Chapter 3: The Inflammatory Reaction

1. Inflammation

1.1. Definition

The term "inflammation" comes from the Latin word *inflammare*, meaning "to burn." It is a central component of innate (non-specific) immunity and is generally defined as a response to disrupted tissue homeostasis, induced by invading pathogens or endogenous signals such as damaged cells. However, injuries or trauma (in the absence of infection) and exposure to foreign particles, irritants, or pollutants are also powerful activators of inflammation. Therefore, it is a vital defense mechanism for health.

The basic signs of inflammation include:

1. **Edema (swelling)**, caused by the progressive accumulation of fluid outside blood vessels.
2. **Pain**, resulting from the pressure exerted by edema on surrounding tissues and/or a direct response to reactions involving prostaglandins, serotonin, and bradykinin.
3. **Redness**, due to vasodilation at the inflammatory site.
4. **Fever**, triggered by pro-inflammatory mediators that contribute to an increase in local and/or systemic temperature.

The three main objectives of the inflammatory reaction are:

- **Elimination of the causative agent**, such as microbes or toxins.
- **Removal of dead tissue**.
- **Replacement of dead tissue** with normal tissue or scar formation.

1.2. Mechanisms of Inflammation

The inflammatory response is a coordinated activation of signaling pathways that regulate the levels of inflammatory mediators in resident tissue cells and inflammatory cells recruited from the blood. Although the processes involved in the inflammatory response depend on the precise nature and location of the initial stimulus, they all share a common mechanism, summarized as follows:

1. **Pattern recognition receptors (PRRs) detect the harmful stimulus**.
2. **Activation of inflammatory pathways**.
3. **Release of inflammatory mediators**.
4. **Recruitment of inflammatory cells** (Figure 1).

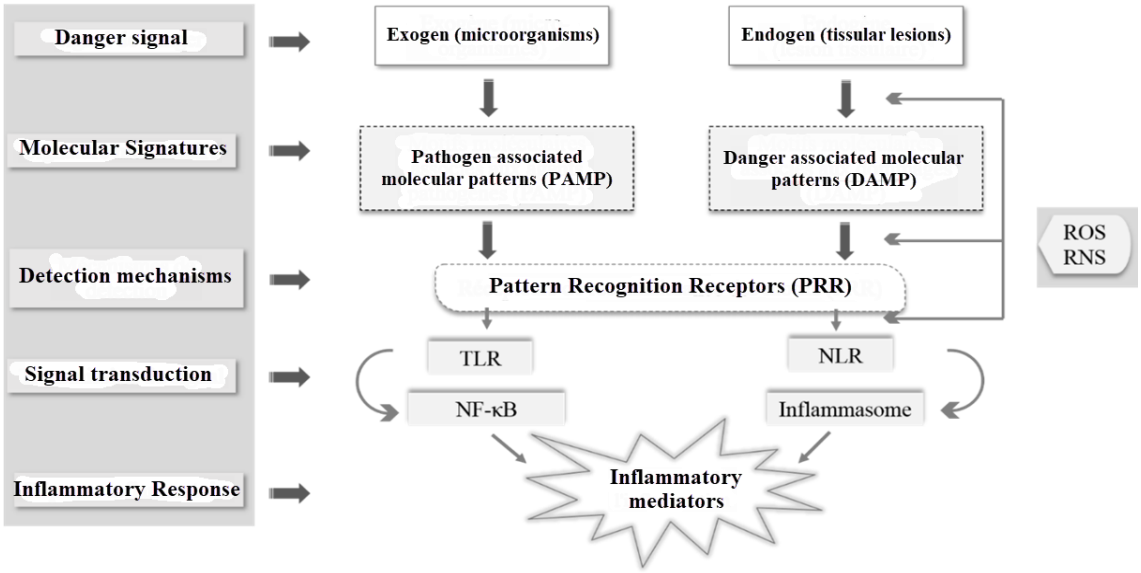


Figure1: Mechanism of Inflammatory Response Initiation

a. Initiation of Inflammation (Pattern Recognition Receptors: PRRs)
(Previously covered in earlier chapters)

Inflammatory stimuli are first recognized by host cells through **pattern recognition receptors (PRRs)**, which are expressed by cells of both the innate and adaptive immune systems.

