Inflammation 2:

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

Key Players in Inflammation

- Injurious agent
  - Microbe
  - Toxin
  - Radiation
  - Burn

- Damaged cell
- Extracellular matrix (ECM)
- Leukocytes (& their mediators)
- Blood vessel
- Resident WBC's
- Plasma proteins
- Endothelial cell
- Macrophage
- Mast cell
Figure 2-14
The principal chemical mediators of inflammation. EC, Endothelial cells.
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

Histamine
- Vasodilation
- widened gaps
- endothelial contraction
- dense body granules
- platelet aggregation
- serotonin release
Hydroperoxyeicosatetraenoic acid

5-Lipoxygenase

5-HPETE

5-HETE

Leukotriene A4 (LTA4)

Leukotriene B4 (LBTB4)

Inhibit neutrophil adhesion and chemotaxis

Lipoxygenases

5-HETE

Hydroxyeicosatetraenoic acid

Chemotactic for PMN's

Vasoconstriction

Bronchospasm

Increased vascular permeability
Adverse effects of anti-inflammatory drugs

COX-1 and COX-2 inhibitors, aspirin, indomethacin inhibit

Cyclooxygenase

Prostaglandin G2 (PGG2)

Prostaglandin H2 (PGH2)

Prostacyclin (PGI2)

Thromboxane A2 (TXA2)

PAF & the 5 P’s:

• Platelet activating factor
• Pro-inflammatory
• Phospholipase A2 involved
• Permeability (↑vasc. permeab.)
• 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

Recruitment
- Increase affinity of integrins for adh. molecules on endothelium
- Organize B & T cell areas in l.n.’s/spleen

- lymph node
- spleen
Chemokines

CXC

---cys-a.a.-cys---

acts on

PMN’s

e.g.

IL-8

acts on

mac

endo

mast

fibroblast

MCP-1: monocyte chemoattractant protein-1

MIP-1α: macrophage inflammatory protein-1α

RANTES: regulated on activation normal T-expressed and secreted

EOTAXIN

CC

---cys-cys---

acts on

monocytes

memory

CD4+

eos

IL-1

TNF

LPS

sepsis

Modified from Robbins Basic Pathology 8/e Fig. 1-20
ROS

- high levels cause tissue injury
- protease activation
- anti-protease inact.
- direct cell injury
- breakdown ECM

- thrombosis
- endothelial permeability
- damage endothelium

anti-oxidants
- catalase
- superoxide dismutase
- glutathione

Nitric Oxide (NO)
free radical gas

L-arg O2 NADPH

\( \text{NOS (nitric oxide synthase)} \)

- \( \text{nNOS (neuronal; not inflammatory)} \)
- \( \text{iNOS (inducible; by IL-1, TNF, IFN}\gamma \)
  -- present in macs/endothel.
- \( \text{eNOS (endothelial)} \)

\( \text{NO} \)

- sm. m. relaxation
- vasodilation

- inhibit plt. adhesion,
  agg. & degranulation

WBC recruitment
Lysosomal enzymes of leukocytes

- **acid proteases** (in phagolysosomes)
- **neutral proteases**
  - elastase
  - collagenase
  - cathepsin

C3 + C5 act on kininogen

C3a + C5a degrade elastin, collagen, basement membrane, other matrix proteins

bradykinin-like peptides

Neuropeptides

- Transmit pain signals
- Regulate vessel tone
- Modulate vasc. perm.
Plasma Protein-Derived Mediators

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)
**Complement roles in inflammation**

**Vascular**
- C3a + C5a
- vasc. permeab.
- vasodilation

**Leukocyte**
- Chemotaxis
- C5a

**Phagocytosis**
- C3b
- iC3b (inactive)

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**mast cell**

- C3a + C5a as "anaphylatoxins"
- histamine

- chemotaxis

- opsonize
- Bact.
Robbins Basic Pathology
8/e Fig.2-19

- Vascular permeability
- Chemotactic for WBC's
### Systemic Effects of Inflammation

**Fever**
- LPS (exogenous pyrogen)
- PGE₂
- Hypothalamus
- Reset temp. set point higher
-Neurotransmitters

**Plasma acute-phase proteins**
- IL-6
- C-reactive protein (CRP)
- Serum Amyloid A (SAA)
- Fibrinogen

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

**RBC rouleaux**
- ESR: erythrocyte Sedimentation rate
Chronic Inflammation

- Acute
- Cell / Tissue Injury
- Vascular phase
- Cellular phase
- De novo chronic disease
  autoimmune, etc.
- Persistent infection
- Persistent exposure
- Abscess
- Resolution
- Fibrosis (scar)

Exceptions:
- Allergy/drugs/
  parasites
- Viral infections
- Eos
- Lymphocytes

Duration:
- 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