

# Inflammation

by

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Source: Robbin's Basic Pathology 9<sup>th</sup>  
Edition

# Inflammation

- It is a response of **vascularized tissues** to infections and damaged tissues that **brings cells** and **molecules** of host defense from circulation to sites where they are needed, in order to eliminate offending agents.
- Actually a protective response that is essential for survival **but may lead to tissue injury if go**

**uncontrolled.**

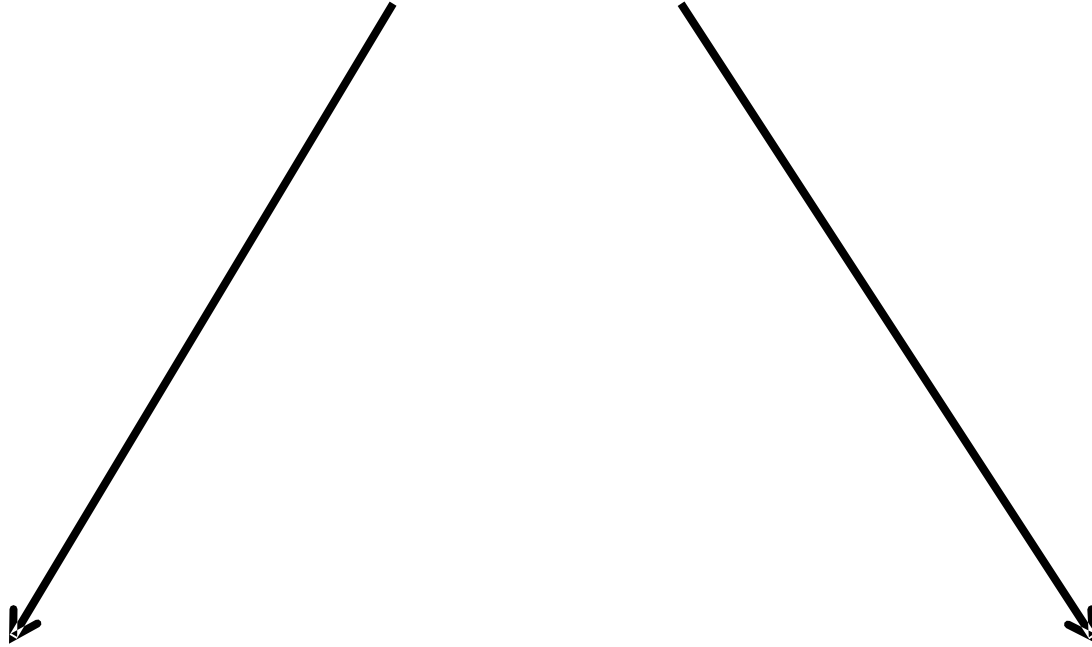
# Inflammation

- Inflammation is defined as **local response of living mammalian tissues to injury from any agent.**
- It is a body defense reaction in order to eliminate or limit spread of injurious agent, followed by removal of the necrosed cells and tissues.

# Inflammation

- Involves **host cells, blood vessels, proteins** and **other mediators**.
- Serves **two main purposes**,
  - a) Removal** of initial cause of cell injury (e.g., microbes, toxins)..... Offending agent removal
  - b) Consequences** of such injury (e.g., necrotic cells and tissues) ultimately resulting in tissue repair.

# **Inflammation**



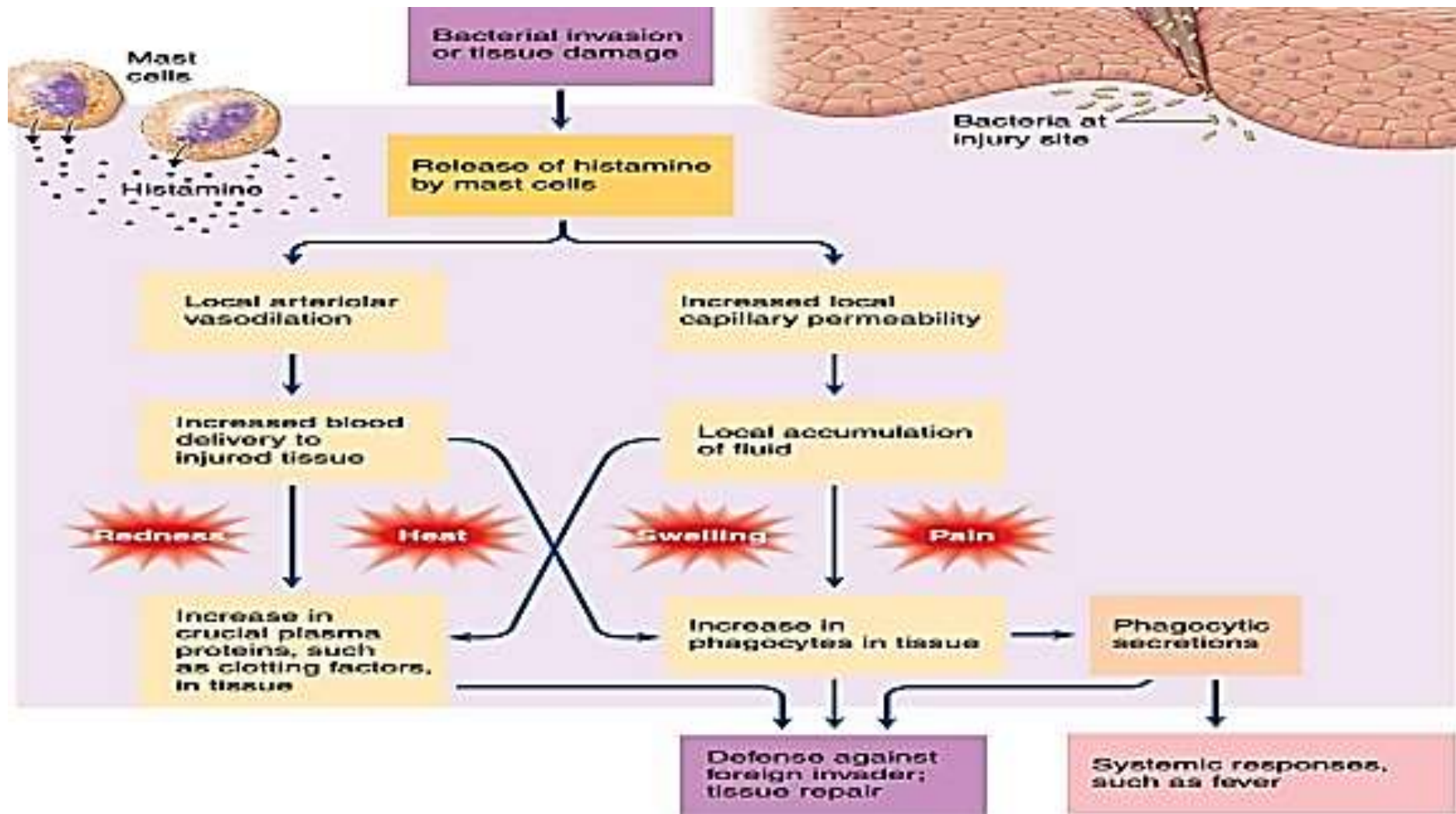
- 1) Beneficial (Protective responses)**
- 2) Controlled process**

- 1) Harmful (Tissue injury)**
- 2) Uncontrolled process**

# Classical signs

- Rubor (redness)
- Calor (heat)
- Tumor (swelling)
- Dolor (pain)
- Functio laesa (loss of function)

# Classical signs





# Steps of Inflammation

- **Recognition** of offending cells/ agent by host cells and molecules.
- **Leukocytes and plasma proteins recruitment.**
- Activation of leukocytes and proteins and **removal** of offending agent.
- The reaction is controlled and terminated/

**regulation** of responses.

# Steps of Inflammation

- Tissue **repair/ resolution**..... Scar formation

## 5 R's of Inflammation

# Stimuli for Inflammation

- **Infections** (bacterial, viral, fungal, parasitic) and microbial toxins.
- **Foreign bodies** (splinters, dirt, sutures) typically elicit inflammation.
- **Immune reactions** (hypersensitivity) (autoimmune disorders)
- **Tissue necrosis** (several molecules including uric acid,

a purine metabolite; adenosine triphosphate).

