Chapter 2
Chemical Mediators of Inflammation

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Injury

Acute inflammation

Chronic inflammation

Resolution

Repair

Abscess
• “Inflame” – to set fire.

• Inflammation is “A dynamic response of vascularised tissue to injury.”

• It is a protective response.

• It serves to bring defense & healing mechanisms to the site of injury.
What is Inflammation?

- A reaction of a living tissue & its micro-circulation to a pathogenic insult.

- A defense mechanism for survival.
• Reaction of tissues to injury, characterized **clinically** by: heat, swelling, redness, pain, and loss of function.

• **Pathologically** by: vasoconstriction followed by vasodilatation, stasis, hyperemia, accumulation of leukocytes, exudation of fluid, and deposition of fibrin.
How Does It Occur?

• The vascular & cellular responses of inflammation are mediated by chemical factors (derived from blood plasma or some cells) & triggered by inflammatory stimulus.

• Tissue injury or death  --->  Release mediators
Etiologies

• Microbial infections: bacterial, viral, fungal, etc.

• Physical agents: burns, trauma--like cuts, radiation

• Chemicals: drugs, toxins, or caustic substances like battery acid.

• Immunologic reactions: rheumatoid arthritis.
Cardinal Signs of Inflammation

- Redness: Hyperaemia.
- Warm: Hyperaemia.
- Pain: Nerve, Chemical mediators.
- Swelling: Exudation
- Loss of Function: Pain
• **Time course**

  • Acute inflammation: Less than 48 hours
  
  • Chronic inflammation: Greater than 48 hours (weeks, months, years)

• **Cell type**

  • Acute inflammation: Neutrophils
  
  • Chronic inflammation: Mononuclear cells (Macrophages, Lymphocytes, Plasma cells).
Pathogenesis: Three main processes occur at the site of inflammation, due to the release of chemical mediators:

- Increased blood flow (redness and warmth).
- Increased vascular permeability (swelling, pain & loss of function).
- Leukocytic Infiltration.
Mechanism of Inflammation

1. Vaso dilatation

2. Exudation - Edema

3. Emigration of cells

4. Chemotaxis
The major local manifestations of acute inflammation, compared to normal.

(1) **Vascular dilation and increased blood flow** (causing erythema and warmth).

(2) **Extravasation and deposition of plasma fluid and proteins** (edema).

(3) **Leukocyte emigration and accumulation in the site of injury.**
Changes in vascular flow (hemodynamic changes)

- Slowing of the circulation
  - outpouring of albumin rich fluid into the extravascular tissues results in the concentration of RBCs in small vessels and increased viscosity of blood.
- Leukocyte margination
  - Neutrophils become oriented at the periphery of vessels and start to stick.
Time scale

- Variable
  - minor damage---- 15-30 minutes
  - severe damage---- a few minutes
Lymphatics in inflammation:

- Lymphatics are responsible for draining edema.

**Edema**: An excess of fluid in the interstitial tissue or serous cavities; either a *transudate* or an *exudate*
Transudate:

- An ultrafiltrate of blood plasma
  - permeability of endothelium is usually normal.
  - low protein content (mostly albumin)
Exudate:

- A filtrate of blood plasma mixed with inflammatory cells and cellular debris.
  - permeability of endothelium is usually altered
  - high protein content.
Pus:

- A purulent exudate: an inflammatory exudate rich in leukocytes (mostly neutrophils) and parenchymal cell debris.
Leukocyte exudation

- Divided into 4 steps
  - Margination, rolling, and adhesion to endothelium
  - Diapedesis (trans-migration across the endothelium)
  - Migration toward a chemotactic stimuli from the source of tissue injury.
  - Phagocytosis
MARGINATION
Phagocytosis

- 3 distinct steps
  - Recognition and attachment
  - Engulfment
  - Killing or degradation
Defects in leukocyte function:

• Margination and adhesion
  – steroids, leukocyte adhesion deficiency

• Emigration toward a chemotactic stimulus
  • drugs
  • chemotaxis inhibitors

• Phagocytosis
  • Chronic granulomatous disease (CGD)
Inflammation Outcome

- Injury
  - Acute Inflammation
    - Abscess
      - Ulcer
        - Fistula
        - Sinus
    - Resolution
      - Fibrosis/Scar
  - Chronic Inflammation
    - Fungus
    - Virus
    - Cancers
    - T.B. etc.
Chemical Mediators:

Chemical substances synthesised or released and mediate the changes in inflammation.

- *Histamine* by mast cells - vasodilatation.

- *Prostaglandins* – Cause pain & fever.

- *Bradykinin* - Causes pain.
Morphologic types of acute inflammation

- Exudative or catarrhal Inflammation: excess fluid.  
  TB lung.

- Fibrinous – pneumonia – fibrin

- Membranous (fibrino-necrotic) inflammation

- Suppuration/Purulent – Bacterial - neutrophils
• Serous – excess clear fluid – Heart, lung

• Allergic inflammation

• Haemorrhagic – b.v. damage - anthrax.

