Inflammation 2:

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

Key Players in Inflammation

- Injurious agent:
  - Microbe
  - Toxin
  - Radiation
  - Burn

- Damaged cell
- Leukocytes & their mediators
- Blood vessel
- Plasma proteins
- Endothelial cell
- Resident WBC's

Extracellular matrix (ECM)

Cell-Derived Mediators

Plasma Protein-Derived Mediators

Vasoactive Amines

Histamine
Serotonin (5-OH-tryptamine)

Px injury: heat/trauma
IgE binding
C3a + C5a
Histamine-releasing prot.
Neuropeptides (subst. P)
IL-1, IL-8

Platelet aggregation
Serotonin release

Vasodilation
Endothelial contraction

Widened gaps
**Adverse effects of anti-inflammatory drugs**

- **COX-1 inhibitors**
  - Prevents production of prostaglandins (PGs)
  - Protects against acid-induced ulcers
  - COX-1 expressed in gastric mucosa

- **COX-2 inhibitors**
  - Promote thrombosis (e.g., coronary arteries)

**Platelet Activating Factor (PAF)**

- **PAF**
  - Platelet activating factor
  - Pro-inflammatory
  - Phospholipase A2 involved
  - Leukocyte adhesion
  - Chemotaxis

**PAF & the 5 P's:**
- Platelet activating factor
- Pro-inflammatory
- Phospholipase A2 involved
- Permeability (vascular permeability)
- Polys (neutrophil chemotaxis)
Cytokines:
- Polypeptides
- From many cells—esp. mac’s and lymphocytes
- e.g. interleukins (communicate between leukocytes)

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

Nitric Oxide (NO)
- Free radical gas
- L-arg \[ \rightarrow \text{NOS} \] \[ \rightarrow \text{NO} \]
- \( \text{NOS} \) (neuronal; not inflammatory)
- \( \text{iNOS} \) (inducible; by IL-1, TNF, IFN-\( \gamma \))
- Present in macs/endothel.
- \( \text{eNOS} \) (endothelial)
- \( \text{NO} \) inhibits plt. adhesion, agg. & degranulation
Lysosomal enzymes of leukocytes

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

C3a and C5a degrade elastin, collagen, basement membrane, other matrix proteins.

Neuropeptides

- Substance P
- Nerve fibers
- Transmit pain signals
- Regulate vessel tone
- Modulate vascular permeability

Plasma Protein-Derived Mediators

Complement

- Present in plasma as 9 inactive proteins C1 – C9
- Progressive conversions from inactive to active forms (C1→C1α, C3→C3α + 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)

Complement roles in inflammation

- Vascular:
  C3a + C5a
  ↑ vascular permeability, vasodilation
  C3a + C5a as "anaphylatoxins"
  → mast cell
  histamine

- Leukocyte Chemotaxis:
  C5a
  → chemotaxis

- Phagocytosis:
  C3b
  iC3b (inactive)
  → opsonize
  Bact.
  C3bIIa
  C3bIIIa

- Neuropeptides:
  Substance P
  Nerve fibers
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- Plasma Protein-Derived Mediators
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Systemic Effects of Inflammation

- Fever
  - PGE
  - LPS
  - TNF
  - IL-1

- Leukocytosis
  - reactive proteins
  - CRP
  - CRP
  - SAA
  - fibrinogen

- Acute-phase proteins
  - IL-6

- Complement
  - CRP

- Periph. Blood WBC:
  - 15,000 - 20,000/µL
  - Normal: 5 - 10,000

- Leukemoid reaction:
  - 40,000 - 100,000

- Serum Amyloid A (SAA)
- CRP
- SAA
- Fibrinogen
- CRP
- SAA

- Complement
- RBC
- rouleaux
- ESR: erythrocyte Sedimentation rate

Chronic Inflammation

- Abscess
- Fibrosis (scar)
- Resolution
- Persistent infection
- De novo chronic disease autoimmunity, etc.

Acute Inflammation

- Vascular phase
- Cellular phase

- Exceptions:
  - allergy/drugs/parasites
  - viral infections

- Hours—days
- Weeks—mos—years

TABLE 2-6 Role of Mediators in Different Reactions of Inflammation

<table>
<thead>
<tr>
<th>Reaction Type</th>
<th>Prostaglandins</th>
<th>Nictic oxide</th>
<th>Histaamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased vascular permeability</td>
<td>Vasocative amines</td>
<td>CAs and CEs</td>
<td>CAs and CEs</td>
</tr>
<tr>
<td></td>
<td>Bradykinin</td>
<td>Leukotrienes A, D, E</td>
<td>PAF</td>
</tr>
</tbody>
</table>

- De novo chronic disease
- Persistent infection
- Persistent exposure
Autoimmune attack agst. the thyroid

CD4+ Helper T cell sensitization
CD8+ T

mac

follicular epithelium
Ab’s
plasma cell

Chronic lymphocytic thyroiditis (Hashimoto thyroiditis)

Normal thyroid

Chronic thyroiditis

Normal

Chronic thyroiditis
Chronic viral hepatitis

HBV

hepatocyte

virus uncoating
MHC
Viral Ag's
T

Chronic viral hepatitis