Path 203 – Principles of Immunology
Lecture for undergraduate studies - Week 3b

Mechanisms of innate immunity

Inflammation

- lnflammation or inflammatory response is defined as the biological response of the immune system especially vascular tissues to harmful stimuli, such as microorganisms or other foreign substances.
- It occurs when tissues are injured by microbes, trauma, toxins, heat, or any other cause and hence is the body's normal protective response against infection or injury.
  The aims and purposes of the inflammatory reaction are:

1. To localize the foreign agent or the injury to its site of entry or development.
2. To destroy the foreign agent or to remove its fragments and to clean the damage caused by an injury.
3. To initiate regeneration of tissue that has been destroyed by injury.
4. To repair the damage done and to fill up any gaps in the tissues by a scar.

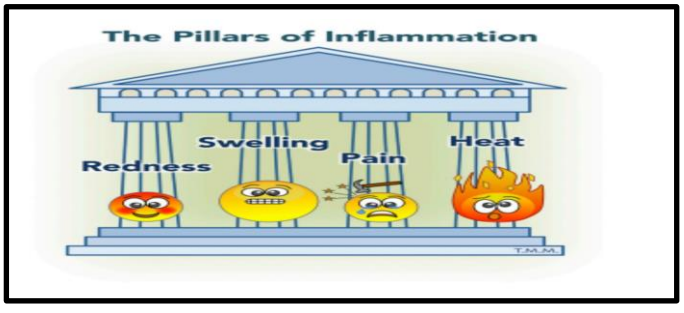
The steps of the inflammatory response can be remembered as the five Reactions:

(1) Recognition of the injurious agent,
(2) Recruitment of leukocytes,
(3) Removal of the agent,
(4) Regulation (control) of the response
(5) Resolution (repair).

Epithelial cells, tissue macrophages and dendritic cells, leukocytes, and other cell types express receptors that sense the presence of microbes and damage. Circulating proteins recognize microbes that have entered the blood. The outcome of acute inflammation is either elimination of the noxious stimulus followed by decline of the reaction and repair of the damaged tissue, or persistent injury resulting in chronic inflammation

Five cardinal signs of inflammation

- rubor (redness)
- calor (heat),
- tumor (swelling)
- dolor (pain)
- Loss of function



Who ignites the first spark of inflammation?

Four important events occur during an inflammatory response to promote these aims (figure 5.1)

1. **Vasodilation** causes increased blood flow to the area, increasing the supply of cells and factors. chemical Mediator of vasodialation Histamine, Bradykinin, Complement (C3a, C5a), Leukotrienes (LTC_4, LTD_4), Prostaglandins (PGI_2, PGE_2, PGD_2, PGF_2)
2. **Activation of endothelial** cells lining the blood vessels causes increased expression of adhesion molecules, making the endothelium more 'sticky' to white blood cells so that blood cells can adhere more strongly to the endothelium, thereby promoting the migration of leukocytes from the blood into the tissue.
3. **Increased vascular permeability** makes it easier for cells and proteins to pass through the blood vessel walls and enter the tissue.
4. **Chemotactic factors** are produced that attract cells into the tissue from the bloodstream. All of these events are controlled by factors that either are produced by cells involved in the inflammatory response or enter the site of inflammation from the blood.

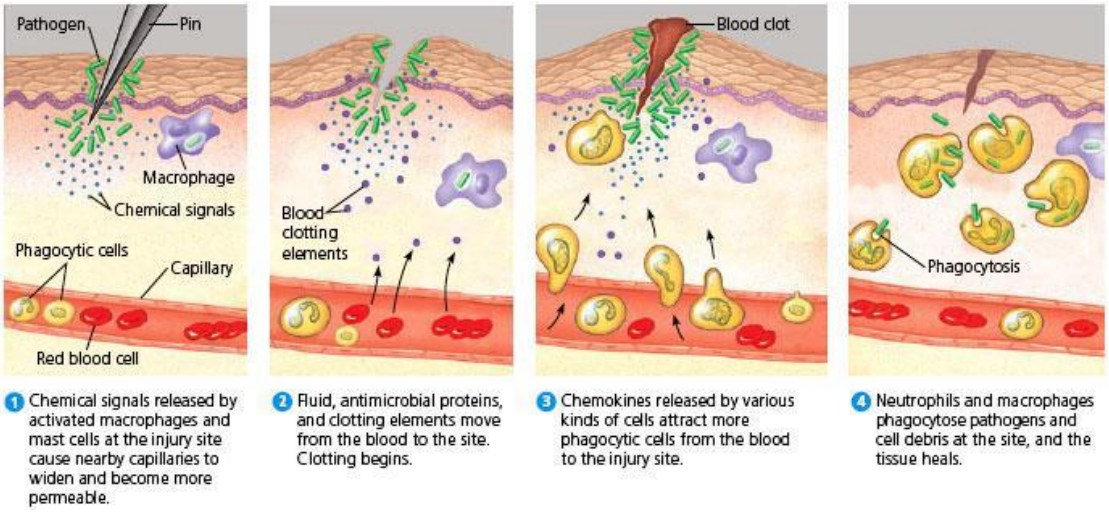
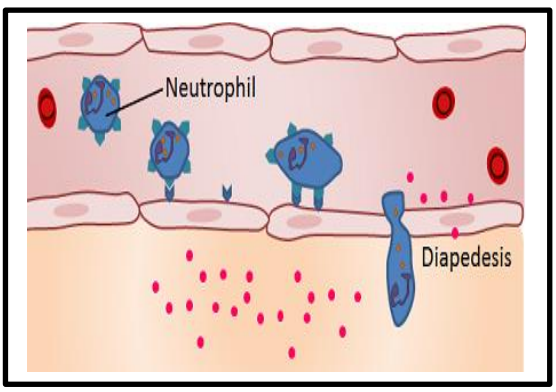


