Acute and chronic inflammation

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Outline

• Introduction to inflammation
• Acute inflammation
  – Clinical examples of acute inflammation
• Chronic inflammation
  – Clinical examples of chronic inflammation
• Leukocyte activation and mechanisms of microbial killing
• Chemical mediators of inflammation
Inflammation
Inflammare
(Latin: to set on fire)
Nobel Prize 1908 for his work on phagocytes. He discovered the process of phagocytosis (ingestion of rose thorns by amebocytes of starfish larvae as a major component of inflammation).

Metchnikoff shared the Nobel prize with Paul Erlich, who recognized the role of serum factors, mainly antibodies, as a critical factor in the defense against microorganisms.
Inflammation

• A protective response involving host cells, blood vessels and proteins

  – Goals are:
    • eliminate the initial cause of cell injury
    • Remove necrotic cells and tissue
    • Initiate the process of repair

• Also a potentially harmful process

  – Components of inflammation that are capable of destroying microbes can also injury bystander normal tissue
Inflammation

• Components of the inflammatory process include white blood cells and plasma proteins
  – Normally present in the blood
  – The inflammatory reaction’s goal is to bring these to the site of infection and/or tissue damage

• Inflammation is induced by chemical mediators produced by damaged host cells
  – Cytokines and other mediators

• Inflammation is normally controlled and self-limited
Excess inflammatory reactions

- Inappropriate inflammatory response when there are no foreign substances to fight off leads to autoimmunity

- Inflammatory process must be **tightly regulated** by the immune system to avoid excessive tissue damage and spillover to normal tissue
Cardinal signs of inflammation

• Heat (calor)
• Redness (rubor)
• Swelling (tumor)
• Pain (dolor)
  – Celsus, *De Medicina*
  – Roman encyclopedia of medicine, >2000 years ago
• Loss of function
  – Rudolf Virchow (“father of modern pathology”)
  – Late 19th century

*Cellulitis*: Severe bilateral inflammation and swelling of the legs
Cells
Platelets
Granulocytes (PMNs, Mast, etc)
Monocyte/Macrophages
Lymphocytes
Fibroblasts

Proteins
Complement, Pentraxins, MBL, Ficolins
Coagulation
Kininogens
Proteoglycans
Cells involved in inflammation

- Vessel
- Many Erythrocytes
- Platelet
- Immature Band Neutrophil
- Lymphocyte
- Mature Segmented Neutrophil (PMN)
- Eosinophil
- Basophil
- Monocyte
- Vasoactive mediators: histamine, bradykinin, leukotriens
- Endothelial Cell
- Endothelial gaps
- Increased permeability
- Mast Cells
- Macrophage
The components of acute and chronic inflammatory responses and their principal functions. The roles of these cells and molecules in inflammation are described in this chapter.
## Acute vs. Chronic inflammation

### Table 2–1
Features of Acute and Chronic Inflammation

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Acute inflammation
Stimuli for Acute Inflammation

- **Infections** (bacterial, viral, fungal, parasitic) & microbial toxins
- **Tissue necrosis**: ischemia, trauma, physical or chemical injury (e.g., thermal injury; irradiation; some environmental chemicals)
- **Foreign bodies** (splinters, dirt, sutures)
- **Immune reactions** (aka hypersensitivity reactions)
Acute inflammation

• Main components:
  – Vascular changes
    • Vasodilation
    • Vascular permeability
    • Increased adhesion of white blood cells
  – Cellular events
    • Cellular recruitment and activation of neutrophils (polymorphonuclear leukocytes)
Acute Inflammation

1. Vasodilation:
   - The reactions of blood vessels
   - Alterations in vascular caliber (diameter)
     - Causes decrease in blood pressure

2. Vascular leakage and edema:
   - The accumulation of fluid and proteins of plasma in the extravascular tissues (interstitium)

3. Leukocyte emigration to extravascular tissues
   A. Margination and rolling
   B. Activation and adhesion
   C. Transmigration
1. Vasodilation

• Change in vessel flow
  – NO, histamine $\rightarrow$ vascular smooth muscle $\rightarrow$ vasodilation $\rightarrow$ increased blood flow (heat & redness)
  – Stasis: slowed blood flow, hyperviscosity
  – Margination of circulating leukocytes & endothelial activation

• Followed by increased permeability of the vasculature
  – Formation of an early transudate (protein-poor filtrate of plasma) gives way to exudate (protein-rich filtrate) into extracellular tissues
2. Vascular leakage and edema