# 1) Recognition

- **1<sup>st</sup> step** in all inflammatory reactions
- **Phagocytes, dendritic cells and epithelial cells ----**  
**----- sense presence of pathogens and**  
**substances released** from dead cells.
- **Pattern recognition receptors -----** recognize  
special structures of microbes and dead cells

# 1) Recognition

- **Cellular receptors for microbes**
- Receptors are present in **plasma membrane (extracellular), endosomes (for ingested microbes), and cytosol (for intracellular microbes).**

# 1) Recognition

1) Best defined of these receptors belong to family of **Toll-like receptors (TLRs)**.

➤ Play essential role in cellular responses to **bacteria** (endotoxins & bacterial DNA), **double-stranded RNA** (produced by some viruses) and **fungus** (polysaccharide).



# 1) Recognition

- **TLRs** are present on **epithelial cells** (through which microbes enter from external environment), **dendritic cells, macrophages, and other leukocytes** (which may encounter microbes in various tissues).
- Triggers **production of** molecules involved in inflammation, including **adhesion molecules** on **endothelial cells, cytokines, and other mediators ---**

----- appearance of **signs of inflammation.**

# 1) Recognition

## 2) Sensors of cell damage

- **Cytosolic receptors** recognize a diverse set of molecules that are liberated or altered as a consequence of cell damage (increased **uric acid**, **ATP**, reduced intracellular **K<sup>+</sup>** concentrations).
- These receptors activate a multiprotein cytosolic

complex called **inflammasome**.

# 1) Recognition of Microbes and Dead Tissues

- Inflammasome ----- activation of caspase-1 ----  
--- activation of interleukin--1(Pro-IL-1 to active IL  
IL  
-1) ----- inflammation ----- recruitment of  
leukocytes ----- phagocytosis ----- removal

## 3) Receptors for opsonins

- Leukocytes express receptors for Fc tails of

antibodies and for complement proteins.

# **3) Recognition of Microbes and Dead Tissues**

## **3) Receptors for opsonins**

- Promote ingestion and destruction of microbes coated with antibodies as well as inflammation.

## **4) Circulating proteins**

- **Mannose-binding lectin** recognizes microbial sugars and promotes ingestion of microbes and

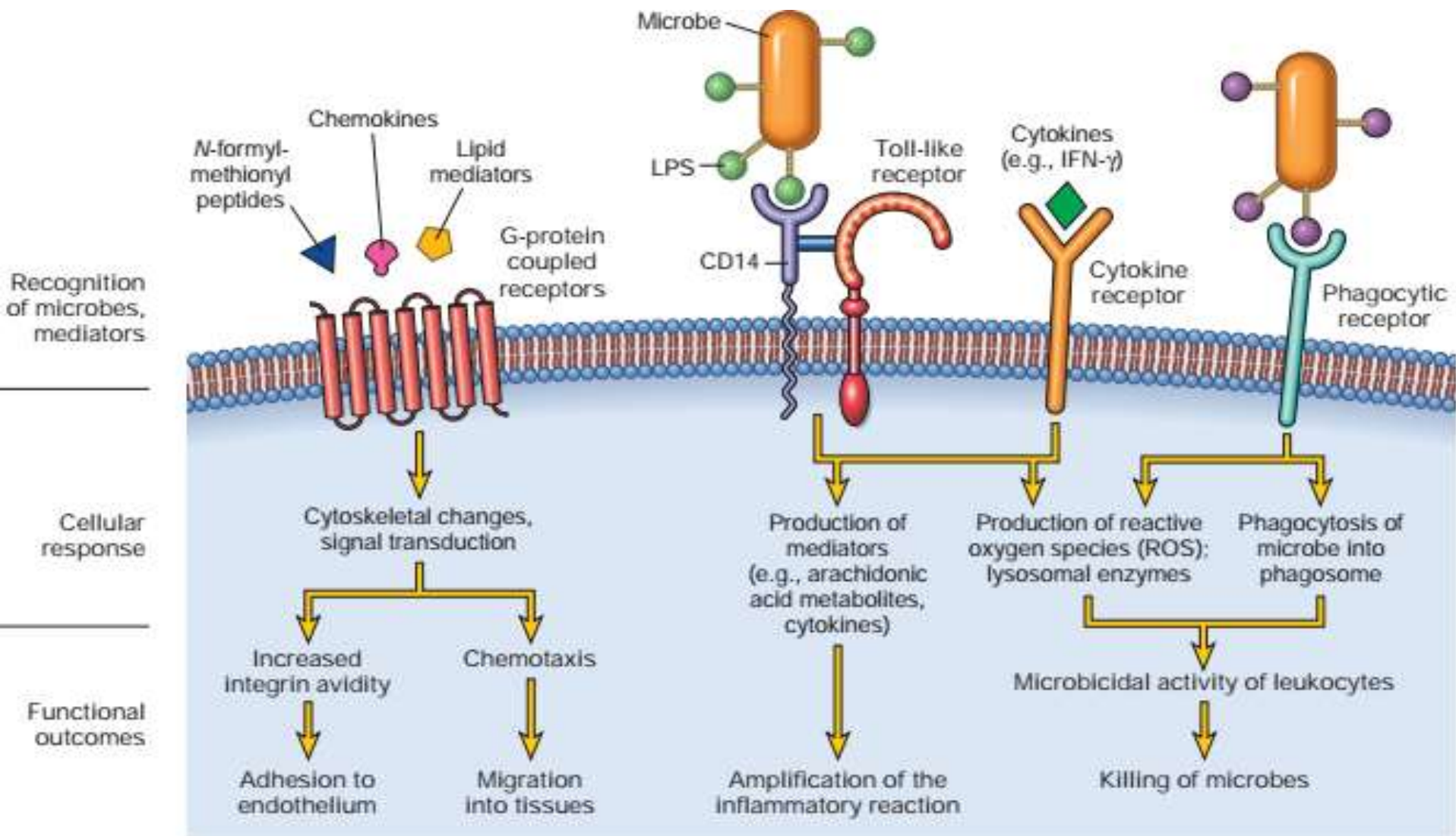
activation of complement system.



# **3) Recognition of Microbes and Dead Tissues**

## **5) Collectins**

- Also bind to and combat microbes.