• Necrotising inflammation.
Acute inflammation has one of four outcomes:

- Abscess formation
- Progression to chronic inflammation
- Resolution—tissue goes back to normal
- Repair—healing by scarring or fibrosis
Abscess formation:

• "A localized collection of pus (suppurative inflammation) appearing in an acute or chronic infection, and associated with tissue destruction, and swelling."
• Site: skin, subcutaneous tissue, internal organs like brain, lung, liver, kidney,…….

• Pathogenesis: the necrotic tissue is surrounded by pyogenic membrane, which is formed by fibrin and help in localize the infection.
Carbuncle

- It is an extensive form of abscess in which pus is present in multiple loci open at the surface by sinuses.

- Occur in the back of the neck and the scalp.
Furuncle or boil

- It is a small abscess related to hair follicles or sebaceous glands, could be multiple furunclosis.
Cellulitis

- It is an acute diffuse suppurative inflammation caused by streptococci, which secrete hyaluronidase & streptokinase enzymes that dissolve the ground substances and facilitate the spread of infection.

- Sites:

  - Areolar tissue; orbit, pelvis, …
  
  - Lax subcutaneous tissue
Leukocyte activation. Different classes of cell surface receptors of leukocytes recognize different stimuli. The receptors initiate responses that mediate the functions of the leukocytes. Only some receptors are depicted.
NECROSIS:
A white blood cell dies after a meal
Ingesting “leukotoxic”
Streptococcus pyogenes
“Chemical substances mediate all phases of acute inflammation”

Thomas, Lewis (1913-1993)

1. Reactions are similar irrespective of tissue or type of injury

2. Reactions occur in absence of nervous connections
Chemical mediators of inflammation (EC: endothelial cells)
Vasodilatation:
- Histamine
- Prostaglandins
- Nitric oxide

Increased vascular permeability:
- Histamine
- Anaphylatoxins C3a and C5a
- Kinins
- Leukotrienes C, D, and E
- PAF
- Substance P

Chemotaxis:
- Complement fragment C5a
- Lipoxygenase products, lipoxins & leukotrienes (LTB4)
- Chemokines

Tissue Damage
- Lysosomal products
- Oxygen-derived radicals
- Nitric Oxide
Diversity of Effects of Chemical Mediators

Prostaglandins:
  • Vasodilation
  • Pain
  • Fever
  • Potentiating edema

IL-1 and TNF:
  • Endothelial-leukocyte interactions
  • Leukocyte recruitment
  • Production of acute-phase reactants
Adipose tissue showing mast cells around blood vessels and in the interstitial space. Stained with metachromatic stain to identify the mast cell granules (dark blue or purple). The red structures are fat globules stained with fat stain (oil red).
The first time an allergy prone person runs across an allergen such as ragweed, he or she makes large amounts of ragweed IgE antibody. These IgE molecules attach themselves to mast cells.

The second time that person has a brush with ragweed, the IgE primed mast cells release granules and powerful chemical mediators, such as histamine and cytokines, into the environment.

These chemical mediators cause the characteristic symptoms of allergy.
Ultrastructure and contents of neutrophil granules, stained for peroxidase activity. The large peroxidase-containing granules are the azurophil granules; the smaller peroxidase-negative ones are the specific granules (SG). N, portion of nucleus.
LEUKOTRINES & PROSTAGLANDINS
Leukotrienes and Prostaglandins: Potent mediators of inflammation

Derived from Arachidonic acid (AA): 20-carbon, unsaturated fatty acid produced from membrane phospholipids.

Principal pathways:
- 5-lipoxygenase: Produces a collection of leukotrienes (LT)
- Cyclooxygenase (COX): Produces prostaglandin H2 (PGH2)

