focus of injury
Acute inflammation

(a) Tissue damage

1. Chemicals such as histamine, kinins, prostaglandins, and leukotrienes (represented as blue dots) are released by damaged cells.

2. Blood clot forms.

3. Abscess starts to form (yellow area).

(b) Vasodilation and increased permeability of blood vessels.

Bacteria entering on knife

Epidermis

Dermis

Subcutaneous tissue

Blood vessel

Nerve
Acute inflammation

4. Margination—phagocytes stick to endothelium
5. Emigration—phagocytes squeeze between endothelial cells
6. Phagocytosis of invading bacteria

(c) Phagocyte migration and phagocytosis
- Scab
- Blood clot
- Regenerated epidermis (parenchyma)
- Regenerated dermis (stroma)

(d) Tissue repair
- Neutrophil
- Macrophage
Acute inflammation

Mediators of inflammation

**CELLULAR**
- Preformed mediators in secretory granules
  - Histamine
  - Serotonin
  - Lysosomal enzymes
- Newly synthesized
  - Prostaglandins
  - Leukotrienes
  - Platelet-activating factors
  - Activated oxygen species
  - Nitric oxide
  - Cytokines

**PLASMA**
- Factor XII (Hageman factor) activation
- Kinin system (bradykinin)
  - Coagulation / fibrinolysis system
- Complement activation
  - C3a
  - C5a
  - C5b
  - C5b-9 (membrane attack complex)

**SOURCE**
- Mast cells, basophils, platelets
- Platelets
- Neutrophils, macrophages
- All leukocytes, platelets, EC
- All leukocytes
- All leukocytes, EC
- All leukocytes
- Macrophages
- Lymphocytes, macrophages, EC
Acute inflammation

Arachidonic acid metabolites

HETE = Monohydroxyeicosatetraenoic acids

Figure 3-18
Generation of arachidonic acid metabolites and their roles in inflammation.
Acute inflammation

Complement activation

- **Alternative pathway**: Microbe
- **Classical pathway**: Antibody
- **Lectin pathway**: Mannose binding lectin

**C3b**: Phagocytosis
- Recognition of bound C3b by phagocyte C3b receptor
- Phagocytosis of microbe

**C3a**: Inflammation
- Recruitment and activation of leukocytes
- Destruction of microbes by leukocytes

**MAC**: Lysis of microbe
- Formation of membrane attack complex (MAC)
Acute inflammation

Chemotaxis & Leukocyte activation

- Exogenous source
  - Bacterial products
  - Amino acids & lipids
- Endogenous source
  - C5a
  - Leukotrience B4
  - Cytokines/chemokine (e.g. IL-8)
Acute inflammation

Adhesion & Migration
Acute inflammation

1. Recognition and Attachment
   Microbes bind to phagocyte receptors
   - Mannose receptor
   - Mac-1 integrin
   - Scavenger receptor

2. Engulfment
   Phagocyte membrane zips up around microbe
   Microbe ingested in phagosome

3. Killing and Degradation
   - INOS
   - Arginine
   - NO
   - Phagocyte oxidase
   - ROI
   - O₂
   - Killing of microbes by ROIs and NO
   - Killing of microbes by lysosomal enzymes in phagolysosome
   - Fusion of phagosome with lysosome
   - Phagolysosome
Activated oxygen species

- Superoxide (\(^{\bullet}O_2\)) - formed via NADPH oxidase
- Hydrogen peroxide (\(H_2O_2\)) - formed via spontaneous dismutation of superoxide
- Hypochlorous acid (HOCl) (Myeloperoxidase)
  - Probably the primary bactericidal agent in neutrophils
  - Myeloperoxidase converts \(H_2O_2\) into HOCl.
- Hydroxyl radical (\(^{\bullet}OH\))
# Tissue Injury by Inflammatory Cells

The relatively primitive and non-specific immune effects of polymorphonuclear leukocytes and macrophages upon invading microorganisms are also capable of damaging the host by the extracellular release of enzymes and activated oxygen species.

## Lysosomal enzymes

Since these enzymes are used to degrade microorganisms in lysosomes, obviously they could damage tissue in the extracellular environment.

## Activated oxygen species

- Can migrate through intact plasma membranes
- Initiate lipid peroxidation
- React with DNA
- Oxidize sulfhydryl groups of proteins
- Degrade extracellular matrix components
Acute inflammation

Systemic effects

- Leukocytosis: may be neutrophils (Bact.), eosinophils (Parasite), or lymphocytes (Virus)
- Leukopenia: some viral infection
- Fever
  - Exogenous pyrogen: bacteria
  - Endogenous pyrogens: IL-1 and TNF –α
- Acute phase reactants - non-specific elevation of many serum proteins
Acute inflammation

Outcomes of acute Inflammation

- Resolution
  - Viral hepatitis
  - Pneumonia
- Abscess formation
- Healing
- Chronic inflammation
Acute inflammation
Chronic inflammation

Lymphocyte-macrophage interaction

Histologic features

- Mononuclear cells – macrophages, lymphocytes, and plasma cells
- Tissue destruction by ongoing inflammation, thought to be due to cytokines produced locally by the mononuclear cells
- Attempts at healing, including fibroblasts and fibrosis
Chronic inflammation
Chronic inflammation

Granulomatous inflammation
- Granuloma formation
- Modified macrophages (epithelioid cell)
- Giant cells
Repair & Regeneration

Normal Cell Types

- **Labile cells**
  - epithelium
  - haematopoietic cells

- **Stable cells**
  - liver
  - smooth muscle

- **Permanent cells**
  - neuron
Repair

NORMAL HOMEOSTASIS
(balance of proliferation and apoptosis)

INJURY

REGENERATION

Renewing tissues
- Epidermis, GI tract epithelium, hematopoietic system
- Compensatory growth of liver and kidney

Stable tissues

HEALING

Wound
- Wound healing, scar formation

Chronic inflammation
- Fibrosis

© Elsevier 2005
- **Angiogenesis** - New vessels budding from old ones
- **Fibrosis**, consisting of emigration and proliferation of fibroblasts and deposition of ECM
- **Scar remodeling**, tightly regulated by proteases and protease inhibitors
Repair

Granulation tissues

- A repair phenomenon
- Loops of capillaries supported by myofibroblasts
- Inflammatory cells
**Vasculogenesis** – development of vascular network during embryogenesis

**Angiogenesis** – neovascularization from pre-existing vessels

---

**Angiogenesis**

1. Proteolysis of ECM
2. Migration and chemotaxis
3. Proliferation
4. Lumen formation, maturation, and inhibition of growth
5. Increased permeability through gaps and transcytosis

**Vascular祖源性**

- VEGF → VEGF-R2 (proliferation)
- VEGF → VEGF-R1 (tube formation)

**Angioblasts**

Induction

**Mature vessels**

- Ang1 → Tie2

**Angiogenesis**

- VEGF → VEGF-R1/2
- Ang2 → Tie2 (inhibitory signal)
EPCs = Endothelial progenitor cells
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
Summary

● Diseases and cause of diseases

● Acute Inflammation
  ● Vascular changes and cellular events
  ● Chemical mediators of inflammation
  ● Systemic effects of inflammation
  ● Outcome of acute inflammation

● Chronic inflammation

● Tissue repair & Angiogenesis