# Types of Inflammation

- Depending upon the defense capacity of the host and duration of responses, inflammation can be classified as,
  - Acute inflammation
  - Chronic inflammation

# Acute Inflammation

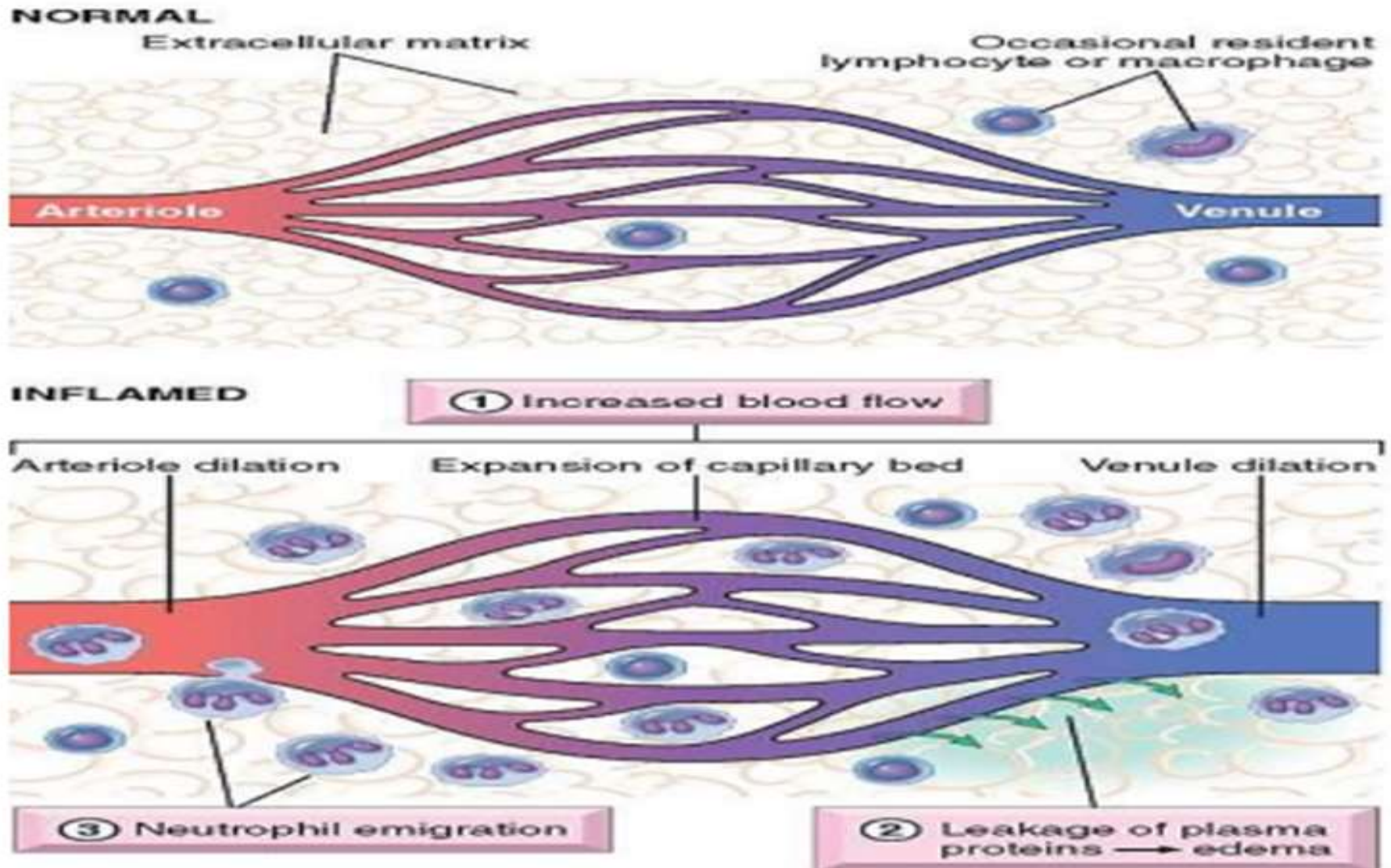
➤ It can be divided into following two events,

I. Vascular events

II. Cellular events

➤ Intimately linked to these two processes is the release of mediators of acute inflammation.

# Acute Inflammation



# 1) Vascular reactions

- a) Changes in **blood flow** and caliber/ **blood vessels diameter**.
  - b) Increased vascular permeability (**vascular leakage**).
- Both processes maximize movement of **plasma proteins** and **leukocytes** out of circulation and into site of infection or injury

## **a) Changes in blood flow and caliber**

- **Vasodilation** is one of the **earliest manifestations** of inflammation induced by histamine and NO.
- 1<sup>st</sup> involves **arterioles** and then leads to opening of **new capillary beds**.
- Net result of these changes is **increased blood flow towards the area**, which is cause of **heat** and

**redness (erythema) at site of inflammation.**



## **a) Changes in blood flow and caliber**

- Vasodilation is quickly followed by increased permeability of the microvasculature, with the outpouring of protein -rich fluid into the extravascular tissues.....edema

## a) Changes in blood flow and caliber

- The loss of fluid and increased vessel diameter.....Slower blood flow.....Concentration of red cells in small vessels.....Increased viscosity of blood.....Engorgement of small vessels with slowly moving red cells, a condition termed **stasis**

## **a) Changes in blood flow and caliber**

vi) Stasis leads to **vascular congestion** and **localized redness** of involved tissue.

vii) As stasis develops, **blood leukocytes**, principally **neutrophils**, **accumulate** along vascular endothelium.

**Normal blood symmetry vs blood symmetry during inflammatory conditions.**

## **b) Vascular Leakage**

- Increased vascular permeability is **hallmark** of **acute inflammation**.
- Leading to escape of a **protein-rich exudate** into extravascular tissue, causing edema.
- Involves **3 steps**;  
  - 1) Contraction of endothelial cells, 2) Endothelial cells

injury, 3) Transcytosis.

## **b) Vascular Leakage**

### **1) Contraction of endothelial cells**

- Results in creation of gaps b/w endothelial cells (Increased interendothelial spaces).
- Elicited by **histamine, bradykinin, leukotrienes, neuropeptide substance P, and many other chemical mediators.**

## **b) Vascular Leakage**

### **1) Contraction of endothelial cells**

- Immediate transient response because it occurs rapidly after exposure to mediator and is usually **short-lived (15–30 minutes)**.
- In case of mild injury vascular leakage begins after a **delay of 2 to 12 hours** and lasts for several hours

or even days (delayed responses)....EC injury



# **b) Vascular Leakage**

## **2) Endothelial injury**

- Resulting in endothelial cell necrosis and detachment.
- **Direct damage** by severe injuries (in burns, or by actions of microbes).
- **By neutrophils attachment** during inflammation.

## **b) Vascular Leakage**

### **3) Transcytosis**

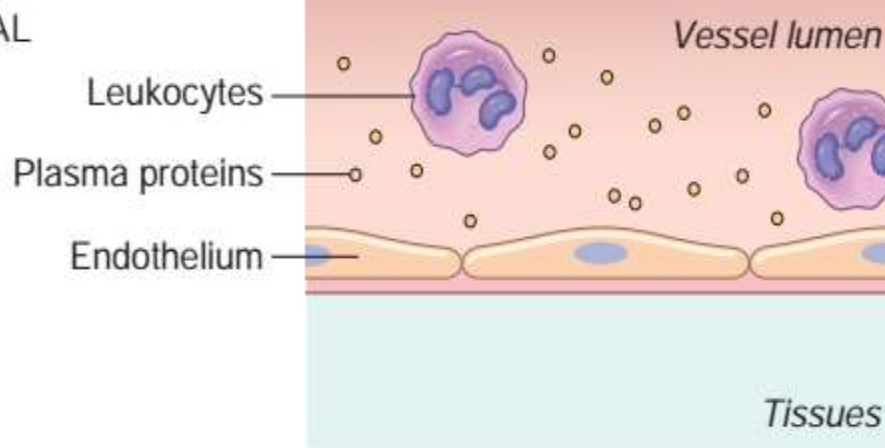
- Increased **transport of fluids and proteins**.
- Involve formation of channels stimulated by VEGF.