Figure 5.1 Steps of inflammation

Mediators of Inflammation

1. generated from cells or plasma proteins
   2. produced in response to various stimuli
   3. can stimulate release of other mediators
   4. vary in range of cellular targets
   5. short half-life



Mechanism	Mediators
Mast cell degranulation	Complement (C3a, C5a)
Chemotaxis	Interleukins (IL-8), PAF, Complement (C5a), Histamine
Lysosomal granule release	Complement (C5a), Interleukins (IL-8), PAF
Phagocytosis	Complement (C3b)
Pain	Prostaglandins (PGE_2), Bradykinin, Histamine
Fever	Interleukins (IL-1, IL-6), TNF-α, Prostaglandins (PGE_2)

Table 1 – Chemical Mediators in Acute Inflammation

The acute inflammation

Three major components of acute inflammation

1. Vascular dilatation (vasodilation) leads to increased blood flow, erythema, induced by histamine and nitric oxide (NO)
2. Microvasculature changes permit plasma proteins and WBCs to leave circulation
3. WBC emigration, accumulation at injury site, activation.

Termination of acute inflammation

1. rapid mediator production
2. short half-life
3. rapid degradation

Inflammation stop signals

1. switch to anti-inflammatory leukotrienes
2. anti-inflammatory cytokines: TGF-B, IL-10
3. resolves, protections'
4. cholinergic discharge inhibits TNF in macrophages

Following the process of acute inflammation, there are several possible results:

- Complete resolution – with total repair and destruction of the insult
- Fibrosis and scar formation – occurs in cases of significant inflammation
- Chronic inflammation – from a persisting insult
- Formation of an abscess
  - An abscess is a localised collection of pus surrounded by granulation tissue. Pus contains necrotic tissue with suspended dead and viable neutrophils and dead pathogens. It forms when the primary insult is a pyogenic bacterium and extensive tissue necrosis occurs.
  - The initial inflammatory exudate forces the tissue apart, leaving a centre of necrotic tissue with the neutrophils and pathogens. Over time, the acute inflammation will cease and, if not surgically drained, the abscess will be replaced by scar tissue.
  - An abscess can be a source for systemic dissemination of a pathogen, with the abscess acting as a harbour for the infection. It can also cause continually rising pressures within the tissue, resulting in pain and destruction of local structures.

IL-6 has a potent effect on hepatocytes, stimulating them to produce a

·series of proteins called acute phase proteins (APPs)

Acute phase proteins are found in the serum at basal (background) levels in healthy normal individuals but rise in concentration following stimulation of the liver. They can be divided into two categories based on the degree to which they increase. The concentration of some acute phase -proteins increases only 1.5- to 5-fold while that of others increases 100 .to 1000-fold

APPs that increase 1.5- to 5-fold

Fibrinogen. This is involved in clotting and the generation of • fibrinopeptides.• Haptoglobulin. This protein binds to iron-containing hemoglobin and reduces the concentration of iron that many bacteria require for their .metabolism, thereby reducing bacterial growth

,Complement component C3. This can be cleaved to generate C3a • which activates mast cells, and C3b, which helps phagocytes recognize . pathogens

Mannose-binding protein (MBP). MBP is able to bind to mannose • containing sugars on the surface of pathogens and also helps Phagocytes recognize pathogens

APPs that increase 100- to 1000-fold

Serum amyloid A (SAA). This protein inhibits fever and platelet • activation. As such, it provides an important negative feedback control .looptypical of that seen in many physiological systems

,C-reactive protein (CRP). This protein binds to phosphoryl choline • which is found on the surface of a variety of bacteria, fungi and parasites and is exposed in damaged cells. As described below, it helps

The acute phase proteins provide .

,additional factors that help in the elimination of infectious agents

especially extracellular dwelling bacteria, yeasts and parasites. Three

importantAPPs are CRP, C3b and MBP, which can act as opsonins to

help phagocytes recognize pathogens.

Chronic inflammation

Inflammation of prolonged duration (weeks or months) in which inflammation, tissue injury, and attempts at repair coexist, in varying combinations.

Chronic inflammation examples

Rheumatoid arthritis, atherosclerosis, tuberculosis, pulmonary fibrosis

Causes of chronic inflammation

1. Persistent infections, difficult to eradicate (mycobacteria, virus, fungi, parasites), delayed hypersensitivity, granulomatous
2. Immune-mediated inflammatory diseases (RA, IBD)
3. Prolonged exposure to toxic agents (silicosis, lipid = atherosclerosis)

Chronic inflammation is characterized by

2. Infiltration with mononuclear cells
3. Tissue destruction
4. Healing by connective tissue replacement of damaged tissue, angiogenesis and fibrosis

Table 1: Characteristics of Acute versus Chronic Inflammation

	Acute Inflammation	Chronic Inflammation
Cells	Infection: Neutrophils. Allergy: eosinophils, mast cells	Macrophages, lymphocytes
Chemical Mediators	Complement, kinins, prostaglandins, leukotrienes, cytokines (Interleukin 1, Interleukin 6) from various immune cells, interferon-gamma from T cells	Cytokines from macrophages and T lymphocytes

	Acute Inflammation	Chronic Inflammation
Lesion	Rash, pus, abscess	Rash, fibrosis, granuloma
Clinical Examples	Abscesses (brain; skin), allergic reaction (anaphylaxis)	Autoimmune conditions (lupus; rheumatoid arthritis), cystic fibrosis