These receptors recognize:

- **Exogenous signals**, such as **lipopolysaccharides (LPS)** and **flagellin** from Gram-negative bacteria, **lipoteichoic acid** from Gram-positive bacteria, and **viral RNA**. These conserved microbial structures (patterns) are referred to as **pathogen-associated molecular patterns (PAMPs)**.
- **Non-infectious molecules**, including allergens and environmental pollutants such as **silica** and **asbestos**.
- **Multiple endogenous signals** released during tissue injury, originating either from dying (necrotic) cells or from the degradation of the extracellular matrix. Examples of **intracellular damage-associated molecular patterns (DAMPs)** include **heat shock proteins (HSPs)**, **high mobility group box 1 (HMGB1) protein**, **ATP**, and **DNA**. **Extracellular DAMPs** include **fibronectin** and **hyaluronic acid**.

To date, several **pattern recognition receptors (PRRs)** have been identified with the selective ability to detect PAMPs, DAMPs, or both. These include:

- **Toll-like receptors (TLRs)**,
- **C-type lectin receptors (CLRs)**,
- **RIG-I-like receptors (RLRs)**,
- **NOD-like receptors (NLRs)**.

b. Signal Transduction

The interaction of **PRRs** with their respective stimuli leads to **signal transduction** to the nucleus, where a selective set of genes is activated. These signaling cascades promote the production of **cytokines, chemokines, enzymes, growth factors, and additional molecules** necessary for **antimicrobial resistance and tissue repair**.

One of the most important inflammatory pathways is that of the **NF-κB transcription factor**, which plays a crucial role in the inflammatory reaction. **NF-κB** is a dimer formed from five proteins, and its activation is induced by a range of stimuli, including **inflammatory cytokines, bacterial or viral patterns, stress, ultraviolet radiation, and ionizing radiation**.

- Under **physiological conditions**, **IκB proteins** in the cytoplasm inhibit NF-κB.
- **Stimulated PRRs activate an IκB kinase (IKK)**, which regulates the activation of the NF-κB pathway.
- **Phosphorylation of IκB** leads to its degradation and the subsequent **release of NF-κB**.
- **NF-κB moves to the nucleus**, where it activates the transcription of target genes.
- This pathway results in the **production of pro-inflammatory cytokines and the recruitment of inflammatory cells**, contributing to the inflammatory response. **Figure 2** summarizes this signaling pathway.