• Change in vessel permeability
  – Histamines, bradykinins, leukotrienes cause endothelial cell contraction that widens intercellular gaps of venules
  – Outpouring of protein-rich fluid (exudate) into the extracellular tissues leads to:
    • Reduction of intravascular osmotic pressure
    • Increase in extravascular/interstitial osmotic pressure
  – Increase of interstitial osmotic pressure leads to edema (water and ions)
A. NORMAL

Increased hydrostatic pressure (venous outflow obstruction, e.g., congestive heart failure)

B. TRANSUDATE
(low protein content, few cells)

Decreased colloid osmotic pressure (decreased protein synthesis, e.g., liver disease; increased protein loss, e.g., kidney disease)

C. EXUDATE
(high protein content, and may contain some white and red cells)

Fluid and protein leakage
Vasodilation and stasis
Increased interendothelial spaces

Inflammation
Transient Perturbation of Endothelial Integrity Induced by Natural Antibodies and Complement

By Soheyla Saadi* and Jeffrey L. Platt†

From the *Department of Surgery, and the †Department of Pediatrics and Immunology, Duke University, Durham, North Carolina 27710

Gap formation in monolayers of porcine endothelial cells induced by the combination of antibody and complement
3. Leukocyte emigration to extravascular tissues

Leukocytes leave the vasculature through the following sequence of events:
A. margination and rolling
B. activation and adhesion
C. transmigration
A. Margination and Rolling

- Fluid (exudate) leaves the vessel, leukocytes "marginate" along the endothelial surface.
- In the process of "rolling" individual and then rows of leukocytes tumble slowly along the endothelium, adhere through surface adhesion molecules on endothelial cells and their complementary ligands on leukocytes.
B. Activation and Adhesion

Adhesion is mediated by selectin family (adhesion molecules)

- **E-selectin** (endothelium)
- **P-selectin** (platelets, endothelium)
- **L-selectin** (leukocytes)

Selectins that are upregulated on endothelium by cytokines (TNF-α, IL-1) at injury sites bind leukocyte surface molecules (i.e., **Sialyl-Lewis X modified GP, P-selectin glycoprotein ligand (PSGL-1), integrins, CD34**)
C. Transmigration (diapedesis)

- Occurs after firm adhesion within the system of venules and capillaries via **PECAM -1 (CD31)** (platelet-endothelial cell adhesion molecule) on endothelial cells, neutrophils, monocytes/macrophages, lymphocytes.

- Upregulation of endothelial cell ligands (integrins) for adhesion molecules results in activation/adhesion of different populations of leukocytes (monocytes, lymphocytes, etc).
The multistep process of leukocyte migration through blood vessels

Marigination (tethering)

Leukocyte
Sialyl-Lewis X-modified glycoprotein
Integrin (low affinity state)

Rolling

Integrin activation by chemokines

Stable adhesion

Migration through endothelium

Chemokines

Leukocyte activation

Integrin (high-affinity state)

Adhesion

PECAM-1 (CD31)

EC activation

CD34

P-selectin
E-selectin

Proteoglycan

Integrin ligand (ICAM-1)

Extravascular space

Stimulus

Cytokines (TNF, IL-1)

Microbes

Macrophage with microbes

Chemotaxis

Fibrin and fibronectin (extracellular matrix)
The multistep process of leukocyte migration through blood vessels
Clinical Examples of Acute Inflammation
Acute skin inflammation

- skin reacts to harmful stimuli such as pathogens, damaged cells, or irritants.

- Inflammation helps get rid of these harmful stimuli and initiates the skin tissue's healing process.

- without inflammation, the skin will not heal.
Time course of inflammatory cell infiltration in the skin

2h  
6h  
48h
1. **Exudate** leaves the vessel

2. Increase of interstitial osmotic pressure

3. Accumulation of PMNs, then Mono/Mac
Acute inflammation: skin blister
Acute Inflammation: Appendicitis

(normal)

(inflamed)
Acute Inflammation: Prostatitis

Marked neutrophilic infiltrate within and around glands. Some glands are partially destroyed.
Acute inflammation: bacterial bronchopneumonia

Figure 2-13: Purulent inflammation with abscess formation. A. Multiple bacterial abscesses in the lung (arrows) in a case of bronchopneumonia. B. The abscess contains neutrophils and cellular debris and is surrounded by congested blood vessels.
Acute Inflammation: Bacterial Pneumonia
Acute Inflammation: Bacterial Pneumonia
Acute inflammation: chronic gastric ulcer