### **4) Lymphatic system responses**

- Lymphatic vessels (**lymphangitis**) and lymph nodes (**lymphadenitis**) are also involved in inflammation,

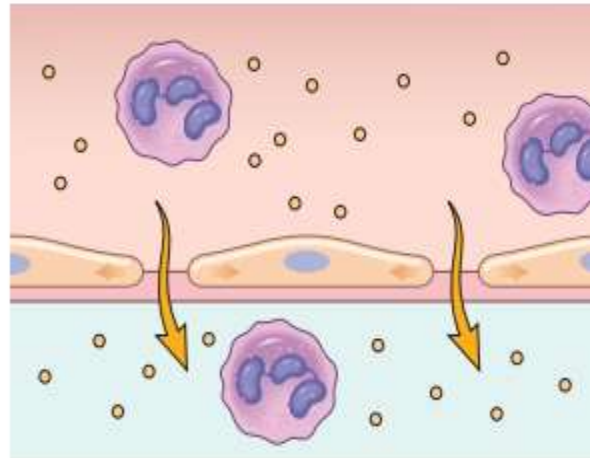
and often show redness and swelling.

### A. NORMAL



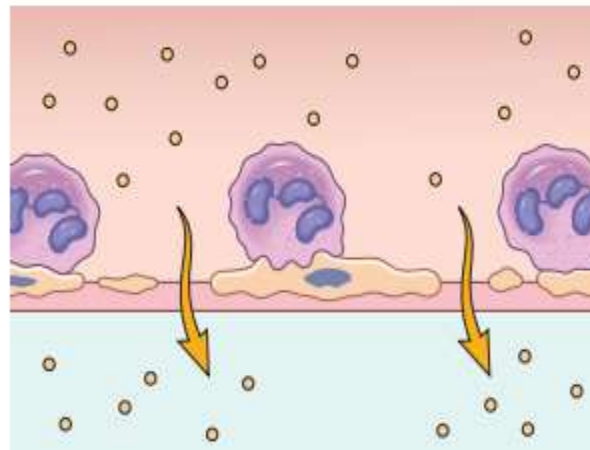
### B. RETRACTION OF ENDOTHELIAL CELLS

- Induced by histamine, other mediators
- Rapid and short-lived (minutes)



### C. ENDOTHELIAL INJURY

- Caused by burns, some microbial toxins
- Rapid; may be long-lived (hours to days)



## 2) Cellular Events

- Cellular phase of inflammation consists of 2 processes:
- Recruitment of leukocytes
- Phagocytosis

## a) Leukocytes Recruitment

- Changes in **blood flow** and **vascular permeability** are quickly followed by an **influx** of **leukocytes** into tissue.
- Leukocytes capable of phagocytosis.....namely **neutrophils** (acute) and **macrophages** (chronic).
- Apart from removal of offending agent, leukocytes

also produce mediators which aid in tissue repair.

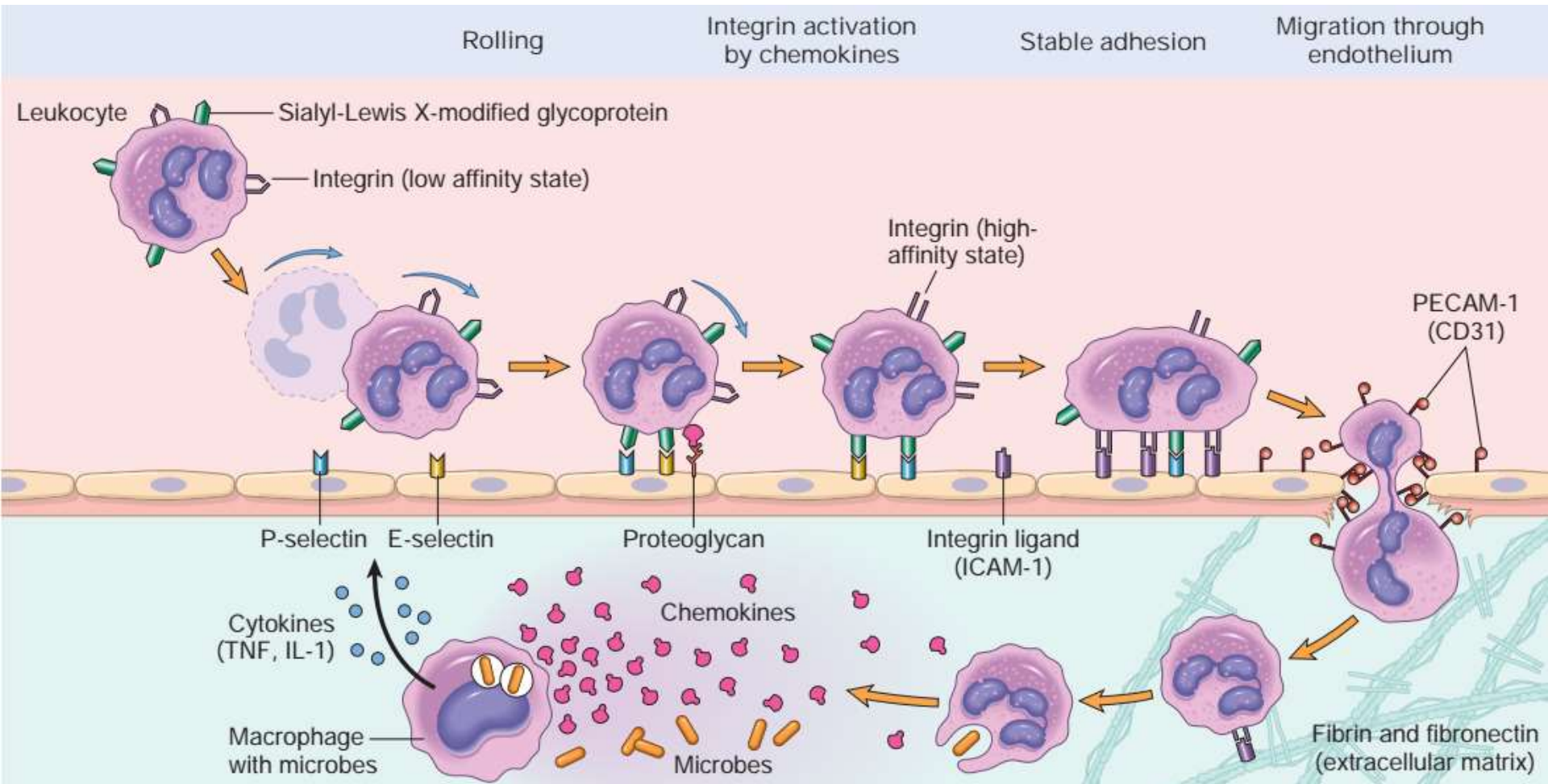
## **a) Leukocytes Recruitment**

- A price that is paid for defensive potency of leukocytes is that, when strongly activated, they may induce tissue damage and prolong inflammation, because the leukocyte products that destroy microbes and help “clean up” necrotic tissues can also injure normal bystander host



tissues..