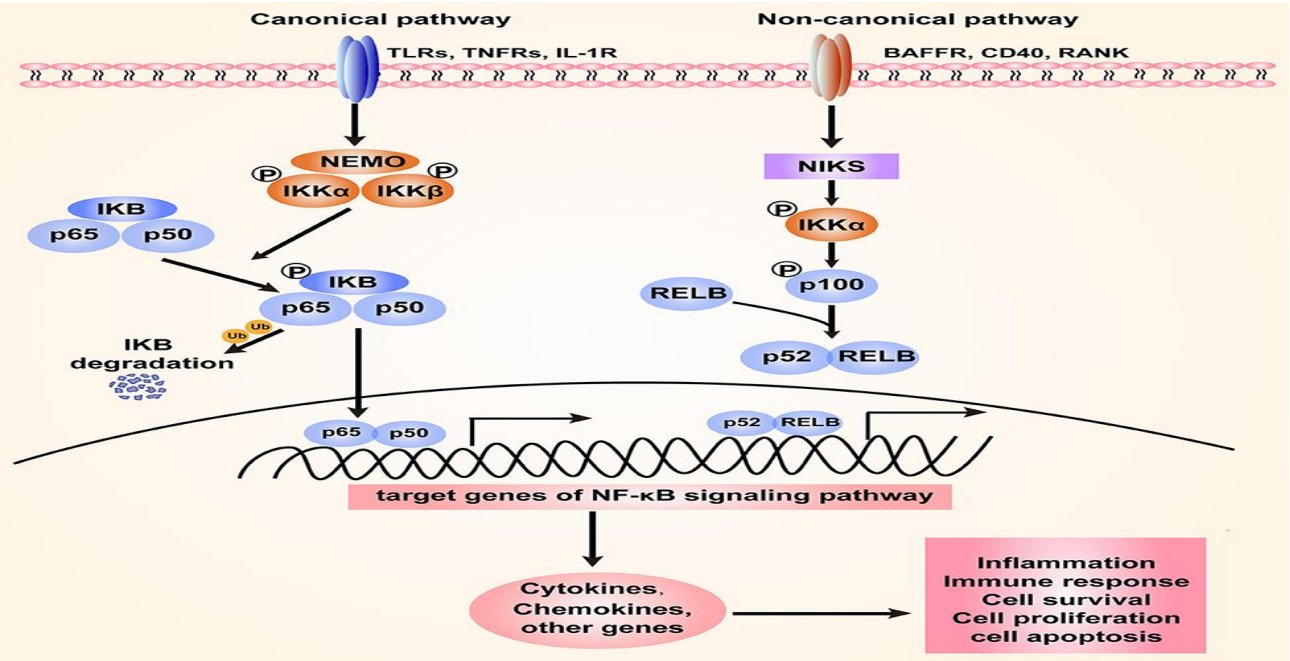


Figure 2: **Figure 2: NF-κB Inflammatory Signaling Pathway**

c. Inflammatory Mediators

Signal transduction to the nucleus induces the production of **a wide array of pro-inflammatory mediators**. These mediators generally have **short half-lives** and are **rapidly inactivated** by various systems. They are primarily released by **immune cells**, including **monocytes, macrophages, and lymphocytes**, but also by **fibroblasts, endothelial cells, and other cell types**.

- Phospholipid Metabolites of the Cell Membrane

Prostaglandins (PGs) and **leukotrienes (LTs)** are derived from **arachidonic acid metabolism**. **Platelet-activating factor (PAF)** is also an important mediator. These fatty acid derivatives play a crucial role in **platelet aggregation** and **increase vascular permeability**. Many **anti-inflammatory drugs** target this group of molecules.

- Cytokines

Cytokines such as **IL-1β, IL-6, IL-8, IL-12, and TNF-α** act to:

- Induce the expression of **cell adhesion molecules (CAMs)** on endothelial cells, enhancing leukocyte adhesion.
- Attract **neutrophils** to the inflammatory site.
- Induce the production of **prostacyclin (PGI_2)**.
- Stimulate the synthesis of **platelet-activating factor (PAF)**.
- Mediate the development of the **acute phase response**.
- Stimulate **fibroblast proliferation** and increase **collagen synthesis**.

- The Complement System

(Explained in **Chapter 2**)

- The Kinin System

Bradykinin is released after the activation of the kinin system by **coagulation factor XII**. The kinin system directly influences **vascular permeability**, generating mediators that **increase vascular permeability**. Additionally, **bradykinin is responsible for two major discomforting effects of inflammation: itching and pain**.

- The Coagulation System

The Coagulation System

The coagulation system is activated at sites of injury. **Fibrinopeptides**, produced during coagulation, act as **chemoattractants for neutrophils** and **increase vascular permeability**. **Thrombin** also promotes **fibroblast proliferation** and **leukocyte adhesion**.

- The Fibrinolytic System

Plasmin plays multiple roles in the inflammatory process, including:

- **Activation of the complement system via C3**.
- **Cleavage of fibrin**, leading to the formation of **fibrin degradation products**, which can increase **vascular permeability**.

- Acute-Phase Proteins

Interleukins have a **strong effect on liver cells**, stimulating them to produce **acute-phase proteins**. Examples include:

- **C-reactive protein (CRP)**,
- **Haptoglobin**,
- **Serum amyloid A**,
- **Fibrinogen**,
- **Alpha-1-acid glycoprotein**.

These proteins help **restore homeostasis** and **limit microbial growth**, acting independently of antibodies during **trauma, stress, or infection**.

- Cellular Mediators

The inflammatory response involves a **coordinated network of various cell types**. **Activated macrophages, monocytes, and other immune cells** play key roles in **local responses to tissue damage and infections**.

At **sites of tissue injury**, **damaged epithelial and endothelial cells** release **factors that trigger the inflammatory cascade**, along with **chemokines and growth factors** that attract **neutrophils and monocytes**.

The first immune cells to reach the inflammatory site are **neutrophils**, followed by **monocytes, lymphocytes (NK cells, T cells, and B cells), and mast cells**.

- **Monocytes** can differentiate into **macrophages** and **dendritic cells** and are recruited to damaged tissues through **chemotaxis**.
- In some cases, inflammation is **initiated by resident mast cells**, which tend to attract **eosinophils** rather than **neutrophils**.

d. Resolution of Inflammation

Resolution is the **final phase of inflammation**, essential for **limiting collateral damage** to the host.

