**Inflammatory response:**
1. Vascular reaction
2. Cellular reaction

**Circulating cells:**
1. Neutrophils
2. Monocytes
3. Eosinophils
4. Lymphocytes
5. Basophils
6. Platelets

**Tissue cells:**
1. Mast cells
2. Blood vessels
3. Fibroblasts
4. Resident MØ
5. Resident lymphocytes

**Extracellular matrix:**
1. Structural fibrous proteins
   - collagen
   - elastin
2. Adhesive glycoproteins
   - fibronectin
   - laminin
   - nonfibrillar collagen
   - tenascin
3. Proteoglycans
Acute Inflammation:
1. Alterations in vascular caliber → increase in blood flow
2. Structural changes in the microvascular → increased permeability
3. Emigration of leukocytes → accumulation at site of injury → activation

**HALLMARK** of acute inflammation = increased vascular permeability

**Stimuli for Acute Inflammation:**
1. Infections
2. Trauma
3. Physical and chemical agents
4. Tissue necrosis
5. Foreign bodies
6. Immune reactions

**Changes in Vascular Flow and Caliber:**
1. Transient vasoconstriction
2. Vasodilation, first at the arterioles (histamine, NO)
3. Increased vascular permeability → protein into extravascular space
4. Increased viscosity of blood → blood stasis
5. Leukocytes move to endothelial wall → roll → adhere → migrate
**Mechanisms of Increased Vascular Permeability:**

1. **Formation of endothelial gaps in venules**
   - venules
   - rapid and short lived (15-30 min)
   - most common mechanism; “immediate transient response”
   - histamine, bradykinin, LTs, substance P → bind to their receptors → intracellular signaling pathways → contraction of cytoskeletal proteins (myosin) → contraction of endothelial cells → separation of intercellular junctions
   - IL-1, TNF, IFN-γ; delayed and long lived (4-6 hrs; lasting 24 hrs or more)

2. **Direct endothelial injury**
   - venules, capillaries, arterioles
   - results in endothelial cell necrosis and detachment
   - immediate sustained response
   - may result in platelet cell adhesion and thrombosis

3. **Delayed prolonged leakage**
   - venules and capillaries
   - begins after a delay of 2-12 hrs; lasts for hrs to days
   - sunburns, x-radiation, UV radiation

4. **Leukocyte-mediated endothelial injury**
   - venules and pulmonary and glomerular capillaries
   - leukocytes that adhere to the endothelium may become activated → release toxic oxygen species and proteolytic enzymes → endothelial injury or detachment → increased permeability

5. **Increased transcytosis**
   - channels consisting of clusters of interconnected, uncoated vesicles and vacuoles; called the “vesiculovacuolar organelle”
   - VEGF increases the number and size of these

6. **Leakage from new blood vessels**
   - angiogenesis; new vessel sprouts remain leaky until the endothelial cells mature
   - VEGF induces angiogenesis and increases vascular permeability
Blood stasis → leukocytes marginate → leukocytes roll → become activated → adhere to the endothelium → transmigrate across the endothelium (venules) → pierce the BM → migrate toward chemoattractants to the source of injury