# a) Leukocytes Recruitment



## **b) Phagocytosis**

- Involves three sequential steps,
  - 1) Recognition and attachment** of foreign particle by leukocyte.
  - 2) Engulfment**, with subsequent formation of a phagocytic vacuole.
  - 3) Killing or degradation** of ingested material.

## **b) Phagocytosis**

**1) Recognition and attachment** of foreign particle by leukocyte.

➤ **Phagocytic Receptors.** Mannose receptors, scavenger receptors, and receptors for various opsonins bind and ingest microbes ----- **binding with phagocytes.**

## **b) Phagocytosis**

### **2) Engulfment**

- Phagocyte receptors + microbe binding -----  
phagocyte membrane (pseudopods) flow around it -  
----- plasma membrane pinches off to form a  
vesicle (phagosome) that encloses the particle.
- Phagosome + lysosome ----- **Phagolysosome.**

## **b) Phagocytosis**

### **3) Killing or degradation of ingested material**

- Final step in the elimination of infectious agents and necrotic cells.
- **Reactive oxygen species (ROS), reactive nitrogen species**, mainly derived from nitric oxide (NO), and **lysosomal enzymes**.

## **b) Phagocytosis**

### **3) Killing or degradation of ingested material**

- **NADPH oxidase** (also called **phagocyte oxidase**) -  
----- **NADPH to NADP** ----- during which it  
converts **O<sub>2</sub>** to **superoxide anion (O<sub>2</sub><sup>•</sup>)**.
- **O<sub>2</sub><sup>•</sup>** is converted into hydrogen peroxide (**H<sub>2</sub>O<sub>2</sub>**) -----  
-- not an efficient antimicrobial.

## **b) Phagocytosis**

### **3) Killing or degradation of ingested material**

- Azurophilic granules of neutrophils contain enzyme **myeloperoxidase (MPO)** ----- converts  $H_2O_2$  to **hypochlorite** (in presence of halide like  $Cl^-$ ).
- Potent antimicrobial agent that destroys **cellular constituents** and **proteins** and **lipids** (lipid



peroxidation) of microbes.

## **b) Phagocytosis**

### **3) Killing or degradation of ingested material**

- **$\text{H}_2\text{O}_2$ --MPO--halide** is most efficient bactericidal system. Destroys cellular constituents and proteins and lipids (lipid peroxidation) of microbes.

## **b) Phagocytosis**

### **3) Killing or degradation of ingested material**

- NO, a soluble gas produced from arginine by the action of **nitric oxide synthase (NOS)**, also participates in microbial killing.
- Endothelial (**eNOS**), neuronal (**nNOS**), and inducible (**iNOS**).

## **b) Phagocytosis**

### **3) Killing or degradation of ingested material**

- eNOS and nNOS generate NO that functions to maintain vascular tone and as a neurotransmitter.
- **iNOS, mainly involved in microbial killing ----**  
induced when **macrophages** and **neutrophils** are activated by **cytokines** (e.g., IFN- $\gamma$ ) or microbial

products.

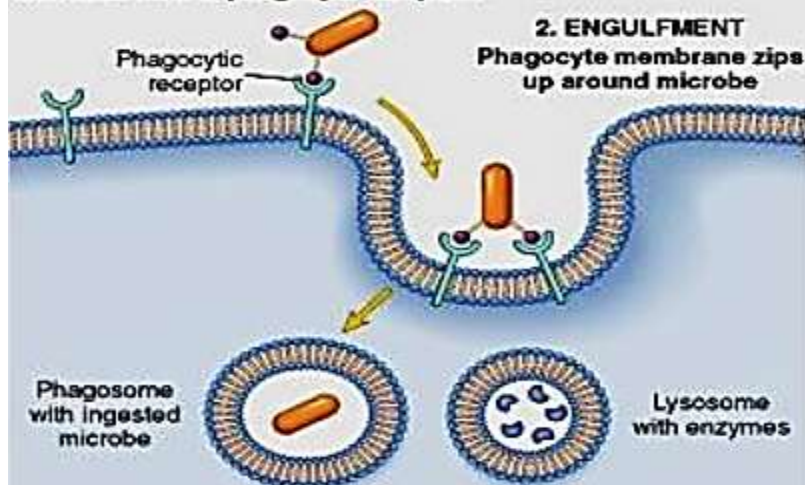
## **b) Phagocytosis**

### **3) Killing or degradation of ingested material**

- In macrophages, NO reacts with superoxide ( $O_2\bullet$ ) to generate the highly reactive free radical **peroxynitrite ( $ONOO^-$ )**.
- Attack and damage **lipids, proteins, and nucleic acids of microbes**.

