INFLAMMATION: Chemical Mediators
CHEMICAL MEDIATORS OF INFLAMMATION

**Definition:** any messenger that acts on blood vessels, inflammatory cells or other cells to contribute to an inflammatory response.

**Exogenous**
- endotoxins

**Endogenous**
- plasma
- leukocytes
- endothelial cells
- fibroblasts
Definition: any messenger that acts on blood vessels, inflammatory cells or other cells to contribute to an inflammatory response.
- **Mechanisms of action**
  - receptor-ligand interactions ($1^\circ$)
  - direct enzymatic activity
  - oxidative damage

- **Network of interacting chemicals**
  - high degree of redundancy
  - guarantees amplification & maintenance of inflammatory response

- **Short half life**

- **Potentially harmful**
CHEMICAL MEDIATORS by EVENT

- **Vasodilation**
  - histamine, nitric oxide, prostaglandins

- **Increased Vascular Permeability**
  - histamine, C3a & C5a, bradykinin, ROS, leukotrienes, PAF

- **Chemotaxis**
  - C5a, LTB₄ & LTC₄ chemokines (TNF-α, IL-1, IL-8), bacterial products (LPS)
CHEMICAL MEDIATORS by EVENT

- **Fever**
  - IL-1, TNF-α, IL-6, Prostaglandins

- **Pain**
  - Kinins (Bradykinin, Substance P), Prostaglandins,

- **Tissue Damage** (leukocyte products)
  - Lysosomal enzymes
  - ROS / ONOO\^·
**VASOACTIVE AMINES**

**Histamine** (& serotonin)
- Histamine mainly from mast cells
  - Vasodilation and Increase Vascular Permeability
  - Contraction of non-vascular smooth muscle (bronchi)
  - Stimulate cells to produce eotaxins (attract eosinophils)
Releasing Stimulators

- Ag binding to IgE on mast cells
- Fragments of C3a and C5a
- Direct physical or chemical injury
- Cytokines (IL-1, IL-8)
- Neuropeptides (substance P)
- etc
PLASMA PROTEASES

All 3 systems are interrelated

Complement system
- killing system
- vasoactive
- chemotactic

Kinin system
- highly vasoactive
- pain

Clotting / fibrinolytic system
- vasoactive
- cleaves C3
COMPLEMENT SYSTEM

Three pathways:

- Classical pathway (antibodies)
- Alternate pathway (microbe LPS)
- Lectin pathway (sugar on microbes)
Important functions:

- C3a and C5a (anaphylatoxins)
  - release histamine (mast cells) → increased vascular permeability
  - chemotactic for many inflammatory cells
- Opsonize microorganisms to facilitate phagocytosis
- Membrane Attack Complex (MAC) → lysis of pathogens
COMPLEMENT SYSTEM (movie – “complement system”)
Bradykinin

- activated by Hageman factor (XIIa)
- generated from plasma proteins (kininogens)
- actions:
  - potent vasodilator
  - stimulates release of histamine (↑ vasc. perm.)
  - contraction of non-vascular smooth muscle
  - produces pain
  - activates the arachidonic acid cascade
Substance P

- secreted by nerve fibers (and some leukocytes)
- similar functions to bradykinin
- also activated by capsaicins
• Factor XII of intrinsic coagulation cascade activated by collagen, etc
  • factor XIIa activates:
    ➢ bradykinin
    ➢ coagulation cascade
    ➢ fibrinolytic system
    ➢ complement
  • also amplification system
    ➢ kallikrein, plasmin
• in both physiologic and pathologic processes (inflammation)
• produced by endothelial cells, leukocytes and platelets
• act locally on smooth muscle, endothelium and platelets
• can mediate most of the steps in acute inflammation!

• origin:
  ➢ arachidonic acid derived from membrane phospholipids (eg linoleic acid)
  ➢ must first be released by activated phospholipases (in injury)

• two important pathways:
  ➢ cyclooxygenase (COX)
  ➢ lipoxygenase
Cell membrane phospholipids → Phospholipases → ARACHIDONIC ACID

- Steroids inhibit

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

ARACHIDONIC ACID → HPETEs → HETEs

5-Lipoxygenase → 5-HPETE → 5-HETE → Chemotaxis

12-Lipoxygenase → Leukotriene A₄ (LTA₄) → Leukotriene B₄ (LTB₄) → Vasoconstriction, Bronchospasm, Increased vascular permeability