Table 2-1 Endothelial/Leukocyte Adhesion Molecules

<table>
<thead>
<tr>
<th>Endothelial Molecule</th>
<th>Leukocyte Receptor</th>
<th>Major Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-selectin (endothel + plt)</td>
<td>Sialyl-Lewis-X; PSGL-1 (P-selectin glycoprotein ligand-1)</td>
<td><strong>Rolling</strong> (neutrophils, monocytes, lymphocytes); selectins bind to sialylated-Lewis-X which themselves are covalently bound to various mucin-like gp (GlyCAM-1, PSGL-1, ESL-1, CD34)</td>
</tr>
<tr>
<td>E-selectin (endothelium)</td>
<td>Sialyl-Lewis-X, Sialyl-Lewis A</td>
<td><strong>Rolling</strong>, adhesion to activ. endothelium (neutrophils, monocytes, T cells) Important in homing of effector + memory T cells; esp. to skin</td>
</tr>
<tr>
<td>ICAM-1 (intercellular adhesion molecule -1)</td>
<td>β 2-integrins: 1) LFA-1 (CD11a/CD18) 2) Mac-1 (CR3) (CD11b/CD18) 3) P150,95 (CR4) (CD11c/CD18)</td>
<td><strong>Adhesion</strong>, arrest, transmigration (all leukocytes) LFA-1 = mediates leukocyte adhesion to APC and vasc. endothelium Mac-1 (CR3) = mediates leukocyte attachment to endothel; func as fibrinogen receptor; func as C′ receptor on phagocytic cells (binds iC3b on opsonized iC3b coated cells) p150,95 (CR4) = mediates leukocyte attachment to endothelium</td>
</tr>
<tr>
<td>VCAM-1 (vascular cell adhesion molecule-1)</td>
<td>β 1-integrins: 1) VLA4 (α4β1) 2) LPAM-1 (α4β7)</td>
<td><strong>Adhesion</strong> (eosinophils, monocytes, lymphocytes) VLA4 (very late activation) = mediates homing of lymphocytes to endothel at peripheral sites of inflammation</td>
</tr>
<tr>
<td>GlyCAM-1; MadCAM-1; CD34</td>
<td>L-selectin</td>
<td>Lymphocyte homing to high endothelial venules (HEV) Also serves to bind neutrophils to activated endothelium</td>
</tr>
<tr>
<td>CD31 (PECAM)</td>
<td>CD31</td>
<td><strong>Transmigration</strong>: Leukocyte migration through endothelium</td>
</tr>
</tbody>
</table>
P-selection redistribution:
1. Histamine
2. Thrombin
3. PAF (Plt activating factor)

E-selectin, VCAM, ICAM expression:
1. TNF
2. Il-1

**Endothelial cell expression of E-selectin is a HALLMARK of acute cytokine-mediated inflammation**

Chemotaxis:
1. Exogenous
   - bacterial products
2. Endogenous
   - C5a
   - LTB4
   - cytokines (IL-8)
Leukocyte activation results from several signaling pathways that are triggered in leukocytes, resulting in increases in cytosolic Ca++ and activation of enzymes such as protein kinase C and phospholipase A2.

**Functional responses induced on leukocyte activation:**
1. Production of AA metabolites
2. Degranulation and secretion of lysosomal enzymes; activ of oxidative burst
3. Secretion of cytokines
4. Modulation of leukocyte adhesion molecules

**Leukocyte receptors:**
1. TLRs
2. 7-transmembrane G-protein-coupled receptor
3. Cytokine receptors (IFN-γ)
4. Opsonin receptors (MBL)

**IFN-γ** is the major MØ activating cytokine; secreted by NK cells and T cells
Phagocytosis:
1. Recognition and attachment
   - mannose receptors
   - scavenger receptors
   - opsonins = IgG, C3b, plasma lectins (MBL)**
2. Engulfment
   - dependent on polymerization of actin filaments
3. Killing or degradation
   - oxygen-dependent mechanisms
     (H$_2$O$_2$-MPO-halide system = most efficient)**
   - oxygen-independent mechanisms
     (bactericidal permeability increasing protein-BPI)
     (lysozyme)
     (lactoferrin)
     (major basic protein)
     (defensins)
     (enzymes—elastase)

Defects in Leukocyte Function (see Slauson & Cooper):
1. Defects in leukocyte adhesion
   - LAD1; LAD 2
2. Defects in phagolysosome function
   - Chediak-Higashi syndrome
3. Defects in microbicidal activity
   - Chronic granulomatous disease
4. Bone marrow suppression
Chemical Mediators of Inflammation:
1. Vasoactive amines
   - Histamine
   - Serotonin
2. Plasma proteins
   - Complement system
   - Kinin system
   - Clotting system
3. AA metabolites: PGs, LTs, Lipoxins
4. PAF (platelet activating factor)
5. Cytokines and chemokines
   - TNF
   - IL-1
6. NO (nitric oxide)
7. Lysosomal constituents of leukocytes
8. Oxygen-derived free radicals
9. Neuropeptides
10. Other mediators

Histamine is released by mast cells when:
1. physical injury (trauma, heat, cold)
2. immune reactions (binding of Ab)
3. fragments of complement (anaphylatoxins)
4. histamine-releasing proteins derived from leukocytes
5. neuropeptides (substance P)
6. cytokines (IL-1, IL-8)
The critical step in the elaboration of the biologic functions of complement is the activation of the third and most abundant component, C3.