# 1. RECOGNITION AND ATTACHMENT

Microbes bind to phagocyte receptors



## 2. ENGULFMENT

Phagocyte membrane zips up around microbe

Phagosome with ingested microbe

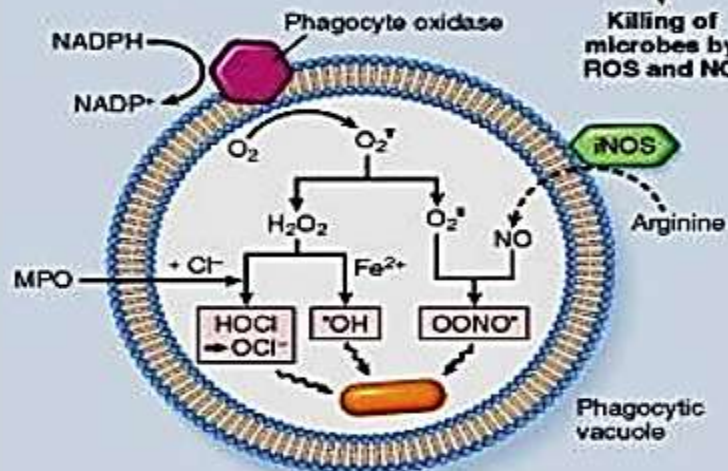
Lysosome with enzymes

Fusion of phagosome with lysosome

## 3. DESTRUCTION OF MICROBES

Killing of microbes by lysosomal enzymes in phagolysosome

Killing of microbes by ROS and NO



# Neutrophils granules

```
graph TD; A[Neutrophils granules] --> B[1) Primary/ azurophilic granules]; A --> C[2) Secondary/ specific granules];
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## 1) Primary/ azurophilic granules

- Larger granules
- Contain myeloperoxidase (MPO), bactericidal factors (lysozyme, defensins), acid hydrolases, neutral proteases (elastase, cathepsin G, nonspecific collagenases, proteinase).

## 2) Secondary/ specific granules

- Contain lysozyme, collagenase, gelatinase, lactoferrin, plasminogen activator, histaminase, and alkaline phosphatase.



# Leukocytes granules

- Different granule enzymes serve different functions.
- **Acid proteases** ----- degrade bacteria and debris within the phagolysosomes.
- **Neutral proteases** ----- degrading various **extracellular components** (collagen, basement membrane, fibrin, elastin, and cartilage, resulting in

the tissue destruction).

# Leukocytes granules

- Different granule enzymes serve different functions.
- **Neutral proteases** ----- cleave **C3** and **C5** complement proteins directly, yielding anaphylatoxins.
- **Neutral proteases** ----- release a kinin-like peptide from kininogen.

# Leukocytes granules

- Different granule enzymes serve different functions.
- **Neutrophil elastase** ----- **degrade virulence factors of bacteria** and thus combat bacterial infections.
- **Macrophages** ----- contain **acid hydrolases, collagenase, elastase, phospholipase, and**

**plasminogen activator.**

# Leukocytes granules

- **Defensins** ----- cationic arginine-rich granule peptides that are **toxic to microbes**.
- **Cathelicidins** ----- **antimicrobial proteins** found in neutrophils and other cells.
- **Lysozyme** ----- **hydrolyzes muramic acid N-acetylglucosamine bond**, found in bacterial

glycopeptide coat

# Neutrophil Extracellular Trap (NET)

- **Extracellular fibrillar network** produced by neutrophils in response to infectious pathogens (mainly bacteria and fungi) and inflammatory mediators.
- Form a **viscous meshwork of nuclear chromatin** that binds and **concentrates granule proteins** such

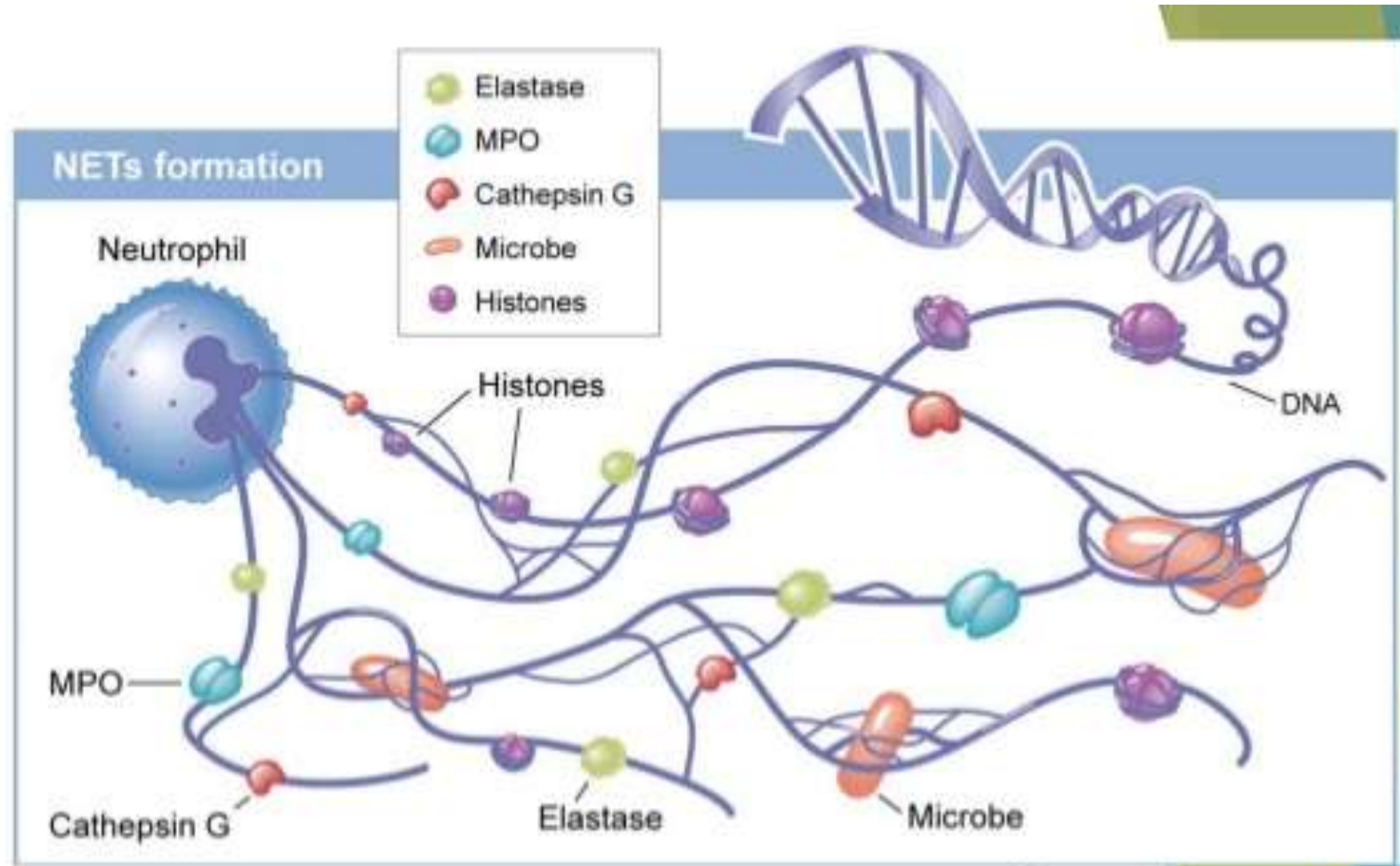


**as antimicrobial peptides and enzymes.**

# Neutrophil Extracellular Trap (NET)

- NET contains **histones** and **associated DNA**.
- Nuclei of neutrophils are lost during this process and neutrophils die.

# Neutrophil Extracellular Trap (NET)



## 5) Termination

➤ Inflammation declines after offending agents are removed simply because;

1) **Neutrophils** ----- **short half-lives** in tissues and die by **apoptosis** within a few hours after leaving the blood.

## 5) Termination

2) Shift of arachidonic acid metabolites balance from pro-inflammatory leukotrienes to **anti-inflammatory lipoxins**.

3) Liberation of **anti-inflammatory cytokines**, including **transforming growth factor-- $\beta$** (TGF- $\beta$ ) and **IL-10**, from macrophages and other cells.

## 5) Termination

4) Effects of harmful proteases, however, are normally controlled by a system of **antiproteases** in the **serum** and **tissue** fluids.

a)  $\alpha_1$ -antitrypsin which is the major **inhibitor** of **neutrophil elastase**.

b)  $\alpha_2$ -Macroglobulin is another **antiprotease** found in serum and various secretions.

# **Morphology of Acute Inflammation**

# Terminologies

1) **Edema** is the accumulation of fluid within the extravascular compartment and interstitial tissues.

2) A **transudate** is edema fluid with a low protein content (specific gravity  $< 1.015$ ).

➤ Tend to occur in non-inflammatory conditions in which **endothelial barrier remains intact** and



**prevents loss of large molecules from vasculature.**

# Terminologies

**3) Exudate** is edema fluid with a **high protein concentration** (specific gravity  $> 1.015$ ), which frequently **contains inflammatory cells**.

➤ Exudates are observed early in **acute inflammatory reactions** and are **produced by mild injuries** such as **sunburn** or **traumatic blisters**.

# **Morphology of Acute Inflammation**

➤ The morphologic hallmarks of acute inflammatory reactions are:

- 1) Dilation of small blood vessels**
- 2) Accumulation of leukocytes and fluid in extravascular tissue.**

# Morphology of Acute Inflammation

- However, special morphological patterns appear depending on;
- a) Severity of reaction.**
  - b) Its specific cause.**
  - c) Particular tissue and site involved.**

# Morphology of Acute Inflammation

## 1) Serous Inflammation

- Marked by **exudation** of **relatively protein poor fluid** into **spaces** created by cell injury or into body cavities lined by **peritoneum, pleura, or pericardium**.
- Typically, fluid **does not contain large numbers of**

**leukocytes.**

# Morphology of Acute Inflammation

## 1) Serous Inflammation

- In body cavities fluid may be derived from **plasma** (as a result of **increased vascular permeability**) or from **secretions of mesothelial cells** (as a result of local irritation).
- **Fluid in serous cavities** is called an **effusion**.

