WELCOME

TO

PATHOPHYSIOLOGY

UNIT 1

TOPIC :

- **Basic mechanism involved in the process of inflammation and repair:**

  Introduction, Clinical signs of inflammation, Different types of Inflammation, Mechanism of Inflammation– Alteration in vascular permeability and blood flow, migration of WBC's, Mediators of inflammation, Basic principles of wound healing in the skin, Pathophysiology of Atherosclerosis

Inflammation

- Inflammation is the body's protective response to injury, infection, or irritation.
- It aims to remove the cause of injury, eliminate damaged cells, and initiate tissue repair.
- It is a non-specific and innate immune response.

Causes of Inflammation:

- Physical agents: heat, cold, trauma, radiation
- Chemical agents: acids, alkalis, toxins
- Biological agents: bacteria, viruses, fungi, parasites
- Immune reactions: hypersensitivity, autoimmunity
- Ischemia (loss of blood supply)

Cardinal (Clinical) Signs of Inflammation

Latin Term	English Meaning	Cause
Rubor	Redness	Vasodilation → ↑ blood flow
Calor	Heat	↑ Blood flow and metabolic activity
Tumor	Swelling	Edema due to fluid leakage
Dolor	Pain	Release of chemical mediators (e.g. bradykinin, prostaglandins)
Functio laesa	Loss of function	Due to pain and swelling (added by Virchow)

Types of Inflammation

1. Acute Inflammation

➢ A short-term process occurring in response to tissue injury, usually appearing within minutes or hours.

- **Duration**: Lasts for a few hours to a few days.
- **Features**:
  - Rapid onset
  - Prominent exudation of fluid and plasma proteins (edema)
  - Migration of neutrophils (a type of white blood cell)
- **Signs**: Redness, swelling, heat, pain, and loss of function.
- **Outcomes**:
  - Resolution (healing)
  - Suppuration (pus formation)
  - Chronic inflammation
  - Fibrosis or scarring

2. Chronic Inflammation

➢ A prolonged inflammatory response where tissue destruction and healing occur simultaneously.

- **Duration**: Weeks, months, or even years.
- **Features**:
  - Infiltration by mononuclear cells (macrophages, lymphocytes, plasma cells)
  - Tissue destruction
  - Attempts at healing by connective tissue replacement (fibrosis) and angiogenesis
- **Causes**:
  - Persistent infections (e.g., tuberculosis)
  - Prolonged exposure to toxins (e.g., silica dust)
  - Autoimmune diseases (e.g., rheumatoid arthritis)

Mechanism of Inflammation

Step 1: Injury or Infection

- Initial trigger: trauma, microbes, etc.
- Cells like macrophages, mast cells, and dendritic cells detect the danger.

Step 2: Release of Chemical Mediators

- Damaged cells release inflammatory mediators such as:
  - Histamine
  - Bradykinin
  - Prostaglandins
  - Cytokines (e.g. IL-1, TNF-α)
- These mediators start the inflammatory process.

Step 3: Vasodilation

- Histamine and nitric oxide cause local blood vessels to dilate, increasing blood flow.
- This causes redness (rubor) and heat (calor).

Step 4: Increased Vascular Permeability

- Capillaries become leaky, allowing plasma and proteins to escape into tissues.
- Leads to swelling (tumor) and pain (dolor) due to nerve compression.

Step 5: Leukocyte Recruitment (Cellular Events)

- White blood cells (mainly neutrophils) move from blood to the injury site.
  - Margination → WBCs move to vessel edges.
  - Rolling and Adhesion → mediated by selectins and integrins.
  - Diapedesis → WBCs pass through capillary walls.
  - Chemotaxis → guided by chemical signals to the injury site.

Step 6: Phagocytosis

- Neutrophils and macrophages engulf and destroy microbes and debris using:
  - Oxygen-dependent killing (ROS)
  - Enzymatic degradation

Step 7: Resolution or Repair

- If the cause is eliminated:
  - Inflammation resolves.
  - Tissues regenerate or heal by fibrosis (scarring).

Alteration in Vascular Permeability and Blood Flow

→ Inflammation causes major changes in blood vessels, especially at the microcirculation level (arterioles, capillaries, venules).