**Biologic functions of the complement system** (cell lysis by MAC or the effects of proteolytic fragments of C)

1. **Vascular phenomena**
   - anaphylatoxins = C3a, C5a, C4a
   - C5a activates the lipoxygenase pathway of AA in neutrophils and monocytes

2. **Leukocyte adhesion, chemotaxis, and activation**
   - C5a is a powerful chemotactic agent for neutrophils, monocytes, eosinophils, basophils

3. **Phagocytosis**
   - C3b and its cleavage product iC3b act as opsonins when fixed to the bacterial cell wall
The Kinin System:
1. Generates vasoactive peptides from plasma proteins (kininogens) by the action of specific proteases (kallikreins).
2. Activation of the kinin system → bradykinin → short lived → inactivated by kininase.
   - Increases vascular permeability
   - Contraction of smooth muscle
   - Dilation of blood vessels
   - Pain
3. Kinin system is activated by Hageman factor (XII) and kallikrein itself is a potent activator of Hageman factor.

Activated Hageman Factor initiates four systems:
1. Kinin cascade
2. Clotting system
3. Fibrinolytic system
4. Complement system

Increased vascular permeability
1. Bradykinin
2. C3a
3. C5a

Mediator of chemotaxis
1. C5a

Thrombin—acts on endothelium

Protease-activated receptors (PARs):
1. 7 transmembrane G protein receptor
2. Expressed on platelets, endothelial cells, smooth muscle cells
3. Activation of PAR-1:
   - Mobilization of P-selectin
   - Production of chemokines
   - Expression of endothelial adhesion molecules
   - Induction of cyclooxygenase-2
   - Production of PGs
   - Production of PAF and NO
   - Changes in endothelial shape

**Thrombin** is the main link between the coagulation system and inflammation:
- Fibrinogen → fibrin
- Major coagulation protease
Table 2-4 Inflammatory Actions of Eicosanoids

<table>
<thead>
<tr>
<th>Action</th>
<th>Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstriction</td>
<td>TXA2, LTC4, LTD4, LTE4</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>PGI2, PGE1, PGE2, PGD2</td>
</tr>
<tr>
<td>Increased vascular permeability</td>
<td>LTC4, LTD4, LTE4</td>
</tr>
<tr>
<td>Chemotaxis, leukocyte adhesion</td>
<td>LTB4, HETE, lipoxins</td>
</tr>
</tbody>
</table>

Key Components

TXA2 = platelet aggregation, vasoconstriction
PGI2 = inhibit platelet aggregation, vasodilation
PGE2 = hyperalgesic

LTB4 = potent chemotactic neutrophils, activation of neutrophils
LTC4, D4, E4 = vasoconstriction, vascular permeability, bronchospasm

Lipoxins = inhibit leukocyte recruitment, inhibit neutrophil chemotaxis, inhibit neutrophil adhesion, negative regulators of LTs
Resolvins = inhibit leukocyte recruitment, inhibit leukocyte activation

© Elsevier 2005
**Chemokines** = proteins that act as chemoattractants for leukocytes; bind to seven transmembrane G-protein-coupled receptor; simulate leukocyte recruitment and control the normal migration of cells through tissue

1. **C-X-C chemokines** (IL-8)
   - acts on neutrophils
   - secreted by activ. MØ, endothelial cells, others
   - induced by microbial products, IL-1, TNF

2. **C-C chemokines** (also called β-chemokines) (MCP-1, eotaxin, MIP-1, RANTES)
   - attract monocytes, eosinophils, basophils, lymphocytes (NOT neutrophils)
   - MCP-1 (monocyte chemoattractant protein)
   - MIP-1 (macrophage inflammatory protein)
   - RANTES (regulated and normal T cell expressed and secreted)

3. **C chemokines** (also called γ-chemokines) (lymptactin)
   - relatively specific for lymphocytes

4. **CX3C chemokines** (fractalkine)
   - surface-bound = promotes strong adhesion of monocytes and T cells to endothelial cells
   - soluble form = potent chemotractant for monocytes and T cells