Chronic ulcer with an acute inflammatory exudate at the base

Robbins Basic Pathology, 9th Ed.
Outcomes of acute inflammation

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

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

**PROGRESSION**

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

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

**INJURY**
- Viral infections
- Chronic infections
- Persistent injury
- Autoimmune diseases

**FIBROSIS**
- Loss of function

**PUS FORMATION (ABSCESS)**
Chronic inflammation
Features of chronic inflammation

• Chronic inflammation = long duration

• Components:
  – Lymphocyte, plasma cell, macrophage (mononuclear cell) infiltration
  – Tissue destruction by inflammatory cells
  – Repair with fibrosis and angiogenesis (new vessel formation)
# Acute vs. Chronic inflammation

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Robbins Basic Pathology, 9th Ed.
Circulating monocyte

Adherent

Emigrating

Tissue macrophage

Activated macrophage

Activated T cell

NON IMMUNE ACTIVATION (endotoxin, fibronectin, chemical mediators)

Cytokine (IFN-γ)

Tissue injury
- Toxic oxygen metabolites
- Proteases
- Neutrophil chemotactic factors
- Coagulation factors
- AA metabolites
- Nitric oxide

Fibrosis
- Growth factors (PDGF, FGF, TGFβ)
- Fibrogenic cytokines
- Angiogenesis factors (FGF)
- "Remodeling" collagenesis
Causes of chronic inflammation

• **Persistent** injury or infection
  – Ulcer, tuberculosis

• **Prolonged** exposure to a toxic agent
  – Pulmonary silicosis (silica in the lung)

• **Autoimmune disease**—self-perpetuating immune reaction that results in tissue damage and inflammation
  – Rheumatoid arthritis
  – Systemic lupus erythematosus
  – Multiple sclerosis
Diseases with chronic inflammation
Clinical examples of chronic inflammation
Chronic inflammation: tuberculous granuloma

Features:
1. Central necrosis
2. Epithelioid macrophages
3. Langhans-type giant cells
4. Peripheral lymphocytes
Chronic inflammation: chronic pancreatitis with fibrosis

Chronic inflammation: pulmonary silicosis

http://radiology.rsna.org/
Rheumatoid Arthritis

- chronic, progressive inflammatory disorder
- caused by the **autoimmune** reactions
- attacks the small synovial joints of the hands and feet and can cause synovitis and erosion of the cartilage of the joints
Inflammation of the skin caused by gout (form of arthritis): characterized by swelling and a smooth appearance of the skin caused by hyperuricemia.

- Hyperuricemia is an excess of uric acid in the blood.
- Gout develops when tiny crystals of urate are deposited on the joints.
- Hyperuricemia may occur without gout or any kidney related problems. This can later lead to further damage of the joints, decreased kidney function and later kidney stones.
Fat cells also produce inflammation molecules...
Leukocyte activation and mechanisms of microbial killing
Receptors involved in leukocyte activation

1. Toll-like receptors (TLRs)
2. Different seven-transmembrane G-protein-coupled receptors
3. Receptors for cytokines (e.g., IFN-γR)
4. Opsonins and their receptors
   - Antibodies (specific opsonins recognized by FcγRs)
   - Complement (mainly CR1 that recognizes breakdown products of C3 by either the classical or the alternative pathway)
   - Plasma “early activation proteins”: C-reactive protein (CRP), Serum amyloid protein (SAP), fibronectin, fibrinogen; lectins: mannose binding lectin (MBL)
Cytokines & Chemokines

**Cytokines**
- small proteins that modify the interactions between cells (15-30 kD)
- produced by activated lymphocytes and macrophages, also by endothelium, epithelium, connective tissue

**Chemokines**
- small proteins (8-10 kD) that act primarily as chemoattractants for specific types of leukocytes (chemotaxis)
Leukocyte activation

Recognition of microbes, mediators

Microbe

N-formyl-methionyl peptides

Chemokines

Lipid mediators

G-protein coupled receptors

Microbe

LPS

Toll-like receptor

Cytokines (e.g., IFN-γ)

CD14

Phagocytic receptor

Cellular response

Cytoskeletal changes, signal transduction

Production of mediators (e.g., arachidonic acid metabolites, cytokines)