- The **harmful agents** that triggered the inflammatory response are **eliminated**.
- The **synthesis of pro-inflammatory mediators** is halted. Cells that produce **prostaglandins** and **pro-inflammatory leukotrienes** rapidly switch to producing **lipoxins**, which **block neutrophil recruitment** and instead promote **monocyte infiltration**, aiding **wound healing**.
- **Pro-inflammatory mediators are degraded**, stopping **leukocyte recruitment** and **edema formation**.

- **Anti-inflammatory cytokines** such as **IL-4, IL-10, and IL-12** are released during this stage. These are **potent anti-inflammatory factors** that **suppress the acute inflammatory response** by stabilizing **IκBα**, which **blocks the activation of NF-κB**.
- **Serine protease inhibitors** are also released to **neutralize proteases** from phagocytic cells, preventing **excessive tissue damage**.
- Regardless of the initial response (**neutrophil-, eosinophil-, or lymphocyte-driven**), **immune cells are ultimately cleared from the affected tissue**.

1.3. Classification of Inflammation

Inflammation can be classified into **two types** based on **duration** and **various immune factors**:

1. **Acute inflammation**
2. **Chronic inflammation** (Figure 3).

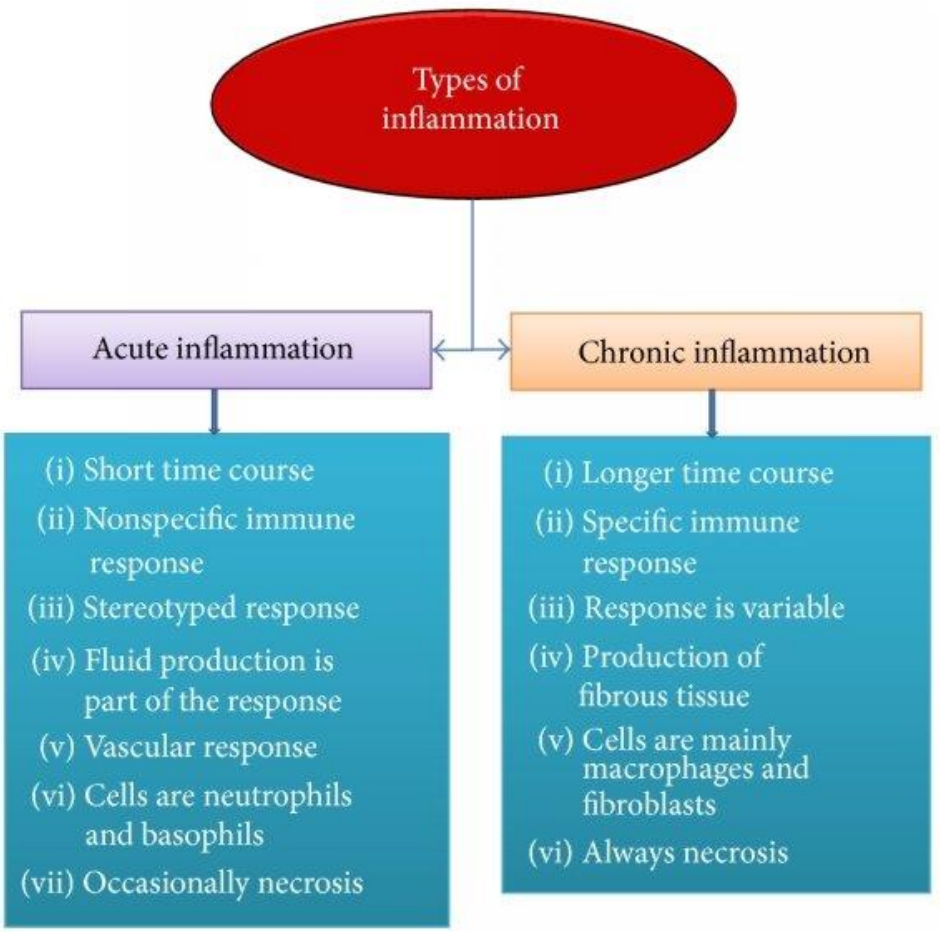


Figure 3: Classification of inflammation

a) Acute Inflammation

Acute inflammation is the **immediate reaction** to **tissue injury**. It is **short-lived**, lasting from **a few minutes to a few days**, and is characterized by:

- **Leakage of plasma proteins and fluid** (**exudate**).
- **Migration of leukocytes** to the extravascular area (**diapedesis**) (Figure 4).

