Pathophysiology of inflammation
Inflammation

- is a protective response
  - to eliminate the initial cause of cell injury
    - diluting, destroying and neutralizing the harmful agents
  - remove the damaged tissue
  - generate new tissue
The inflammatory response

- to immune reaction
- to injury
- to ischemic damage
The classic signs of inflammation

- redness
- swelling
- heat
- pain or discomfort
- loss of function

rubor

tumor

calor

dolor

functio laesa
Reparing mechanisms:

- Thrombotic and fibrinolytic system
- Inflammation
- Immunreaction
- Oral defense
Common mechanisms in all systems:

1. serum protease – antiprotease system
2. oxidative – reductive systems, free radicals
3. complement system
4. phagocytosis
Causes of inflammation:

A. Exogenous
   - Mechanical
   - Physical
   - Chemical
   - Biological

B. Endogenous
   - Circulatory disorder, hypoxia
   - Endogenous protease release
   - Immunocomplex formation
# Characteristics of inflammations

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
<td>Single injury</td>
<td>Permanent present of the causing agent /bacteria, etc./</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Hours, days</td>
<td>Weeks, months, years; depending on the causing agent</td>
</tr>
<tr>
<td><strong>Presentative symptom</strong></td>
<td>↑ permeability, exudation</td>
<td>Proliferative fibroblasts No exudation</td>
</tr>
<tr>
<td><strong>Main components in the process</strong></td>
<td>Liquid Proteins /proteases and antiproteases/ PMN leukocytes Macrophages</td>
<td>Macrophage Lymphocytes Eosinophyl granulocytes Connective tissue hiperplasy</td>
</tr>
<tr>
<td><strong>Connecting reactions</strong></td>
<td>Thrombosis</td>
<td>Immune response</td>
</tr>
</tbody>
</table>
ACUTE INFLAMMATION
Acute inflammatory response

- immediate vascular changes
- influx of inflammatory cells
  - neutrophils
- widespread effects of inflammatory mediators
Triggered by

- variety stimuli
  - infections
  - immune reactions
- blunt and penetrating trauma
- physical and chemical agents
  - burns
  - frostbite
  - irradiation
  - caustic chemicals
- tissue necrosis
Involved tissues and cells

- endothelial cells
- circulating WBC
- connective tissue cells
  - mast cells
  - fibroblasts
  - tissue macrophages
  - Lymphocytes
- components of extracellular matrix
  - fibrous proteins (collagen and elastine)
  - adhesive glikoproteins
  - proteoglikans
Endothelial cells

• selective permeability barrier to exogenous and endogenous inflammatory stimuli

• regulate leukocyte extravasation by expression of cell adhesion molecules and receptors

• contribute to the regulation and modulation of immune response

• regulate immune cell proliferation through CSF
Endothelial cells
Activated platelets

- increasing vascular permeability
- altering the chemotactic, adhesive and proteolytic properties of the endothelial cells
Neutrophils

- phagocytic leukocytes
- mannose receptors
  - bind glicoproteins of bacteria
- Toll-like receptors
  - respond to different types and components of microbes
- cell communication receptors
  - recognise specific cytokines and chemokines
- cell adhesion molecules
  - affect leukocyte adhesion
- complement receptors
  - Recognise degraded fragments of complement deposited on the microbial surface
Neutrophils
Monocyte / Macrophages

• produce potent vasoactive mediators
  • prostaglandins
  • leukotriens
  • platelet activating factors (PAF)
  • inflammatory cytokines
  • growth factors
Eosinophils, Basophils and Mast cells

- Produce
  - lipid mediators
  - cytokins
Mast cells

- The distribution places the mast cell in a sentinel position between environmental antigens and the host for a variety of acute and chronic inflammatory conditions.
Mast cells

- **activation** – release of preformed contents of granules
  - histamin
  - proteoglycans
  - proteases
  - cytokines – TNFα and IL-6

- **stimulation**
  - synthesis – cytokine and chemokines
  - Monocytes and macrophages
Two major components of inflammation:

• **Vascular stages**
  - leads to an increased in blood flow
  - changes in the small blood vessels of the microcirculation

• **Cellular stages**
  - leads to the migration of leukocytes from the circulation
  - their activation to eliminate the injurious agent
Vascular stages:

- characterized – response triplet:
  1. momentary vasoconstriction (seconds)
  2. vasodilatation – arterioles, venules (minutes)
  3. increased capillary permeability consequences:
    - swelling
    - mediator release
    - increased viscosity
    - Increased blood clotting (hours)

- mediators:
  - histamine
  - NO
Cellular stages:

• The cellular stage of acute inflammation is marked by changes in the endothelial cells lining the vasculature and movement of phagocytic leukocytes into the area of injury or infection.
Cellular response:

- Rolling
- L-selectin
- Neutrophil
- Shedding of L-selectin
- Integrin E-selectin
- Adhesion
- Diapedesis
- Blood-vessel wall
- Sialyl-LewisX
- Activating substances released by bacteria and damaged tissues
- Lipopolysaccharides, interleukin-1, and tumor necrosis factor α
- C3a, C5a, chemokines, histamine, prostaglandins, and leukotrienes
- Phagocytosis and destruction of C3b-coated bacteria
Cellular stages

1. rolling
2. margination
3. adhesion
4. transmigration across the endothelium – diapedesis
5. chemotaxis - migration
6. formation of inflammatory barrier
7. opsonization
8. phagocytosis
9. killing
10. digestion of bacteria
Exudation of neutrophil leukocytes I.:

- **Main stages:**
  - 1. margination
    - vasodilatation – stasis
      - RBC forms coils in the middle of blood vessels
      - granulocytes are at the wall of vessels
  - 2. adhesion
    - Granulocyte adhere to the epithelium
    - Function of adhesive proteins
    - Pavementing
Exudation of neutrophil leukocytes II:

- 3. emigration (diapedesis)
  - extravasation through pores
- 4. chemotaxis – migration
  - migration to the target
  - Origin and function of chemotactic substances
Chemotaxis

R = Receptor of chemotactic factor
SCF = Soluble chemotactic factor
Chemotaxis

Chemokine concentration

Direction of chemotaxis
Exudation of neutrophil leukocytes II.:

- 3. emigration (diapedesis)
  - extravastion through pores
- 4. chemotaxis – migration
  - migration to the target
- Origin and function
  - of chemotactic substances
- 5. formation of inflammatory barrier
- 6. opsonization
  - the coating of an antigen with antibody or complement to enhance binding
Exudation of neutrophil leukocytes III:

- **7. phagocytosis**
  - recognition and adherence
  - engulfment
  - intracellular killing
    - toxic oxygen
    - nitrogen products
    - Lysozymes
- **8. killing**
- **9. digestion of the bacteria**
Phases of acute inflammation

<table>
<thead>
<tr>
<th>Response</th>
<th>Adhesion</th>
<th>Chamotactic factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute phase: early stage (from minutes to hours)</td>
<td>Vasodilatation</td>
<td>Oedema</td>
</tr>
<tr>
<td><strong>Cascade</strong></td>
<td><strong>Histamine</strong></td>
<td><strong>Histamine</strong></td>
</tr>
<tr>
<td>Mast cell</td>
<td>Histamine</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Trombocyte</td>
<td><strong>Bradykinin</strong></td>
<td></td>
</tr>
<tr>
<td>Plasma components</td>
<td><strong>C5a/3a</strong></td>
<td><strong>C5a/3a</strong></td>
</tr>
<tr>
<td>Complement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
<td><strong>IL-1</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>IL-8</strong></td>
</tr>
<tr>
<td>Lipid mediators</td>
<td><strong>LTC₄/D₄</strong></td>
<td><strong>LTC₄/B₄</strong></td>
</tr>
<tr>
<td></td>
<td><strong>PGE₂/I₂</strong></td>
<td><strong>PAF</strong></td>
</tr>
</tbody>
</table>
Classified by function of inflammatory mediators:

1. vasoactive and smooth muscle – constricting properties
   - histamine
   - arachidonic acid metabolites
     - Prostaglandins
     - Platelet – activating factor
Arachinodic Acid Metabolites

Injured tissue, inflammatory mediators

Cell membrane phospholipids

Corticosteroid medications

Arachidonic acid

Lipoxygenase pathway

Leukotrienes (LTC₄, LTD₄, LTE₄)
Induces smooth muscle contraction
Constricts pulmonary airways
Increases microvascular permeability

Cyclooxygenase pathway

Prostaglandins (PGI₂, PGF₂ₐ)
Induces vaso-dilation and bronchoconstriction
Inhibits inflammatory cell function

Thromboxane (TXA₂)
Vasoconstriction
Bronchoconstriction
Promotes platelet function
Cell membrane phospholipids

Stimulus (phospholipase) (Inhibition by steroids)

Arachidonic

5 Lipoxigenase acid

5HETE Chemotaxis

LTB₄ Chemotaxis

O₂

O₂

PGG₂

PGH₂ + [O₂]

PGG₂ sintetase peroxidase PGH₂ sintetase

Prostacyclin PGI₂ Inhibits thrombocyte aggr. Vasodilatation

LTC₄

Vasodilatation

LTD₄ Enhances oedema formation

LTE₄

Vasoconstriction

Bronchoconstriction

↑Vascular permeability

PGE PGD2 PGF2α

Vasodilatation

Oedema formation

Isomerase

Reductase

Chemotactic lipids

Thromboxane A₂ Vasoconstrictio

Thrombocyte aggregation

Chemotactic lipids
Inhibition of the cyclo-oxygenase and prostaglandin synthesis by non-steroid anti-inflammatory drugs

Physiological stimulus

Inhibition w/ NSAID

Inflammatory stimulus

Cox-1
constitutive
Stomach   Kidney
Intestines Thrombocyte
Endothelium

PGE₂   TXA₂   PGI₂

Physiological function

Cox-2
inductable
Inflammatory places
(macrophages, synoviocyte)

Inflamm PGs   Proteases   O₂

Inflammation
Classified by function of inflammatory mediators:

• 1. vasoactive and smooth muscle – constricting properties
  • contribute to the inflammatory response
    - vasodilatation
    - increasing vascular permeability
    - enhancing the activity of phagocytes
  • kininogens – release of bradykinin
    • increases vascular permeability
    • contraction of smooth muscle
    • Dilatation of blood vessels

coagulation factors
vasoactive peptides
Classified by function of inflammatory mediators:

1. vasoactive and smooth muscle – constricting properties
2. plasma proteases, coagulation factors, vasoactive peptides
3. chemotactic factors
4. reactive molecules and cytokins – liberated from leukocytes
Interaction of the kinin, thrombotic, fibrinolytic and complement systems

Hageman factor
High molecular weight kininogene (HMWK)
Prekallikrein
Surface-active agents

Prekallikrein → Kallikrein

HMWK → Bradykinin (kinin)

Plasminogene → Plasmin (Fibrinolitic)

C3 → C3a (Complement)

XI → XIA

Prothrombin → Thrombin

Fibrinogene → Fibrin

Results of fibrin-split

Fibrinopeptids (clotting)
Important inflammatory mediators I.: 

• 1. classic mediators:
  • Histamine, serotonine, prostaglandins and derivates, PAF and other thromocyte derivates

• 2. oxidant agents:
  • superoxide derivetives, NO
Formation and inactivation of superoxide $O_2^-$-metabolites

**Formation of hydroxi-radicals**

**superoxide-anion**

**hydrogen-peroxide**

**hydroxi-radicals**

**endogene antioxidants**

- **superoxide-dismutase**
  - $2 O_2 + 2 H^+ \rightarrow H_2O_2 + O_2$

- **catalase**
  - $2 H_2O_2 \rightarrow 2 H_2O + O_2$

- **glutation-peroxidase**
  - $H_2O_2 + 2 GSH \rightarrow 2 H_2O + GSSG$

- $O_2 \rightarrow O_2^-$

- $H_2O_2 \rightarrow \text{hydroxi-radicals}$

- $\text{hydroxi-radicals} \rightarrow H_2O$
Important inflammatory mediators I.:

1. classic mediators:
   - Histamine, serotonin, prostaglandins and derivates, PAF and other thromocyte derivates

2. oxidant agents:
   - superoxide derivatives, NO

3. cytokines

4. chemokines

5. proteases:
   - Hagemann - factor
Important inflammatory mediators II:

- 6. complement and derivatives
- 7. adhesive proteins:
  - selectin group - antiflamin
- 8. antibodies
- 9. neurogene mediators:
  - substance P, CGRP
- 10. other factors
  - growth factor (somatomedins)
  - colony stimulating factor (CSF)
## Inflammatory mediators and their function I.

<table>
<thead>
<tr>
<th>Mediators</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine, serotonin, bradykinin, C3a, C5a, PGD₂, PGE₂, PGI₂, LTC₄, active Hageman factor, fibrinopeptids</td>
<td>Increase the permeability of small vessel</td>
</tr>
<tr>
<td>FMLP, C5a, TXA₂, LTB₄, LTC₄, LTD₄, LTE₄</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Hisztamin, szerotonin, bradykinin, C3a, C5a, TXA₂, LTB₄, LTC₄, LTD₄, LTE₄, PAF</td>
<td>Smooth muscle contraction</td>
</tr>
<tr>
<td>C3a, C5a, MCP-1, IL-8</td>
<td>Degranulation of mast and basophil cells</td>
</tr>
<tr>
<td>LPS, LTD₄, IL-1, TNF-α, MCP-1</td>
<td>Increased endothel cell cohesion</td>
</tr>
<tr>
<td>Bradykinin, PGE₂</td>
<td>Pain</td>
</tr>
<tr>
<td>IL-1, IL-6, TNF-α, MIP-1, PGE₂</td>
<td>Pirogenes</td>
</tr>
<tr>
<td>TXA₂, PAF</td>
<td>Thrombocyte aggregation</td>
</tr>
</tbody>
</table>
Inflammatory mediators and their function II.

<table>
<thead>
<tr>
<th>Mediators</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMLP, C5a, IL-8 and other chemokins, LTB₄, PAF, laminin, kollagene fragments, fibrinopeptids, C3b, iC3b, IgG (Fc rész), fibronectin, C5a, PAF, TNF-α, IL-8, most chemoattractant, phagocytic materials</td>
<td>-phagocytes -chemotaxis -cohesion and phagocytosis -reactive, intermedier O₂ formation and release of lysosomol granules</td>
</tr>
<tr>
<td>Serum amyloid A (SAA), CRP, fibrinogene, α₁-antitripsin, haptoglobin, ceruloplasmin, stb.</td>
<td>Acute phase proteins</td>
</tr>
<tr>
<td>TNF-α, TNF-β, PAF, reactive O₂ intermediers (ROI), reactive N₂ intermediers (RNI), lysosomal enzymes</td>
<td>Possible injury of mast cells and tissues</td>
</tr>
<tr>
<td>bFGF, GM-CSF, TGF- β, TGF- α, IGF-1, PDGF, VEGF/VPF, IL-1, IL-6, IL-8, TNF-α, interferons</td>
<td>Angiogenezis</td>
</tr>
</tbody>
</table>
Main protease inhibitors of the serum

- C-1 inhibitor
  - Hagemann f., XI.f., kallikrein, plasmin
  - Effect mainly local, substrates: plasmin, kallikrein
  - Acute phase protein

- α-2 macroglobulin
  - Substrate: XI. factor
  - Phagocytes break down this inhibitor