Steps Involved:

1. *Vasodilation*

- Triggered by histamine and nitric oxide (NO)
- Increases blood flow to the area → causes redness (rubor) and heat (calor)

2. *Increased Vascular Permeability*

- Mediators like histamine, bradykinin, leukotrienes cause endothelial cells to contract
- Gaps form between cells → plasma proteins and fluid leak into tissue
- Results in swelling (tumor)

3. *Slowing of Blood Flow (Stasis)*

- Loss of fluid into tissues causes blood viscosity to increase
- Circulating cells (especially WBCs) move slower → start margination

4. *Margination and Adhesion*

- WBCs (mostly neutrophils) line the blood vessel walls and prepare to exit into tissues

Migration of White Blood Cells (WBCs)

- The migration of white blood cells (WBCs), also called leukocyte migration or leukocyte recruitment, is a vital part of the inflammatory response. When tissues are injured or infected, WBCs move from the bloodstream to the affected tissues to eliminate pathogens, clear debris, and promote healing.
- This process occurs in a well-regulated multistep sequence and involves chemical signals (chemokines and cytokines) and adhesion molecules on endothelial cells and leukocytes.

Phases of WBC Migration

1. Margination

- As blood flow slows down in inflamed tissues, WBCs move toward the periphery (margin) of blood vessels, particularly in small venules.
- **Reason**: In normal conditions, WBCs flow in the center of the blood vessel due to axial flow, but in inflammation, vasodilation and slowing of flow bring WBCs closer to the vessel wall.

2. Rolling

- WBCs begin to **tumble and roll** along the inner wall of blood vessels.
- **Mediators**: This is mediated by **selectins**:
  - **E-selectin** (on endothelial cells)
  - **P-selectin** (from Weibel-Palade bodies of endothelial cells and platelets)
  - **L-selectin** (on leukocytes)
- **Mechanism**: These selectins bind weakly to glycoprotein ligands on leukocytes, causing intermittent adhesion and rolling movement.

3. Adhesion (Firm Binding)

- WBCs **firmly attach** to the endothelial surface.
- **Mediators**:

  - **Integrins** on leukocytes (e.g., LFA-1, Mac-1)
  - **ICAM-1 and VCAM-1** on endothelial cells
- **Regulation**: Chemokines (like IL-8) activate integrins on WBCs, increasing their affinity for endothelial adhesion molecules.

4. Transmigration (Diapedesis)

- WBCs squeeze through the endothelial cell junctions to enter the tissue.
- **Location**: Mainly occurs in **postcapillary venules.**
- **Mediators**:
  - **PECAM-1 (CD31)** – found on both endothelial cells and leukocytes – helps in passage.
- WBCs then secrete **collagenases** to penetrate the basement membrane.

