Inflammation 2:

1. Chemical mediators
2. Systemic effects
3. Chronic inflammation

Key Players in Inflammation

- Injurious agent
  - Microbe
  - Toxin
  - Radiation
  - Burn
- Blood vessel
- Damaged cell
- Resident WBC's
- Extracellular matrix (ECM)
- Plasma proteins
- Endothelial cell

Cell-Derived Mediators

Plasma Protein-Derived Mediators

Vasoactive Amines

- Histamine
  - Serotonin (5-OH-tryptamine)

- Px injury: heat/trauma
- IgE binding
- C3a + C5a
- Histamine-releasing protein
- Neuropeptides (substance P)
- IL-1, IL-8
Adverse effects of anti-inflammatory drugs

PG's protective COX-1 inhib. ulcers

COX-1 expressed in gastric mucosa

COX-2 inhibitors pro-thrombosis (e.g., cor. arteries)

Platelet Activating Factor (PAF)

phospholipase A2

PAF
• vasodilatation
• 1 vascular permeab.
• leukocyte adhesion
• chemotaxis

PAF & the 5 P's:
• Platelet activating factor
• Pro-inflammatory
• Permeability (vasc. permeab.)
• Polys (neutrophil chemotaxis)
Cytokines:
- polypeptides
  - from many cells—esp. mac’s and lymphocytes
  - e.g. interleukins (communicate between leukocytes)

**Diagram**

Chemokines
- Chemoattractant cytokines
  - Small: 8-10 kD
  - Bind to G-protein-coupled receptors on target cells

**Diagram**

Chemokines
- CXC
  - acts on PMN’s
  - IL-8: chemokine
- CC
  - MIP-1α: macrophage inflammatory protein-1α
  - MCP-1: monocyte chemoattractant protein-1

**Diagram**

Nitric Oxide (NO)
- Free radical gas
  - L-arg → NOS → NO
  - nNOS (neuronal; not inflammatory)
  - iNOS (inducible; by IL-1, TNF, IFNγ)
  - eNOS (endothelial)

**Diagram**
Lysosomal enzymes of leukocytes

- Acid proteases (in phagolysosomes)
- Neutral proteases
  - Elastase
  - Collagenase
  - Cathepsin

Complement

- Present in plasma as 9 inactive proteins: C1 – C9
- Progressive conversions from inactive to active forms: C1→C1a, C3→C3a + C3b, etc.
- Membrane attack complex: C5-9 forms channel in lipid membranes → entry of fluid & ions, cell lysis

Activation pathways:
1. Classical (Ag-Ab complexes; IgG/IgM)
2. Alternative (bacterial polysaccharides, e.g., endotoxin, cell wall components)
3. Lectin (plasma mannose-binding lectin binds to mannose residues on microbes)

Neuropeptides

- Transmit pain signals
- Regulate vessel tone
- Modulate vasc. perm.

Plasma Protein-Derived Mediators

Complement roles in inflammation

Vascular
- C3a + C5a → mast cell (Nastamine)
- C3a + C5b as “anaphylatoxins”

Leukocyte Chemotaxis
- C5a → chemotaxis

Phagocytosis
- C3b → iC3b (inactive)
- Opsonize → Bact.
**Systemic Effects of Inflammation**

- **Fever**
  - LPS (endogenous pyrogen)
  - TNF (endogenous pyrogen)
  - IL-1 (endogenous pyrogen)
  - PGE₂
  - Reset temp. set point higher

- **Plasma acute-phase proteins**
  - CRP
  - Fibrinogen

- **Leukocytosis**
  - Peripheral Blood WBC: 15,000-20,000 / µL (normal 5-10,000)
  - Leukemoid reaction: 40,000 – 100,000

**Chronic Inflammation**

**TABLE 24** Role of Mediators in Different Reactions of Inflammation

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Vascular Phase</th>
<th>Chemotactic, Leukocyte recruitment and activation</th>
<th>Fever</th>
<th>Acute Cell / Tissue Injury</th>
<th>Tissue damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular phase</td>
<td>Vasodilation</td>
<td>Thromboxane A₂, Leukotrienes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased permeability</td>
<td></td>
<td>Neutrophil and macrophage</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**De novo chronic disease autoimmune, etc.**

**Acute Inflammation**

- PMN
- Abscess

**Chronic Inflammation**

- Vascular phase
- Cellular phase
- Fibrosis (scar)

**Hours—days** **Weeks—mos—years**
Autoimmune attack agst. the thyroid

Chronic lymphocytic thyroiditis (Hashimoto thyroiditis)

Normal thyroid

Chronic thyroiditis

Normal

Chronic thyroiditis
Chronic viral hepatitis