PGH2 serves as substrate for two enzymatic pathways:
- Prostaglandins (PG)
- Thromboxanes (Tx).
Biosynthesis of leukotrienes and lipoxins by cell-cell interaction.
AA: arachidonic acid –derived; LTA4: Leukotriene A4; LTC4: Leukotriene C4
NITRIC OXIDE
Functions of nitric oxide (NO) in blood vessels and macrophages, produced by two NO synthase enzymes. NO causes vasodilation, and NO free radicals are toxic to microbial and mammalian cells. NOS: nitric oxide synthase.
IL-1 & Tumor Necrosis Factor (TNF)
Major effects of interleukin-1 (IL-1) and tumor necrosis factor (TNF) in inflammation
COMPLEMENT
Complement Activation Pathways
The activation and functions of the complement system. Activation of complement by different pathways leads to cleavage of C3. The functions of the complement system are mediated by breakdown products of C3 and other complement proteins, and by the membrane attack complex (MAC).
OXYGEN FREE RADICALS
Production of microbicidal reactive oxygen intermediates within phagocytic vesicles.
OXIDATIVE BURST:
Neutrophils kill microbes by producing reactive oxygen species, demonstrated here with the dye nitroblue tetrazolium (NBT)
Interrelationships between the four plasma mediator systems triggered by activation of factor XII (Hageman factor). Note that thrombin induces inflammation by binding to protease-activated receptors (principally PAR-1) on platelets, endothelium, smooth muscle cells, and other cells.
<table>
<thead>
<tr>
<th>Role of Mediators in Different Reactions of Inflammation</th>
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<tr>
<td><strong>Vasodilatation</strong></td>
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<tr>
<td>Prostaglandins</td>
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<tr>
<td>Nitric oxide</td>
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<tr>
<td>Histamine</td>
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<tr>
<td><strong>Increased vascular permeability</strong></td>
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<tr>
<td>Vasoactive amines</td>
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<tr>
<td>C3a and C5a (through liberating amines)</td>
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<tr>
<td>Bradykinin</td>
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<tr>
<td>Leukotrienes C4, D4, E4</td>
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<td>PAF</td>
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<tr>
<td>Substance P</td>
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<tr>
<td><strong>Chemotaxis, leukocyte recruitment and activation</strong></td>
</tr>
<tr>
<td>C5a</td>
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<tr>
<td>Leukotriene B4</td>
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<tr>
<td>Chemokines</td>
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<td>IL-1, TNF</td>
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<tr>
<td>Bacterial products</td>
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<tr>
<td><strong>Fever</strong></td>
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<td>IL-1, TNF</td>
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<tr>
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<td><strong>Pain</strong></td>
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<tr>
<td>Bradykinin</td>
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<tr>
<td><strong>Tissue damage</strong></td>
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<tr>
<td>Neutrophil and macrophage lysosomal enzymes</td>
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<td>Oxygen metabolites</td>
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<tr>
<td>Nitric oxide</td>
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## Summary of Mediators of Acute Inflammation

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Source</th>
<th>Vascular Leakage</th>
<th>Chemotaxis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine and serotonin</td>
<td>Mast cells, platelets</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Plasma substrate</td>
<td>+</td>
<td>-</td>
<td>Pain</td>
</tr>
<tr>
<td>C3a</td>
<td>Plasma protein via liver</td>
<td>+</td>
<td>-</td>
<td>Opsonic fragment (C3b)</td>
</tr>
<tr>
<td>C5a</td>
<td>Macrophages</td>
<td>+</td>
<td>+</td>
<td>Leukocyte adhesion, activation</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Mast cells, from membrane phospholipids</td>
<td>Potentiate other mediators</td>
<td>-</td>
<td>Vasodilatation, pain, fever</td>
</tr>
<tr>
<td>Leukotriene B₄</td>
<td>Leukocytes</td>
<td>-</td>
<td>+</td>
<td>Leukocyte adhesion, activation</td>
</tr>
<tr>
<td>Leukotrienes C₄ D₄ E₄</td>
<td>Leukocytes, mast cells</td>
<td>+</td>
<td>-</td>
<td>Bronchoconstriction, vasoconstriction</td>
</tr>
<tr>
<td>Platelet Activating Factor (PAF)</td>
<td>Leukocytes, mast cells</td>
<td>+</td>
<td>+</td>
<td>Bronchoconstriction, leukocyte priming</td>
</tr>
<tr>
<td>IL-1 and TNF</td>
<td>Macrophages, other</td>
<td>-</td>
<td>+</td>
<td>Acute-phase reactions, endothelial activation</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Leukocytes, others</td>
<td>-</td>
<td>+</td>
<td>Leukocyte activation</td>
</tr>
<tr>
<td></td>
<td>Macrophages, endothelium</td>
<td>+</td>
<td>+</td>
<td>Vasodilatation, cytotoxicity</td>
</tr>
</tbody>
</table>
Generation of arachidonic acid metabolites and their roles in inflammation. The molecular targets of some anti-inflammatory drugs are indicated by a red X.

COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid.
GLOSSARY

Prostaglandin
Arachidonic acid
Eicosanoid
Eicosanoids
Leukotriene
Prostacyclin
Thromboxane
Thromboxane-A synthase
Essential fatty acid interactions
Leukotriene B4
Leukotriene E4
Prostacyclin synthase
Leukotriene A4
Leukotriene D4
Leukotriene C4
Thromboxane A2
Arachidonate 5-lipoxygenase
Prostaglandin H2
Prostaglandin E synthase
Arachidonic acid 5-hydroperoxide
Leukotriene C4 synthase

abscess
acute inflammation
adhesion molecules
chemokinesis
chemotactic agent
chemotaxis
chronic inflammation
contact inhibition
degranulation
empyema
emigration
eosinophil
erosion
exudate
fibrin/fibrinous
fibrinogen
fibrous/fibrosis
free radicals
granulation tissue
granuloma
hyperemia
infection
keloid
left shift
leukocyte
leukemoid reaction
leukocytosis
lymphocyte
lysosomes
macrophage (AKA...)
margination
myeloperoxidase
neutrophil
neutrophilia
opsonization
organization
phagocytosis
plasma cell
pseudomembrane
purulent
pus
regeneration
resolution
scar
suppurate
transudate
ulcer