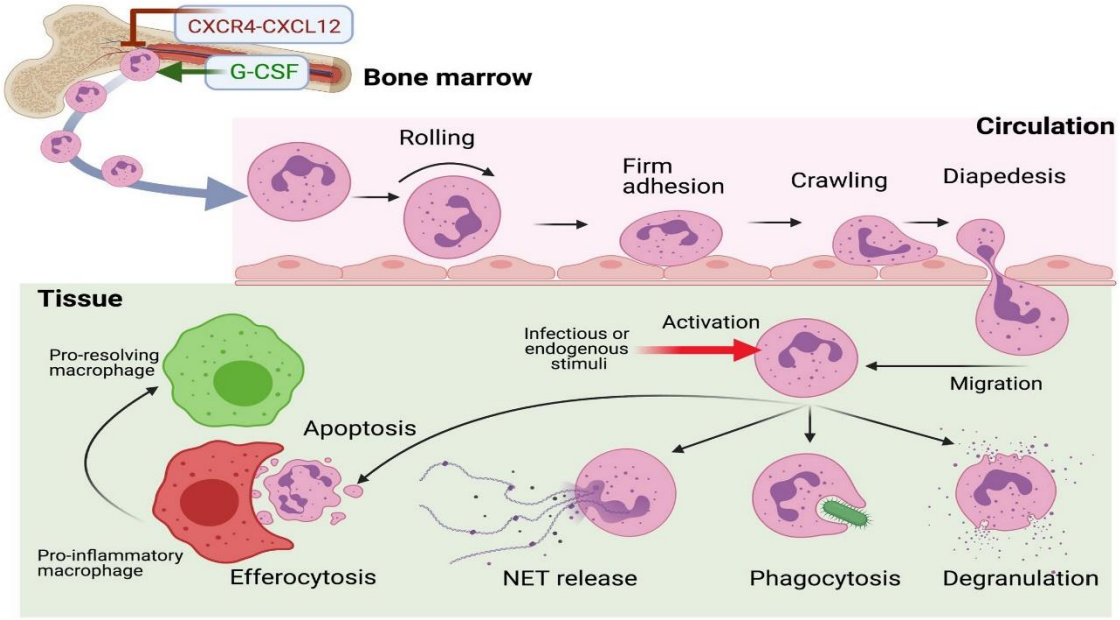


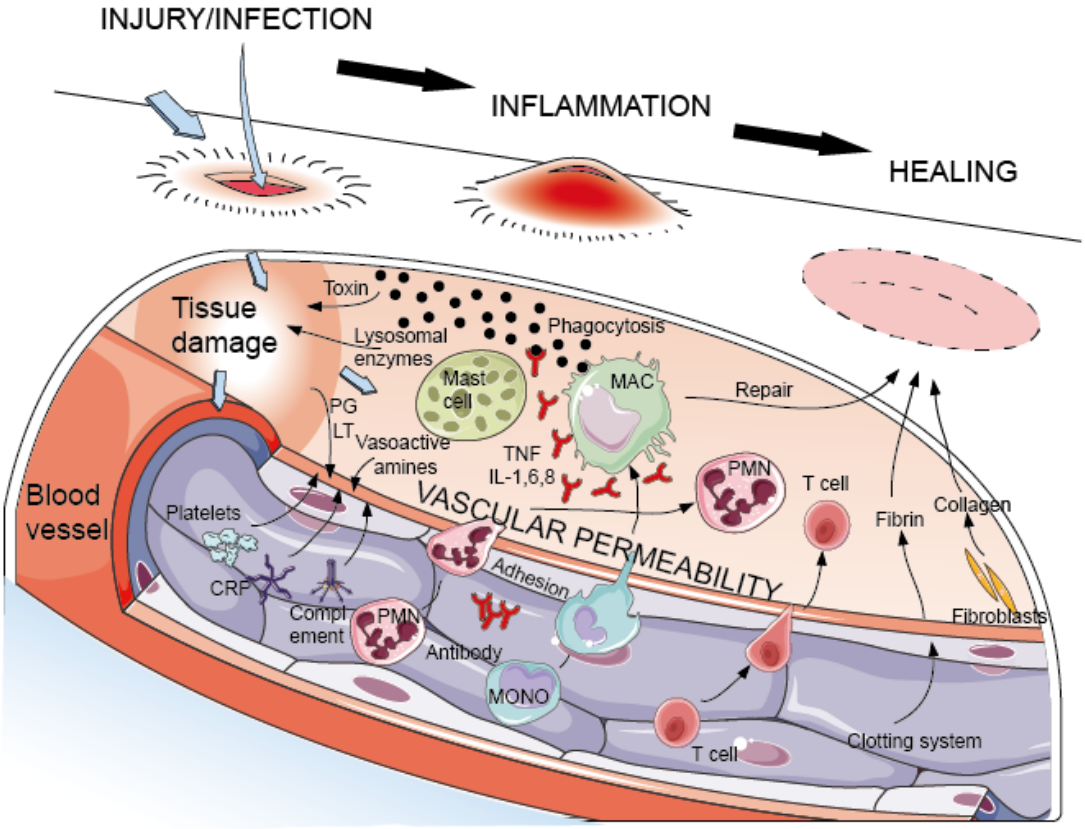
Figure 4: Key Functional Mechanisms of Neutrophils in Inflammation