- α-1 protease inhibitor
  - Most effective protease inhibitor

- Antithrombin - III
  - Heparin activates it
Cytokines and chemokines

• Produce:
  • Macrophages
  • Lymphocytes
  • Endothelium
  • Epithelium
  • Connective tissue types
<table>
<thead>
<tr>
<th>Cytokins:</th>
<th>Most important members</th>
<th>Main effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukins</td>
<td>IL-1, IL-8, IL-6, IL-11</td>
<td>see separately</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Transforming GF-β</td>
<td>Monocyte, macrophage chemotaxis, Ly proliferation</td>
</tr>
<tr>
<td>Stimulating factors</td>
<td>Granulocyte colony, Macrophage colony</td>
<td>Phagocytosis enhancement</td>
</tr>
<tr>
<td>Tumor necrosis factors</td>
<td></td>
<td>Vascular effects of inflammation</td>
</tr>
<tr>
<td>Interferons</td>
<td>INF</td>
<td>NK citotoxicity↑, adhesion ↑</td>
</tr>
<tr>
<td>Inhibitory factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYTOKINES</td>
<td>SOURCE</td>
<td>BIOLOGIC ACTIVITY</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Interleukin-1 (IL-1)</td>
<td>Macrophages, endothelial cells, some epithelial cells</td>
<td>Wide variety of biologic effects; activates endothelium in inflammation; induces fever and acute-phase response; stimulates neutrophil production</td>
</tr>
<tr>
<td>Interleukin-2 (IL-2)</td>
<td>CD4+, CD8+ T cells</td>
<td>Growth factor for activated T cells; induces synthesis of other cytokines; activates cytotoxic T lymphocytes and NK cells</td>
</tr>
<tr>
<td>Interleukin-3 (IL-3)</td>
<td>CD4+ T cells</td>
<td>Growth factor for progenitor hematopoietic cells</td>
</tr>
<tr>
<td>Interleukin-4 (IL-4)</td>
<td>CD4+ T helper cells, mast cells</td>
<td>Promotes growth and survival of T, B, and mast cells; causes T&lt;sub&gt;H&lt;/sub&gt;2 cell differentiation; activates B cells and eosinophils and induces IgE-type responses</td>
</tr>
<tr>
<td>Interleukin-5 (IL-5)</td>
<td>CD4+ T&lt;sub&gt;H&lt;/sub&gt;2 cells,</td>
<td>Induces eosinophil growth and development</td>
</tr>
<tr>
<td>Interleukin-6 (IL-6)</td>
<td>Macrophages, endothelial cells, T lymphocytes</td>
<td>Stimulates the liver to produce mediators of acute-phase inflammatory response; also induces proliferation of antibody-producing cells by the adaptive immune system</td>
</tr>
<tr>
<td>Interleukin-7 (IL-7)</td>
<td>Bone marrow stromal cells</td>
<td>Primary function in adaptive immunity; stimulates pre-B cells and thymocyte development and proliferation</td>
</tr>
<tr>
<td>Interleukin-8 (IL-8)</td>
<td>Macrophages, endothelial cells</td>
<td>Primary function in adaptive immunity; chemoattracts neutrophils and T lymphocytes; regulates lymphocyte homing and neutrophil infiltration</td>
</tr>
<tr>
<td>Interleukin-10 (IL-10)</td>
<td>Macrophages, some T-helper cells</td>
<td>Inhibitor of activated macrophages and dendritic cells; decreases inflammation by inhibiting T&lt;sub&gt;T&lt;/sub&gt;1 cells and release of IL-12 from macrophages</td>
</tr>
<tr>
<td>Interleukin-12 (IL-12)</td>
<td>Macrophages, dendritic cells</td>
<td>Enhances NK cell cytotoxicity in innate immunity; induces T&lt;sub&gt;H&lt;/sub&gt;1 cell differentiation in adaptive immunity</td>
</tr>
<tr>
<td>Type I interferons (IFN-α, IFN-β)</td>
<td>Macrophages, fibroblasts</td>
<td>Inhibit viral replication, activate NK cells, and increase expression of MHC-I molecules on virus-infected cells</td>
</tr>
<tr>
<td>Interferon-γ (IFN-γ)</td>
<td>NK cells, CD4+ and CD8+ T lymphocytes</td>
<td>Activates macrophages in both innate immune responses and adaptive cell-mediated immune responses; increases expression of MHC-I and -II and antigen processing and presentation</td>
</tr>
<tr>
<td>Tumor necrosis factor-α (TNF-α)</td>
<td>Macrophages, T cells</td>
<td>Induces inflammation, fever, and acute-phase response; activates neutrophils and endothelial cells; kills cells through apoptosis</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Macrophages, endothelial cells, T lymphocytes</td>
<td>Large family of structurally similar cytokines that stimulate leukocyte movement and regulate the migration of leukocytes from the blood to the tissues</td>
</tr>
<tr>
<td>Granulocyte-macrophage CSF (GM-CSF)</td>
<td>T cells, macrophages, endothelial cells, T lymphocytes</td>
<td>Promotes neutrophil, eosinophil, and monocyte maturation and growth; activates mature granulocytes</td>
</tr>
<tr>
<td>Granulocyte CSF (G-CSF)</td>
<td>Macrophages, fibroblasts, endothelial cells</td>
<td>Promotes growth and maturation of neutrophils consumed in inflammatory reactions</td>
</tr>
<tr>
<td>Monocyte CSF (M-CSF)</td>
<td>Macrophages, activated T cells, endothelial cells</td>
<td>Promotes growth and maturation of mononuclear phagocytes</td>
</tr>
</tbody>
</table>