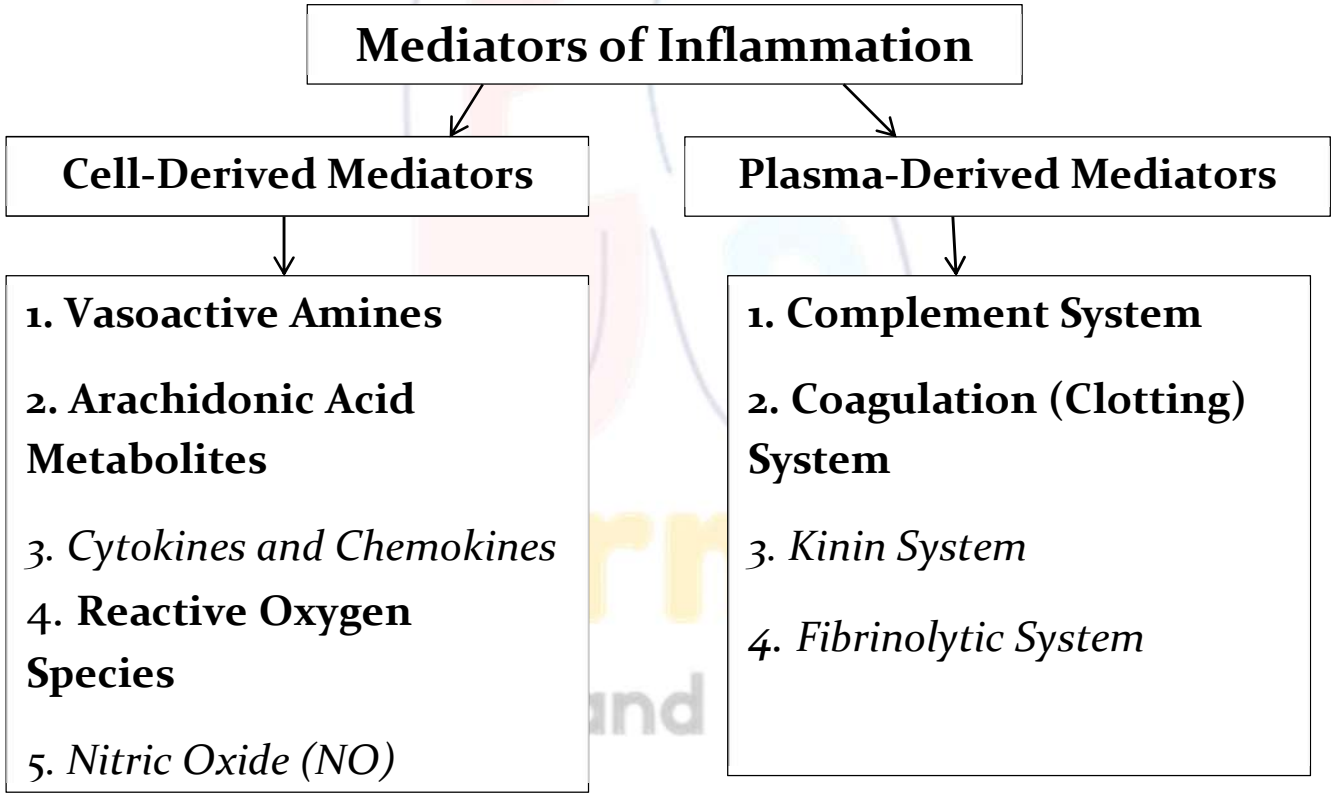
5. Chemotaxis

- Directed movement of WBCs toward the site of infection/injury along a chemical gradient.
- **Chemotactic agents**:
  - **Bacterial products** (e.g., N-formyl methionine peptides)
  - **Complement proteins** (e.g., C5a)
  - **Cytokines** (e.g., IL-8)
  - **Leukotriene B4 (LTB4)**
- WBCs follow this gradient using **cytoskeletal rearrangements** and **surface receptors**.

Mediators of Inflammation

- Inflammatory mediators are chemical substances that initiate, regulate, and sustain the inflammatory response.
- These mediators may be derived from cells or plasma proteins and act on blood vessels, immune cells, and tissues to produce the characteristic signs of inflammation: redness, heat, swelling, pain, and loss of function.

Classification of Inflammatory Mediators



I. Cell-Derived Mediators

- Produced locally by cells such as mast cells, macrophages, endothelial cells, and leukocytes.

1. *Vasoactive Amines*

These act quickly and are the **first mediators** to be released.

- **Histamine**
  - Source: Mast cells, basophils, platelets
  - Actions: Vasodilation, increased vascular permeability, bronchoconstriction
  - Role: Early phase of inflammation
- **Serotonin (5-HT)**
  - Source: Platelets and enterochromaffin cells
  - Actions: Vasoconstriction (in some cases), increased permeability

2. *Arachidonic Acid Metabolites (Eicosanoids)*

Derived from membrane phospholipids via **phospholipase A2**.

- **Prostaglandins (PGs)**
  - Source: All nucleated cells
  - Actions: Vasodilation, fever, pain (especially PGE2)
- **Leukotrienes (LTs)**
  - Source: Leukocytes, mast cells
  - Actions: Bronchoconstriction, increased vascular permeability, chemotaxis
- **Lipoxins**
  - Source: Leukocytes & platelets
  - Actions: Inhibit inflammation, oppose actions of leukotrienes

3. Cytokines and Chemokines

- **Cytokines** (e.g., **TNF-α**, **IL-1**, **IL-6**)
  - Source: Activated macrophages, T-cells, endothelial cells
  - Actions: Fever, leukocyte recruitment, acute-phase protein production in liver
- **Chemokines** (e.g., **IL-8**, **MCP-1**)
  - Source: Various cells
  - Actions: Attract and activate leukocytes (chemotaxis)

4. Reactive Oxygen Species (ROS)

- Source: Neutrophils and macrophages
- Actions: Destroy microbes, damage host tissues if excessive

5. Nitric Oxide (NO)

- Source: Endothelial cells, macrophages
- Actions: Vasodilation, inhibits platelet aggregation, microbial killing

II. Plasma-Derived Mediators

➢ Circulate in an inactive form and get activated during inflammation.

