CHEMICAL MEDIATORS OF ACUTE INFLAMMATION

Learning objectives

• At the end of the lecture, students should be able to:
  • Know and describe the chemical mediators released during acute inflammation.

![Chemical mediators of inflammation (EC: endothelial cells)]
Leukocyte activation. Different classes of cell surface receptors of leukocytes recognize different stimuli. The receptors initiate responses that mediate the functions of the leukocytes. Only some receptors are depicted.

Events in Acute Inflammation:

Vasodilatation:
- Histamine
- Prostaglandins
- Nitric oxide

Increased vascular permeability:
- Histamine
- Anaphylatoxins C3a and C5a
- Kinins
- Leukotrienes C, D, and E
- PAF
- Substance P

Chemotaxis:
- Complement fragment C5a
- Lipoxygenase products, lipoxins & leukotrienes (LTB4)
- Chemokines

Tissue Damage
- Lysosomal products
- Oxygen-derived radicals
- Nitric Oxide
Effects of Chemical Mediators:

**Prostaglandins:**
- Vasodilation
- Pain
- Fever
- Potentiating edema

**IL-1 and TNF:**
- Endothelial-leukocyte interactions
- Leukocyte recruitment
- Production of acute-phase reactants

Adipose tissue showing mast cells around blood vessels and in the interstitial space.
Stained with metachromatic stain to identify the mast cell granules (dark blue or purple).
The red structures are fat globules stained with fat stain (oil red)
Ultrastructure and contents of neutrophil granules, stained for peroxidase activity. The large peroxidase-containing granules are the azurophil granules; the smaller peroxidase-negative ones are the specific granules (SG). N, portion of nucleus.

**LEUKOTRINES & PROSTAGLANDINS**

**Leukotrienes and Prostaglandins: Potent mediators of inflammation**

- Derived from Arachidonic acid (AA): 20-carbon, unsaturated fatty acid produced from membrane phospholipids.

Principal pathways:
- 5-lipoxygenase: Produces a collection of leukotrienes (LT)
- Cyclooxygenase (COX): Produces prostaglandin H2 (PGH2)

PGH2 serves as substrate for two enzymatic pathways:
- Prostaglandins (PG)
- Thromboxanes (Tx).
Biosynthesis of leukotrienes and lipoxins by cell-cell interaction.

AA: arachidonic acid –derived; LTA4: Leukotriene A4; LTC4: Leukotriene C4

NITRIC OXIDE:
Functions of nitric oxide synthase enzymes. NO free radicals are toxic to microbial and mammalian cells.

IL-1 & Tumor Necrosis Factor (TNF)
Major effects of interleukin-1 (IL-1) and tumor necrosis factor (TNF) in inflammation

**COMPLEMENT:**

The activation and functions of the complement system. Activation of complement by different pathways leads to cleavage of C3. The functions of the complement system are mediated by breakdown products of C3 and other complement proteins, and by the membrane attack complex (MAC).
Production of microbicidal reactive oxygen intermediates within phagocytic vesicles.

Interrelationships between the four plasma mediator systems triggered by activation of factor XII (Hageman factor). Note that thrombin induces inflammation by binding to protease-activated receptors (principally PAR-1) on platelets, endothelium, smooth muscle cells, and other cells.
## Role of Mediators in Different Reactions of Inflammation

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilatation</td>
<td>Prostaglandins, Nitric oxide, Histamine</td>
</tr>
<tr>
<td>Increased vascular permeability</td>
<td>Vasoactive amines, C3a and C5a (through liberating amines), Bradykinin, Leukotrienes C4, D4, E4, PAF, Substance P</td>
</tr>
<tr>
<td>Chemotaxis, leukocyte recruitment and activation</td>
<td>C5a, Leukotriene B4, Chemokines, IL-1, TNF, Bacterial products</td>
</tr>
<tr>
<td>Fever</td>
<td>IL-1, TNF, Prostaglandins</td>
</tr>
<tr>
<td>Pain</td>
<td>Prostaglandins, Bradykinin</td>
</tr>
<tr>
<td>Tissue damage</td>
<td>Neutrophil and macrophage lysosomal enzymes, Oxygen metabolites, Nitric oxide</td>
</tr>
</tbody>
</table>
Generation of arachidonic acid metabolites and their roles in inflammation.
The molecular targets of some anti-inflammatory drugs are indicated by a red X.
COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid.

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Source</th>
<th>Vascular Leakage</th>
<th>Chemotaxis Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine and serotonin</td>
<td>Mast cells, platelets</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Plasma substrate</td>
<td>+</td>
<td>Pain</td>
</tr>
<tr>
<td>C3a</td>
<td>Plasma protein via liver</td>
<td>+</td>
<td>Opsonic fragment (C3b)</td>
</tr>
<tr>
<td>C5a</td>
<td>Macrophages</td>
<td>+</td>
<td>Leukocyte adhesion, activation</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Mast cells, from membrane phospholipids</td>
<td>Potentiate other mediators</td>
<td>Vasodilatation, pain, fever</td>
</tr>
<tr>
<td>Leukotriene B4</td>
<td>Leukocytes</td>
<td>-</td>
<td>Leukocyte adhesion, activation</td>
</tr>
<tr>
<td>Leukotrienes C4 D4 E4</td>
<td>Leukocytes, mast cells</td>
<td>+</td>
<td>Bronchoconstriction, vasoconstriction</td>
</tr>
<tr>
<td>Platelet Activating Factor (PAF)</td>
<td>Leukocytes, mast cells</td>
<td>+</td>
<td>Bronchoconstriction, leukocyte priming</td>
</tr>
<tr>
<td>IL-1 and TNF</td>
<td>Macrophages, other</td>
<td>-</td>
<td>Acute-phase reactions, endothelial activation</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Leukocytes, others</td>
<td>-</td>
<td>Leukocyte activation</td>
</tr>
</tbody>
</table>

REFERENCES
• Pathological basis of disease
• Robbins & Cotran
• 8th edition
• Ch 2: Acute & Chronic Inflammation
• Pgs # 56-66