**Major cytokines that mediate inflammation:**

- **IL-1**
  - produced by activated MØ

- **TNF**
  - stimulated by endotoxin, immune complexes, physical injury, inflammatory stimuli

- most important actions
  1. effects on endothelium
  2. effects on leukocytes
  3. effects on fibroblasts
  4. induction of systemic acute-phase rxns
  5. priming of neutrophils

- induce the systemic acute-phase responses
  1. fever
  2. loss of appetite
  3. slow wave sleep
  4. release of neutrophils into circulation
  5. release of corticotropin
  6. release of corticosteroids
  7. septic shock
Nitric Oxide
- produced by endothelial cells, MØ, neurons
- paracrine stimulation
- induction of cyclic GMP
- synthesized from L-arginine by the enzyme nitric oxide synthase (NOS)
  - eNOS – endothelial NOS
  - nNOS – neuronal NOS
  - iNOS – inducible NOS
- is microbicidal

1. potent vasodilator
2. reduces plt aggregation and adhesion
3. inhibits mast cell induced inflammation
4. endogenous regulator of leukocyte recruitment
5. endogenous reducer of inflammatory responses

Neutrophils have two types of granules:

**Specific (secondary) granules**
- lysozyme
- collagenase (type IV)
- gelatinase
- lactoferrin
- plasminogen activator
- histaminase
- alkaline phosphatase
- phospholipase A2
- leukocyte adhesion molecules

**Azurophil (primary) granules**
- myeloperoxidase
- lysozyme
- defensins
- acid hydrolases
- elastase
- cathepsin G
- nonspecific collagenases
- proteinase 3
- cationic proteins
- BPI
- phospholipase A2

BPI – bactericidal permeability increasing protein

**Anti-proteases:**
1. α1-antitrypsin – inhibits neutrophil elastase
2. α2-macroglobulin

---

Vascular smooth muscle relaxation and vasodilation

© Elsevier 2005
Table 2-5 Summary of Mediators of Acute Inflammation

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Source</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine and serotonin</td>
<td>Mast cells, platelets</td>
<td>Vascular Leakage</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Plasma substrate</td>
<td>+</td>
</tr>
<tr>
<td>C3a</td>
<td>Plasma protein via liver</td>
<td>+</td>
</tr>
<tr>
<td>C5a</td>
<td>Macrophages</td>
<td>+</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Mast cells, from membrane phospholipids</td>
<td>Potentiate other mediators</td>
</tr>
<tr>
<td>Leukotriene B₄</td>
<td>Leukocytes</td>
<td>-</td>
</tr>
<tr>
<td>Leukotriene C₄, D₄, E₄</td>
<td>Leukocytes, mast cells</td>
<td>+</td>
</tr>
<tr>
<td>Oxygen metabolites (O₂⁻, H₂O₂, OH)</td>
<td>Leukocytes</td>
<td>+</td>
</tr>
<tr>
<td>PAF</td>
<td>Leukocytes, mast cells</td>
<td>+</td>
</tr>
<tr>
<td>IL-1 and TNF</td>
<td>Macrophages, other</td>
<td>-</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Leukocytes, others</td>
<td>-</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Macrophages, endothelium</td>
<td>+</td>
</tr>
</tbody>
</table>

VA = vasoactive amines
PP = plasma protein
AA = arachadonic acid metabol
CK = cytokines