# Morphology of Acute Inflammation

## 1) Serous Inflammation

- **Skin blister** resulting from a **burn** or **viral infection** represents accumulation of serous fluid within or immediately beneath damaged epidermis of skin.



# **Morphology of Acute Inflammation**

## **2) Fibrinous Inflammation**

- **With greater increase in vascular permeability, large molecules such as fibrinogen pass out of blood, and fibrin is formed and deposited in extracellular space.**
- **Most common sites are, meninges, pericardium**

and **pleura.**

# **Morphology of Acute Inflammation**

## **2) Fibrinous Inflammation**

- A fibrinous exudate contains **large amounts of fibrin** as a result of **activation of coagulation system**.
- Example: **Pneumococcal and rheumatic pericarditis**.

# Morphology of Acute Inflammation

## 2) Fibrinous Inflammation

- Fibrinous exudates **dissolved** by **fibrinolysis** and **cleared** by **macrophages**.
- **If fibrin is not removed**, over time it may **stimulate ingrowth** of **fibroblasts** and **blood vessels** and thus **lead to scarring (scar tissue)**.

# Morphology of Acute Inflammation

## 3) Purulent Inflammation

- Also known as **Suppurative** inflammation.
- Characterized by **production of pus** (an **exudate** consisting of **neutrophils**, liquefied **debris** of **necrotic cells**, and **edema fluid**).

# Morphology of Acute Inflammation

## 3) Purulent Inflammation

- The most frequent cause is **infection with bacteria** that causes **liquefactive tissue necrosis**, such as **staphylococci**, known as **pyogenic (pus-producing) bacteria**.
- A common example of an acute suppurative

inflammation is **acute appendicitis**.

# Morphology of Acute Inflammation

## 4) Ulcers

- **Local defects of the surface of an organ produced by the sloughing (shedding) of inflamed necrotic tissue/ cells.**
- **Can occur only when tissue necrosis and resultant inflammation exist on or near the surface.**



# Morphology of Acute Inflammation

## 4) Ulcers

- Most commonly encountered in **mucosa** of the **mouth, stomach, intestines, or genitourinary tract**, and **skin and subcutaneous tissue of lower extremities** in older persons.
- Best exemplified by **peptic ulcer** of **stomach** or

**duodenum.**

# **Outcomes of Acute Inflammation**

# Outcomes of Inflammation

- Many variables may modify the basic process of inflammation. All acute inflammatory reactions typically have **one of three outcomes**.
- 1) **Complete resolution**
    - Usual outcome when injury is **limited** or **short--lived** or when there has been **little tissue destruction** and

**damaged parenchymal cells can regenerate.**

# Outcomes of Inflammation

## 1) Complete resolution

- Involves **removal of cellular debris and microbes** by **macrophages**, and **drainage/resorption** of **edema fluid** by **lymphatics**.

# Outcomes of Inflammation

## 2) Fibrosis/ Scar formation

- Occurs after **substantial tissue destruction** and when **inflammatory injury** involves **tissues that are incapable of regeneration**, or
- When there is **abundant fibrin exudation** in tissue
- Or in **serous cavities (pleura, peritoneum)** that

**cannot be adequately cleared.**



# Outcomes of Inflammation

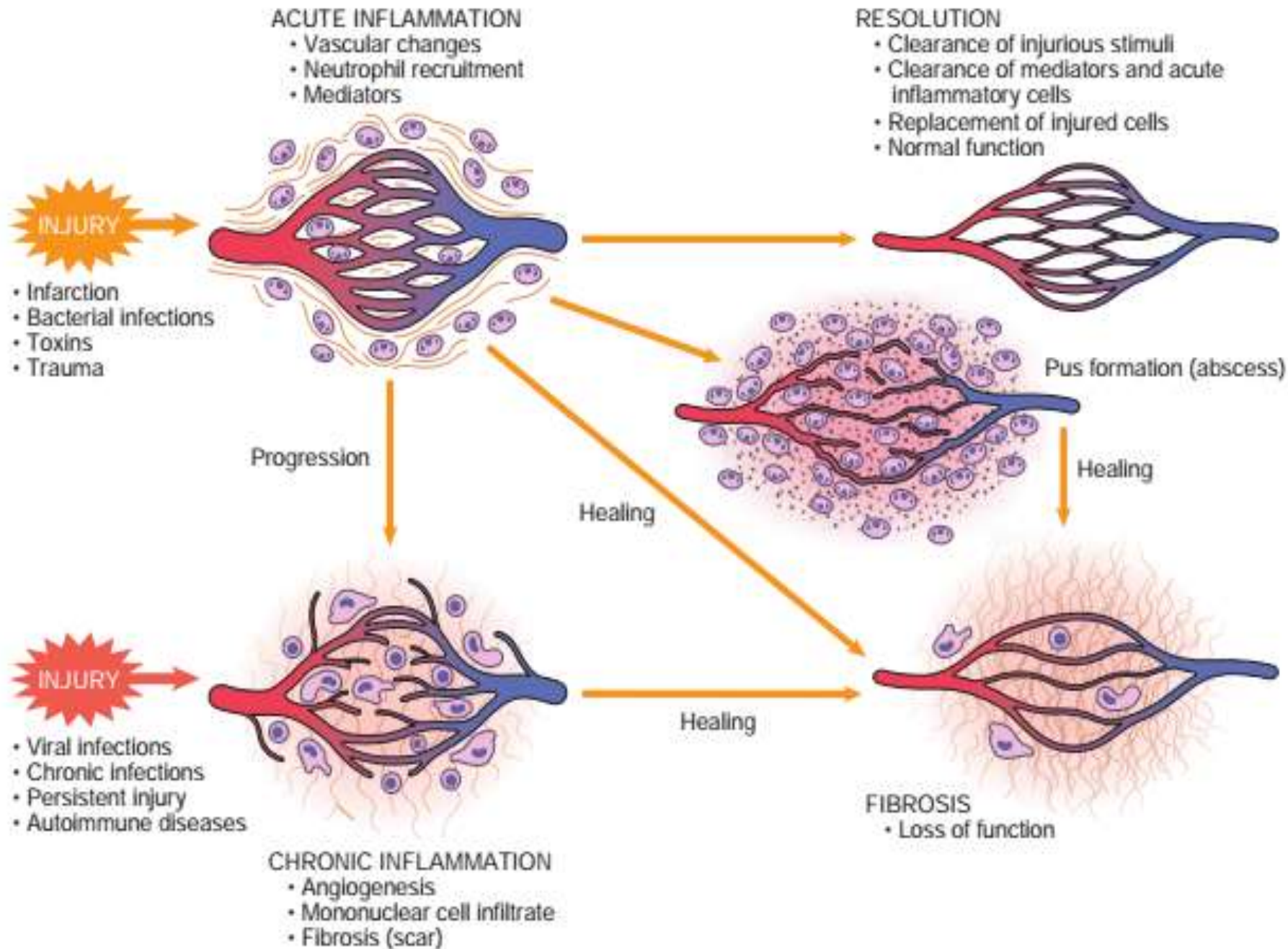
## 2) Fibrosis/ Scar formation

- **Connective tissue grows into area of damage or exudate**, converting it into a mass of fibrous tissue, a process known as **fibrosis**.
- **Fibrosis leads to loss of function.**

# Outcomes of Inflammation

## 3) Chronic inflammation

- **Acute to chronic transition** occurs when acute inflammatory response cannot be resolved,
  - a) As a result of either **persistence of injurious agent**.
  - b) Or some **interference** with **normal process of healing**.



# **Systemic Effects of Inflammation**

# Systemic effects of Inflammation

- **Inflammation**, even if it is localized, is **associated** with **cytokine-induced systemic reactions** that are collectively called **acute-phase response**.
- Reactions to cytokines whose production is stimulated by bacterial products such as LPS and by other inflammatory stimuli.

# Systemic effects of Inflammation

- The cytokines **TNF, IL-1, IL-6** and type I interferons are **important mediators** of the acute-phase reaction.
- The acute -phaseresponse consists of several clinical and pathologic change.

# 1) Fever

- Characterized by an **elevation of body temperature**, usually by **1° to 4°C**, is one of the most prominent manifestations of the acute phase response.
- Especially when inflammation is associated with **infection**.
- Substances that induce fever are called **pyrogens**.

# 1) Fever

- **Bacterial products** (LPS, exogenous pyrogens) -----  
stimulation of **leukocytes** ----- release **cytokines**  
(**IL-1**  
and **TNF** (endogenous pyrogens) ----- increase the  
**enzymes** (cyclooxygenases) **activity** -----  
conversion of **AA** into **prostaglandins**.



➤ Prostaglandins (**PGE<sub>2</sub>**) produced in **vascular** and **perivascular** cells of **hypothalamus** increase **body temperature**.

## 2) Acute-phase proteins

- **Plasma proteins**, mostly **synthesized** in **liver**.
- Plasma **concentrations increase** several hundred-fold as part of response to inflammatory stimuli.
- Three of the best-known of these proteins are **C-reactive protein (CRP)**, **fibrinogen**, and **serum amyloid A (SAA)** protein.

## 2) Acute-phase proteins

- Synthesis of these molecules in **hepatocytes** is stimulated by cytokines, especially **IL-6**(for CRP and fibrinogen) and **IL-1**or **TNF** (for SAA).