CSF: colony-stimulating factor; NK: natural killer; T<sub>H</sub>1, T-helper type 1; T<sub>H</sub>2, T-helper type 2; MHC, major histocompatibility complex.
Cytokines

Diagram:

- Eicosanoids
- Chemokines
- Oxygen radicals

- Neutrophils:
  - Aggregation
  - Priming

- Acute-Phase Response:
  - Fever
  - Anorexia
  - Hypotension
  - Increased heart rate
  - Corticosteroid and ACTH release

- T cells

- Macrophage

- LPS

- IFN-γ

- TNF-α, IL-1

- Gram-negative bacteria
Chemokins

• chemoattractant

• recruit and direct the migration of immune and inflammatory cells

• two classes:
  • inflammatory chemokines
    • produce in response to bacterial toxins and inflammatory cytokines
  • homing chemokines
    • constitutively expressed
    • up-regulated during inflammatory reactions and immune responses
Chemokins I.

8-10 kD proteins, amino acid sequence identical in 20-70%. Subcategories according to the intramolecular place of cystein (Cyst) groups:

1. α-chemokin: 4 Cyst; one amino acid (x) between the first two Cyst:

-C-x-C- structure

Two subgroups:

1.1 Before -C-x-C- group, near N-terminal a Glu-Leu-Arg sequence
   Chemotactic onto neutrophyl granulocytes

1.2 Not belonging to the 1.1 group,
   Chemotactic onto lymphocytes
Chemokins II.

2. β-chemokin: First two Cyst are neighbours, -C-C- structure
- mononuclear leukocytes in chronic inflammation

3. fractalkin: 3 amino acids between first two Cyst, -C-x-x*-x**-C- structure
Chemokin receptors

The different receptors of chemokins are coupled to G proteins, so likely to belong to the 7-helix receptor superfamily. There exist cell specific and non-specific chemokin receptors. The most important classes:

1. α-chemokin receptors: 4 receptor belong here, structure: beside -C-x-C- group binding domain contains R1, R2-R4 amino acids -C-x-C-R1.

2. β-chemokin receptors: 8 receptor belong here
Acute-phase response

• The constellation of systemic manifestations that may occur during acute inflammation.

• alteration in WBC count and fever

• These response are generated by the release of cytokines (IL-6, IL-1, TNFα)

• Acute-phase proteins!
Chronic inflammatory response

- infiltration
  - macrophages
  - lymphocytes
  - fibroblasts
- leading
  - persistent inflammation
  - fibroblast proliferation
  - scar formation
Thank You for Your Attention!