Neuropeptides (substance P and neurokinin A):
Substance P = transmission of pain
regulation of BP
inc. vascular permeability
stim. secretion by endocrine cells
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilation</td>
<td>Prostaglandins</td>
</tr>
<tr>
<td></td>
<td>Nitric oxide</td>
</tr>
<tr>
<td></td>
<td>Histamine</td>
</tr>
<tr>
<td>Increased vascular permeability</td>
<td>Vasoactive amines</td>
</tr>
<tr>
<td></td>
<td>C3a and C5a (through liberating amines)</td>
</tr>
<tr>
<td></td>
<td>Bradykinin</td>
</tr>
<tr>
<td></td>
<td>Leukotrienes C₄, D₄, E₄</td>
</tr>
<tr>
<td></td>
<td>PAF</td>
</tr>
<tr>
<td></td>
<td>Substance P</td>
</tr>
<tr>
<td>Chemotaxis, leukocyte recruitment and activation</td>
<td>C5a</td>
</tr>
<tr>
<td></td>
<td>Leukotriene B₄</td>
</tr>
<tr>
<td></td>
<td>Chemokines</td>
</tr>
<tr>
<td></td>
<td>IL-1, TNF</td>
</tr>
<tr>
<td></td>
<td>Bacterial products</td>
</tr>
<tr>
<td>Fever</td>
<td>IL-1, TNF</td>
</tr>
<tr>
<td></td>
<td>Prostaglandins</td>
</tr>
<tr>
<td>Pain</td>
<td>Prostaglandins</td>
</tr>
<tr>
<td></td>
<td>Bradykinin</td>
</tr>
<tr>
<td>Tissue damage</td>
<td>Neutrophil and macrophage lysosomal enzymes</td>
</tr>
<tr>
<td></td>
<td>Oxygen metabolites</td>
</tr>
<tr>
<td></td>
<td>Nitric oxide</td>
</tr>
</tbody>
</table>

Table 2-6  Role of Mediators in Different Reactions of Inflammation
Outcomes of Acute Inflammation
1. Complete resolution
2. Healing via fibrosis
3. Progression to chronic inflammation

Morphologic Patterns of Acute Inflammation:
1. Serous
2. Fibrinous
3. Suppurative / purulent
4. Ulcers
Figure 2-22 Events in the resolution of inflammation:

1. return to normal vascular permeability;
2. drainage of edema fluid and proteins into lymphatics;
3. by pinocytosis into macrophages;
4. phagocytosis of apoptotic neutrophils and
5. phagocytosis of necrotic debris; and
6. disposal of macrophages. Macrophages also produce growth factors that initiate the subsequent process of repair.

Note the central role of macrophages in resolution.
Causas de la inflamación crónica:
1. Inflamación persistente
2. Exposición prolongada a agentes tóxicos (endógenos o exógenos)
3. Autoinmunidad

Características morfológicas de la inflamación crónica:
1. Células mononucleares (MØ, linfocitos, plasma cells)
2. Destrucción tisular
3.Intentos de curación (angiogénesis y fibrosis)

**IFN-γ** = estimulador potente de MØ
- Secreto por células T, NK

Accumulación de macrófagos persistente:
1. Recrudecimiento de monocitos desde la circulación
   - MCP-1
   - C5a
   - PDGF
2. Proliferación local
3. Inmovilización

© Elsevier 2005
Other Cells in Chronic Inflammation:
1. Lymphocytes
   - TNF, IL-1 secreted from activated MØ promote leukocyte recruitment
   - activated T cells produce IFN-γ – major activator of MØ

2. Eosinophils
   - abundant in immune rxns mediated by IgE and parasitic infections
   - eotaxin is very important in eosinophil recruitment
   - contain major basic protein = highly cationic protein; toxic to parasites; lysis of epithelial cells

3. Mast cells
   - in both acute and persistent infections
   - binding of IgE causes degranulation – release of histamine, products of AA (anaphylactic rxn)
Systemic Effects of Inflammation:

1. Fever – produced in response to pyrogens
   - exogenous pyrogens = LPS
   - endogenous pyrogens = IL-1, TNF

2. Acute phase proteins – plasma proteins, mostly synthesized in the liver
   - C-reactive protein (CRP)
   - fibrinogen
   - serum amyloid A (SAA)
   - synthesis of these is upregulated by IL-6 (CRP, fibrinogen) and IL-1, TNF (SAA)
   - they serve as opsonins and fix complement

3. Leukocytosis
   - accelerated release of cells from the BM (due to IL-1, TNF)
   - left shift
   - proliferation of precursors in the BM (due to CSFs)

4. Increase pulse and BP

5. Sepsis
   - LPS induces large releases of IL-1 and TNF
   - high levels of TNF → DIC
   - LPS and TNF induce tissue factor (TF) expression on endothelial cells → initiates coagulation and inhibit anticoagulation (via tissue factor pathway inhibitor- TFPI and endothelial cell thrombomodulin)
   - over production of NO → heart failure, loss of perfusion pressure → hemodynamic shock

**Clinical triad of hemodynamic shock**
1. Hypoglycemia
2. DIC
3. Cardiovascular failure