Objectives: After learning, students should be able to describe and discuss in the topics of…

1. Inflammation
2. Acute inflammation
3. Morphological patterns of acute inflammation
4. Chemical mediators and regulators of inflammation
5. Chronic inflammation
6. Systemic effects of inflammation

Inflammation

- It is a defensive host response to foreign invaders and necrotic tissues.
- To eliminate the initial cause of cell injury and necrotic tissues
- To initiate the process of tissue repair
- Two types of inflammation--- acute inflammation and chronic inflammation
Features of acute and chronic inflammation

<table>
<thead>
<tr>
<th>Feature</th>
<th>Acute inflammation</th>
<th>Chronic inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Fast: minutes or hours</td>
<td>Slow: days</td>
</tr>
<tr>
<td>Cellular infiltrate</td>
<td>Mainly neutrophils</td>
<td>Monocytes/macrophages and lymphocytes</td>
</tr>
<tr>
<td>Tissue injury, fibrosis</td>
<td>Usually mild and self-limited</td>
<td>Often severe and progressive</td>
</tr>
<tr>
<td>Local and systemic signs</td>
<td>Prominent</td>
<td>Less prominent; may be subtle</td>
</tr>
</tbody>
</table>

(Modified from Kumar et al, 2013)

- Inflammation is induced by chemical mediators.
- Macrophages, dendritic cells, mast cells and plasma cells secrete molecules (cytokines, and other mediators) that induce and regulate the subsequent inflammatory response.
- The mediators promote the efflux of plasma and the recruitment of circulating leukocytes to sites of injury.
- The recruited leukocytes are activated and they try to remove the offending agent by phagocytosis.
- Side effect of the activation of leukocytes may be damage to normal host tissues.

The external manifestations of inflammation

- Calor (Heat)
  - Rubor (Redness)
  - Tumor (Swelling)
  - Dolor (Pain)
  - Functio laesa (Loss of function)

(http://inflam.jst.go.jp/en/illust/)
Acute inflammation

- The response rapidly delivers leukocytes and plasma proteins to sites of injury.
- Once there, leukocytes clear the invaders and begin the process of digesting and getting rid of necrotic tissues.
- Acute inflammation has two major components:
  - Vascular changes
  - Cellular events

The stimuli for acute inflammation

- Infections---most common and medically important causes of inflammation
- Trauma and various physical and chemical agents
- Tissue necrosis
- Foreign bodies
- Immune reaction---hypersensitivity reaction

Leukocyte infiltrates in inflammatory reactions

1. Vascular dilation and increased blood flow---erythema and warmth
2. Extravasation of plasma fluid and proteins---edema
3. Leukocyte emigration and accumulation---mainly neutrophils

(Kumar et al, 2009)

(Kumar et al, 2013)
Vascular changes

- The main vascular reaction of acute inflammation are increased blood flow, vasodilation, and increased vascular permeability.
- Increasing vascular permeability--- the movement of protein-rich fluid (transudate, exudate) and blood cells into the extravascular tissues.
- The changes in blood vessels are initiated rapidly after infection or injury.

Cellular events

- Leukocyte recruitment and activation
- The recruitment of leukocyte from vascular lumen to the extravascular space
  - Margination and rolling along the vessel wall
  - Adhesion to the endothelium
  - Transmigration between endothelial cells
  - Chemotaxis--- migration in interstitial tissues toward a chemotactic stimulus.
Major roles of leukocyte adhesion molecules in the leukocyte migration

<table>
<thead>
<tr>
<th>Endothelial molecule</th>
<th>Major role(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectins and selectin ligands</td>
<td></td>
</tr>
<tr>
<td>P-selectin</td>
<td>- Rolling</td>
</tr>
<tr>
<td>E-selectin</td>
<td>- Rolling and adhesion</td>
</tr>
<tr>
<td>Integrons and integrin ligands</td>
<td></td>
</tr>
<tr>
<td>Intercellular adhesion molecule-I (ICAM-I)</td>
<td>- Firm adhesion, arrest, transmigration</td>
</tr>
<tr>
<td>Vascular cell adhesion molecule-I (VCAM-I)</td>
<td>- Adhesion</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>CD-31</td>
<td>- Transmigration of leukocytes through endothelium</td>
</tr>
</tbody>
</table>

(Modified from Kumar et al, 2013)

The first immune cells that arrive at an injured site are mostly neutrophils. Neutrophils have several different types of receptors that recognize several different pathogen-associated molecular patterns.

Outcomes of acute inflammation

Morphologic patterns of acute inflammation

Serous inflammation
Fibrinous inflammation
Suppurative (purulent) inflammation & Abscess formation
Ulcer
- **Serous inflammation**
  - It is characterized by the outpouring of a water, relatively protein-poor fluid that, depending on the site of injury.
  - Skin blister--- burn or viral infection
  - Fluid in a serous cavity is called an effusion.

- **Fibrinous inflammation**
  - It occurs as a consequence of more severe injuries.--- greater vascular permeability that allows large molecules such as fibrinogen to pass the endothelial barrier.
  - This reaction is characteristic of inflammation in the lining of body cavities.--- meninges, pericardium, and pleura
Suppurative (purulent) inflammation & Abscess formation

- The collection of amount of purulent exudate (pus) --- neutrophils, necrotic cells, and edema fluid
- Abscesses are focal collections of pus.
- Abscesses typically have a central, largely necrotic region rimmed by a layer of preserved neutrophils with a surrounding zone of dilated vessels and fibroblast proliferation.

Ulcer

- It is a local defect, or excavation of the surface of an organ or tissue that produced by necrosis of cells and sloughing (shedding) of necrotic and inflammatory tissue.
- Ulcerations are best exemplified by peptic ulcer of the stomach or duodenum.
- Neutrophils and exudates present in an acute stage.
Chemical mediators and regulators of inflammation

The roles of cytokines in acute inflammation

Actions of the mediators of inflammation

Chronic inflammation

- Chronic inflammation is inflammation of prolonged duration (weeks to years).
- Infiltration with mononuclear cells—macrophages, lymphocytes, plasma cells
- Tissue destruction—largely induced by the products of the inflammatory cells
- Repair process—new vessel proliferation (angiogenesis) and fibrosis
The stimuli for chronic inflammation

- Persistent infections by microbes--- *Mycobacterium tuberculosis*, *Treponema pallidum*, Virus, and Fungi
- Immune-mediated inflammatory diseases--- autoimmune diseases, allergic diseases
- Prolonged exposure to potentially toxic agents

Chronic inflammation cells and mediators

- The combination of prolonged and repeated inflammation, tissue destruction, and fibrosis
- Chronic inflammation involved complex interaction between several cell populations and their secreted mediators.

Pathways of macrophage activation

(Kumar et al, 2009)
Granulomatous inflammation

- It is a distinctive pattern of chronic inflammation characterized by aggregates of activated macrophages with scattered lymphocytes.

- Granulomas can form under three settings:
  - Persistent T-cell responses to certain microbes—*M. tuberculosis*, *T. pallidum*, or fungi
  - Some immune-mediated inflammatory diseases—Crohn disease
  - Sarcoidosis—unknown etiology

Systemic effects of inflammation

- Acute-phase reaction or the systemic inflammatory response syndrome
- TNF, IL-1, and IL-6 are the most important mediator.

- Clinical and pathologic changes:
  - Fever— the most prominent manifestations
  - Elevated plasma levels of acute-phase proteins—C-reactive protein, fibrinogen, and SAA protein
  - Leukocytosis
  - Others manifestations—increased heart rate and blood pressure
  - In severe bacterial infection—sepsis

References