Caption:
This figure illustrates the sequential steps by which neutrophils contribute to the innate immune response. After activation by inflammatory signals, neutrophils undergo rolling and firm adhesion to endothelial cells through adhesion molecules. They then transmigrate across the endothelium toward the site of infection or tissue damage. Once at the target site, neutrophils deploy a range of mechanisms to eliminate pathogens, including opsonization, phagocytosis, degranulation of pre-formed mediators, oxidative burst (ROS production), and NETosis — the release of neutrophil extracellular traps (NETs) that capture and kill microbes.

These **vascular and cellular events** are triggered by **chemical mediators** released by **cells or plasma proteins**. They are responsible for the **classic clinical symptoms** of inflammation:

- **Swelling**,
- **Redness**,
- **Pain**,
- **Heat**,
- **Loss of function**.

Stages of Inflammation



1. Vascular Events

The first observable changes during inflammation involve **alterations in blood flow** and **changes in the diameter** of small blood vessels (**vasodilation**). Newly formed blood vessels, capillaries, and **dilated arterioles** increase blood flow to the affected area.

- **Danger signals** activate **resident tissue cells**, including **mast cells** and **macrophages**.
- These cells **secrete inflammatory mediators** (**histamine, TNF-α**) that:
    - Increase **vascular permeability**.
    - Induce **vasodilation**.
    - Activate **endothelial cells**, leading to the expression of **adhesion molecules**.
- **Histamine** acts on the vascular wall, **reversibly opening the tight junctions** between endothelial cells.

2. Tissue Events

- **Activated endothelial cells** express **adhesion molecules** such as **ICAM-1, E-selectin, and P-selectin** to facilitate **neutrophil recruitment**.

- After **vascular changes**, **leukocytes begin migrating** by first adhering to the endothelium, rolling along it, and then firmly adhering before crossing the vessel wall (**transmigration**) into the interstitial tissue (**Figure 4**).

This process occurs in several steps:

1. **Margination**:
    - Neutrophils **adhere** to the vessel wall.
    - This occurs in two phases:
        1. **Attachment and rolling**
        2. **Activation and firm adhesion**
    - Neutrophils interact with **cell adhesion molecules (CAMs)**, including **immunoglobulin superfamily members, selectins, and integrins**.
    - For successful interaction with the **extracellular matrix**, neutrophils express **β1 integrins**, which bind to **collagen and laminin**.
2. **Diapedesis (Extravasation)**:
    - Neutrophils **migrate between endothelial cells** into the tissue.
3. **Chemotaxis**:
    - Neutrophils **move towards the site of infection** in response to **chemotactic signals**.

Once neutrophils reach the inflammatory site, they:

- **Phagocytose** foreign particles.
- **Release enzymes** (**Figure 5**).

However, **leukocytes** can also **release proteases, free radicals, and metabolites** during **chemotaxis and phagocytosis**, which can damage **host tissues**. This **collateral damage** is unavoidable in inflammation.

- **Neutrophils die** during this process, contributing to the formation of **pus**.