Production of reactive oxygen species (ROS); lysosomal enzymes

Phagocytosis of microbe into phagosome

Functional outcomes

Increased integrin avidity

Adhesion to endothelium

Chemotaxis

Migration into tissues

Amplification of the inflammatory reaction

Microbicidal activity of leukocytes

Killing of microbes

Robbins Basic Pathology, 9th Ed.
Phagocytosis

1. RECOGNITION AND ATTACHMENT
   Microbes bind to phagocyte receptors

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

3. KILLING AND DEGRADATION
   Degradation of microbes by lysosomal enzymes in phagolysosome
   Killing of microbes by ROS and NO

Figure 2–8

Robbins Basic Pathology, 9th Ed.
Neutrophil extracellular traps (NETs)

- Extracellular fibrillar networks that are produced by neutrophils in response to infectious pathogens and inflammatory mediators
  - contain a framework of **nuclear chromatin** with embedded granule proteins, such as **antimicrobial peptides** and **enzymes**
Chemical mediators of inflammation
Chemical mediators

• **Source** of chemical mediators:
  – May be produced locally by cells at the site of inflammation
  – may be derived from circulating inactive precursors (typically synthesized by the liver) that are activated at the site of inflammation

• **Cell-derived mediators:**
  – normally sequestered in intracellular granules
  – rapidly secreted upon cellular activation or are synthesized de novo in response to a stimulus

• **Plasma protein–derived mediators:**
  – complement proteins, kinins
  – circulate in an inactive form
  – typically undergo proteolytic cleavage to acquire their biologic activities.
Chemical mediators

**Preformed mediators in secretory granules**
- Histamine
- Serotonin
- Prostaglandins
- Leukotrienes
- Platelet-activating factor
- Reactive oxygen species
- Nitric oxide
- Cytokines
- Neuropeptides

**Cell-derived source**
- Mast cells, basophils, platelets
- Platelets
- All leukocytes, mast cells
- All leukocytes, mast cells
- All leukocytes
- All leukocytes, EC
- All leukocytes
- Macrophages, EC
- Macrophages, lymphocytes, EC, mast cells
- Leukocytes, nerve fibers

**Plasma protein-derived**
- C3a, C5a, C3b, C5b-9 (membrane attack complex)
- Complement activation
- Factor XII (Hageman factor) activation
- Kinin system (bradykinin)
- Coagulation / fibrinolysis system

Figure 2-15 Mediators of inflammation. The principal cell-derived and plasma protein mediators are shown. EC, endothelial cells.
Chemical mediators

BLOOD
- Monocyte
  - VAL-4
  - VCAM-1
- Neutrophil
  - IL-8
  - PSGL-1
  - P-selectin
- Lymphocyte
  - LFA-1
  - ICAM-1

TISSUES
- Mast cell
  - C3a, C5a
  - C5b67
- Bacteria
  - Complement activation
- Endothelial damage
- Activated macrophage
  - IL-1, IL-6, TNF-α
  - Prostaglandins
  - Leukotrienes
- Chemokines
- Chemotaxis
- Plasmin
- Fibrin
- Fibrinopeptides
- Bradykinin

http://wenliang.myweb.uga.edu/
Mechanisms of increasing leukocyte-endothelial adhesion

1. Redistribution of P-selectin & vWF
2. Cytokine activation of endothelium
3. Increased binding avidity of integrins (adhesion molecules) expressed by leukocytes
Mechanisms of increasing leukocyte-endothelial adhesion:
1. Redistribution of P-selectin and von Willebrand factor (vWF) stimulated by complement, histamine and thrombin.
Mechanisms of increasing leukocyte-endothelial adhesion

2. CYTOKINE INDUCTION OF ENDOTHELIAL ADHESION MOLECULES (E-selectin or ICAM-1)

Neutrophil

Cytokines → ESL-1, P-SGL-1, integrins, Complementary adhesion molecules

IL-1, TNF, Complement

Endothelial Cell

E, P-selectin, ICAM-1 Adhesion molecules
Mechanisms of increasing leukocyte-endothelial adhesion

3. INCREASED AVIDITY OF INTEGRINS

Chemokine
Integrin in low avidity stage
Chemokines
Complement C5a
Platelet-activating factor

High avidity
Strong interaction with adhesion molecule on EC
Important points

• Know the 5 **cardinal signs** of inflammation
• Know the main features of **acute vs chronic** inflammation and the predominant **cell types** in each
• Know some clinical examples of acute and chronic inflammation
• Know the **stages of immune cell emigration** from the blood vessels
• Understand the basics of **immune cell activation** and **chemical mediators**
Recommended books

• Robbins Basic Pathology, Ninth Edition
  – Vinay Kumar, Abul K. Abbas, and Jon C. Aster