Cyclooxygenase

Prostaglandin G₂ (PGG₂) → Prostaglandin H₂ (PGH₂)

- Prostacyclin (PGI₂)
  - Causes vasodilation, inhibits platelet aggregation
  - PGD₂
  - Vasodilation, Increased vascular permeability

- Thromboxane A₂ (TXA₂)
  - Causes vasoconstriction, promotes platelet aggregation
  - PGE₂
  - Inhibit neutrophil adhesion and chemotaxis
CYCLOOXYGENASE PATHWAY

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

Endothelium

Platelets

PGI synthetase

TxA synthetase

Prostaglandin G₂ (PGG₂)

Prostaglandin H₂ (PGH₂)

Prostacyclin (PGI₂)

Causes vasodilation, inhibits platelet aggregation

Causes vasoconstriction, promotes platelet aggregation

Thromboxane A₂ (TXA₂)

PGD₂

PGE₂

Vasodilation

Increased vascular permeability

+ Pain

ARACHIDONIC ACID

Cyclooxygenase

-
LIPOXYGENASE PATHWAY

ARACHIDONIC ACID

Other lipoxygenases → HPETEs → HETEs

5-Lipoxygenase

5-HPETE → 5-HETE

Chemotaxis

Leukotrienes

C4, D4, E4

10^3 X histamine potency

HETE = hydroxyeicosatetraenoic acid

Leukotrienes C4, D4, E4

10^3 X histamine potency

Antiinflammatory
LYSOSOMAL CONSTITUENTS

Lysosomes of neutrophils, macrophages, lymphocytes

Degradation of ECM

• collagenase, hydrolase, protease (trypsin), elastase

Kill infectious organisms &/or infected cells

• lactoferrin, lysozyme, myeloperoxidase, major basic protein
• granzyme/perforin in cytotoxic T lymphocytes
Granzyme / Perforin (movie - “cell killing”)
OXYGEN- DERIVED FREE RADICALS

• include: $H_2O_2$, $O_2^-$ and $OH^-$
• injury to variety of cells (microbes & host cells)
• endothelial damage $\Rightarrow$ increased vascular permeability
• inhibit antiproteases $\Rightarrow$ damage to ECM
PLATELET ACTIVATING FACTOR

- produced by platelets, endothelial cells, leukocytes

- functions:
  - platelet aggregation and release
  - bronchoconstriction & vasoconstriction [high]
  - vasodilation and vascular permeability [low]
  - increases leukocyte adhesion & chemotaxis
  - increases leukocyte degradation / oxidative burst
• peptide transmitters for cell-to-cell chatting
  ➢ modulate cell functions

• primarily from activated macrophages & lymphocytes

• esp. IL-1 & TNF-α
Cytokine signaling (movie - “cytokine signaling”)
IL-1 and TNF - “Master Cytokines”

Microbial products, other cytokines, toxins

ACTIVATION OF MACROPHAGES (and other cells)

TNF / IL-1

LOCAL EFFECTS

Vascular endothelium
- ↑ Expression of leukocyte adhesion molecules
- Production of IL-1, chemokines
- ↑ Procoagulant and ↓ anticoagulant activity

Leukocytes
- Activation
- Production of cytokines

Fibroblasts
- Proliferation
- ↑ Collagen synthesis

INFLAMMATION

REPAIR

SYSTEMIC EFFECTS

- Fever
- Leukocytosis
- ↑ Acute-phase proteins
- ↓ Appetite
- ↑ Sleep

SYSTEMIC MANIFESTATIONS OF INFLAMMATION
Other Cytokines

- **IL-5**
  - eosinophils (chemotaxis, activation, proliferation)

- **IL-6**
  - B and T cells proliferation (master cytokine)

- **IL-8**
  - attracts neutrophils (chemokine)

- **IF-γ**
  - activates macrophages & T lymphocytes (in viral infections)

- **PDGF**
  - chemotactic to fibroblasts and leukocytes

- **TGF-β & VEGF**
  - important in repair
NITRIC OXIDE (NO)

- nitric oxide (NO) synthesized from L-arginine by NOS (iNOS in inflammation)
- effects:
  - smooth muscle relaxation → vasodilation
  - reduce platelet aggregation & adhesion
  - bactericidal (forms peroxynitrite)
- uncontrolled NO production (sepsis) → massive vasodilation → shock