3. Outcomes of Acute Inflammation

- **Tissue restoration and resolution**
- **Healing through collagen scar formation**
- **Abscess formation**
- **Chronic inflammation**

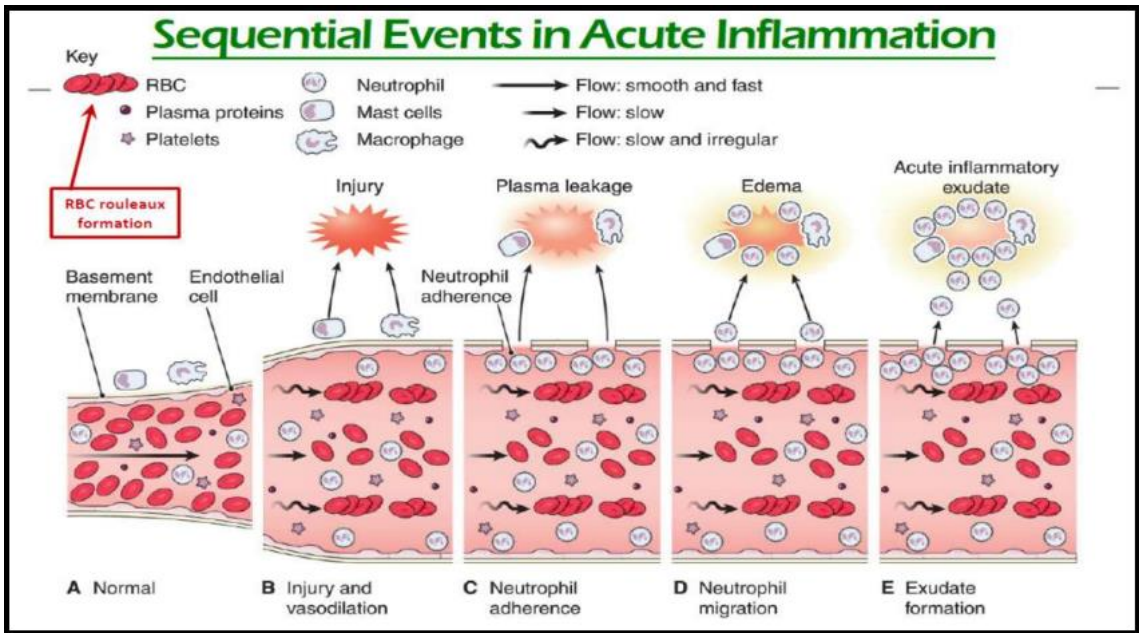


Figure 5: Development of acute inflammation

Chronic Inflammation

Proper **regulation of inflammatory mechanisms** is crucial to prevent **uncontrolled amplification** of the initial response, which can shift from **tissue repair** to **collateral damage**. However, in some situations, tissue restoration fails, leading to **persistent cellular stress** that sustains and amplifies the inflammatory response. In these conditions, inflammation becomes **maladaptive**, causing **significant tissue dysfunction, systemic disturbances, and chronic inflammation** that can last for **weeks, months, or even years**.

Causes of Chronic Inflammation

Chronic tissue inflammation occurs in the following cases:

- **Persistent antigenic stimulation** due to the **inability to eliminate the causal agent**.
    - Some microorganisms, such as *Mycobacterium tuberculosis*, have evolved to **evade immune responses**, leading to prolonged inflammation.
- **Autoimmune diseases** (e.g., **systemic lupus erythematosus (SLE)** and **rheumatoid arthritis**).
    - The immune system **fails to eliminate autoantigens**, leading to continuous immune activation.
- **Exposure to physical or chemical agents** that **cannot be metabolized** by the body.
- **Genetic predisposition** or **recurrent acute inflammation**.

Histological Features of Chronic Inflammation

Chronic inflammation is characterized by:

- **Infiltration of mononuclear cells**:
    - **Macrophages, lymphocytes, and plasma cells** gradually replace **neutrophils**.
- **Tissue destruction** caused by inflammatory mediators.
- **Tissue repair mechanisms**, including:
    - **Angiogenesis** (formation of new blood vessels).
    - **Fibroblast proliferation**.
    - **Collagen fiber production**.
    - **Connective tissue formation**, which may lead to **granuloma formation**.
- Depending on the **severity** of the inflammatory reaction, the **classic signs of acute inflammation** may not appear.
    - For example, **CRP levels** tend to be **lower** than in acute inflammation caused by tissue injury or infection.

Role of Macrophages in Chronic Inflammation

- **Macrophages accumulate** due to recruitment by **chemotactic factors** (e.g., **platelet-derived growth factor (PDGF), C5a**) and their **retention** in the tissue by **migration inhibitory factors**.
- **Macrophage secretions** play a major role in sustaining chronic inflammation:
    - **TNF-α** is crucial for **local inflammation maintenance**.
        - At **high levels**, it has **systemic effects**, including:
            - **Weight loss** (due to **fat catabolism** and **appetite suppression**).
            - **Fatigue**.
    - **Tissue damage** via **proteases and reactive oxygen species (ROS)**.
    - **Neovascularization** via **angiogenic factors**.
    - **Fibroblast migration and proliferation** via **growth factors** (e.g., **PDGF**) and **cytokines** (**IL-2, TNF-α**).
    - **Collagen synthesis** via **growth factors** (**PDGF**) and **cytokines** (**IL-1, TNF-α**).
    - **Tissue remodeling** via **collagenases**.
    - **Activation of T lymphocytes** by **IL-12 secretion**.