1. Complement System

- Source: Liver (produced as inactive precursors)
- Key components:
  - **C3a, C5a** – Anaphylatoxins: increase vascular permeability, chemotaxis
  - **C3b** – Opsonization (enhances phagocytosis)
  - **C5b-9** – Membrane attack complex (MAC): causes cell lysis

2. Coagulation (Clotting) System

- Generates **fibrin**, which acts as a barrier
- **Thrombin** promotes leukocyte adhesion and chemotaxis

3. Kinin System

- Produces **Bradykinin**:
  - Actions: Vasodilation, increased permeability, pain

4. Fibrinolytic System

- Helps in clot breakdown and may influence inflammation indirectly.

Basic Principles of Wound Healing in the Skin

→ Wound healing in the skin is a complex and dynamic biological process that restores the integrity of injured tissue. It involves a series of coordinated cellular and molecular events. The process aims to restore the skin's structure and function after injury from trauma, burns, surgery, or infection.

Phases of Wound Healing

➢ Wound healing occurs in four overlapping phases:

1. Hemostasis (Immediate Phase)

- **Time**: Immediately after injury (minutes to hours)
- **Purpose**: To stop bleeding and form a clot
- **Key Events**:
  - Vasoconstriction of blood vessels
  - Platelet aggregation at injury site
  - Formation of **fibrin clot** (temporary matrix)
  - Release of **cytokines and growth factors** (e.g., PDGF, TGF-β)

2. Inflammatory Phase

- **Time**: 1–4 days post-injury
- **Purpose**: Remove debris and pathogens; prepare wound for repair
- **Key Events**:
  - Vasodilation and increased vascular permeability
  - Infiltration of **neutrophils** (early) and **macrophages** (later)
  - Phagocytosis of bacteria and dead tissue
  - Release of pro-inflammatory mediators (e.g., histamine, TNF-α, IL-1)

3. Proliferative Phase

- **Time**: 4–21 days post-injury
- **Purpose**: Rebuild tissue structure

- **Key Events**:
  - **Fibroblast proliferation** and **collagen (type III) synthesis**
  - Formation of **granulation tissue** (new connective tissue & capillaries)
  - **Angiogenesis**: New blood vessel formation
  - **Re-epithelialization**: Migration and proliferation of keratinocytes to restore the epidermal layer

4. Maturation/Remodeling Phase

- **Time**: 21 days to months or even years
- **Purpose**: Strengthen and reorganize the tissue
- **Key Events**:
  - Replacement of **type III collagen with type I collagen**
  - Apoptosis of unnecessary cells (e.g., fibroblasts, endothelial cells)
  - Scar formation and wound contraction (by **myofibroblasts**)
  - Restoration of tensile strength (up to 70–80% of original)

Pathophysiology of Atherosclerosis

- Atherosclerosis is a chronic inflammatory disease of large and medium-sized arteries characterized by the formation of atheromatous plaques (atheromas) within the intimal layer of the blood vessel wall. These plaques lead to narrowing of the arteries, reduced blood flow, and can cause ischemia, infarction, or thromboembolic events.

Mechanism of Atherogenesis:

1. **Endothelial Injury**
   - Caused by hypertension, smoking, or high LDL
   - Leads to increased permeability and adhesion of monocytes
2. **LDL Accumulation and Oxidation**
   - Oxidized LDL is taken up by macrophages → forms **foam cells**
3. **Fatty Streak Formation**
   - Foam cells accumulate beneath the endothelium
4. **Inflammation and Smooth Muscle Migration**
   - Cytokines attract more macrophages
   - Smooth muscle cells migrate from media to intima
5. **Fibrous Plaque Formation**
   - Collagen and lipids form a raised lesion (atheromatous plaque)
6. **Plaque Rupture and Thrombosis**
   - Plaques can rupture → trigger **blood clots (thrombosis)** → heart attack or stroke

Complications of Atherosclerosis:

- Myocardial infarction (heart attack)
- Stroke
- Peripheral artery disease
- Aneurysms
- Sudden cardiac death

Prevention/Treatment:

- Lifestyle changes (diet, exercise, quit smoking)
- Statins (lower LDL)
- Anti-hypertensives
- Antiplatelet therapy (aspirin)
- Surgery (angioplasty, bypass)