Role of Lymphocytes and Plasma Cells

- **Lymphocytes** and **plasma cells** are also present at the inflammation site.
- In **chronic infections**, **macrophages and T lymphocytes** play essential roles in **controlling infection (Figure 6)**.

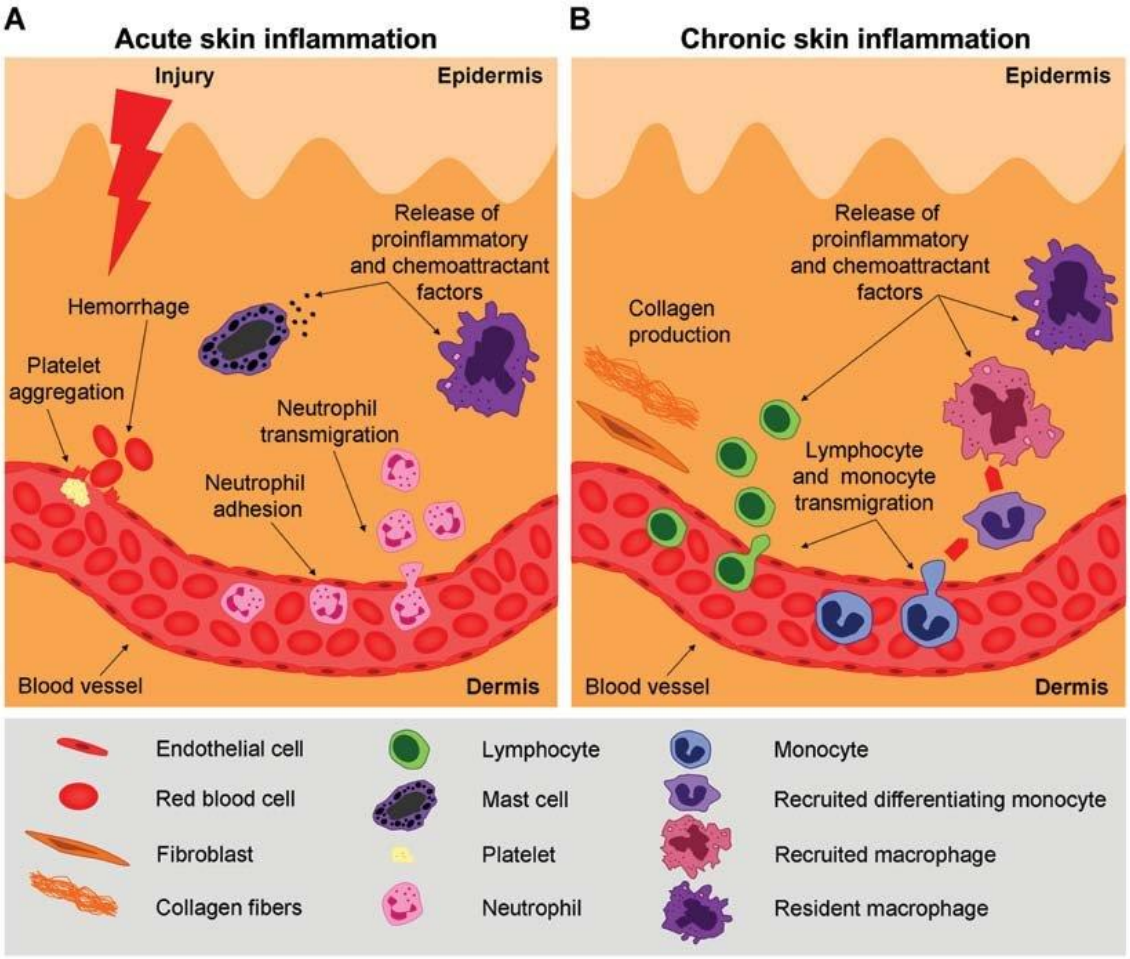


Figure 6: Comparison between acute and chronic inflammation