- **CRP** and **SAA**, bind to **microbial cell walls**, and they may act as **opsonins**.
- **CRP** and **SAA**, bind to **chromatin** and possibly help

**in clearing necrotic cell nuclei.**

## 2) Acute-phase proteins

- **Fibrinogen binds to red cells** and causes them to **form stacks** (rouleaux) that **sediment more rapidly** at unit gravity than do individual red cells -----  
**basis for measuring the erythrocyte sedimentation rate** ----- a simple test for an inflammatory response caused by any stimulus.

## 2) Acute-phase proteins

➤ Acute phase proteins have beneficial effects during acute inflammation, but prolonged production of these proteins (especially SAA) in states of chronic inflammation causes secondary amyloidosis.

### 3) Leukocytosis

- Common feature of inflammatory reactions, especially those induced by bacterial infections.
- May reach extraordinarily high levels (40,000 to 100,000 cells/mL), a condition known as **leukemoid reactions**.

### 3) Leukocytosis

- Cytokines including TNF and IL-1 result in **accelerated release of cells from bone marrow postmitotic reserve pool.**
- Associated with a **rise in number of more immature neutrophils in blood**, referred to as a **left shift.**



### 3) Leukocytosis

- Prolonged infection also induces proliferation of precursors in the bone marrow, caused by **increased production of colony-stimulating factors**. Thus, the bone marrow output of leukocytes is increased to compensate for the loss of these cells in the inflammatory reaction.

### 3) Leukocytosis

- Most bacterial infections induce an **increase in blood neutrophil count**, called **neutrophilia**.
- **Viral infections** (mumps and German measles), cause an absolute **increase in the number of lymphocytes** called **lymphocytosis**.

### 3) Leukocytosis

- **Allergies and parasitic infestations ----- an increase in absolute number of eosinophils, a condition known as eosinophilia.**
- **Certain infections (typhoid fever and infections caused by some viruses, rickettsiae, and certain protozoa) are associated with a decrease in number**

of circulating **white cells** ----- **leukopenia**.

## 4) Other manifestations

- Increased pulse and blood pressure.
- Decreased sweating, mainly because of redirection of blood flow from cutaneous to deep vascular beds, to minimize heat loss through skin.
- Rigors (shivering), chills, anorexia, somnolence, and malaise.

➤ Actions of cytokines on brain cells main cause.

## 4) Other manifestations

- **Excessive inflammation** is underlying cause of many human diseases including cancer.
- **Defective inflammation** is responsible for increased susceptibility to infections ----- **leukocyte deficiency** caused by leukemias, metastatic tumors and suppression of marrow by therapies for cancer

and graft rejection.



# **Scar formation (CT deposition)**

- **Fibrosis**, describes **extensive deposition of collagen** that occurs in **lungs, liver, kidney, and other organs** as a consequence of **chronic inflammation**, or in **myocardium** after extensive **ischemic necrosis** (infarction).
- If **fibrosis develops** in a **tissue space** occupied by an **inflammatory exudate**, it is called **organization** (as

in organizing pneumonia affecting the lung).

# **Fibrosis vs Organization**

- **Fibrosis**, describes **extensive deposition of collagen** that occurs in **lungs, liver, kidney, and other organs** as a consequence of **chronic inflammation**, or in **myocardium** after extensive **ischemic necrosis** (infarction).
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in organizing pneumonia affecting the lung).

# **Chronic Inflammation**

**(Leukocyte infiltration, tissue damage,  
and fibrosis)**

# Chronic Inflammation

- Inflammation of **prolonged duration** (**weeks or months**) in which **inflammation, tissue injury, and attempts at repair coexist**, in varying combinations.
- It may follow **acute inflammation** or **chronic inflammation** may **begin insidiously**, as a low-grade, smoldering response without any

manifestations of an acute reaction.

# Causes of Chronic Inflammation

- **Persistent infections by microorganisms that are difficult to eradicate** (Mycobacteria and certain viruses, fungi, and parasites).
- May evoke an immune reaction called **delayed-type hypersensitivity** or **granulomatous reaction**.
- An **unresolved acute inflammation ---- chronic inflammation** (acute bacterial lung infection into



chronic lung abscess).

# Causes of Chronic Inflammation

- **Autoimmune disorders** ---- chronic tissue damage & inflammation ----- **rheumatoid arthritis** & multiple sclerosis.
- **Unregulated immune responses** against microbes ---
  - Inflammatory Bowel Disease (IBD).

# Causes of Chronic Inflammation

- **Prolonged exposure to potentially toxic agents** (exogenous or endogenous) ---- **particulate silica** when inhaled for prolonged periods, results in an **inflammatory lung disease** called **silicosis**.
- **Atherosclerosis**, a chronic inflammatory process of arterial wall induced, **at least in part, by excessive production** and tissue deposition of **endogenous**

**cholesterol and other lipids.**

# Morphological features

- **Infiltration** with **mononuclear cells** including **macrophages, lymphocytes, and plasma cells.**
- **Tissue destruction**, induced by **persistent offending agent** or by **inflammatory cells.**
- **Attempts at healing** by **connective tissue** replacement of damaged tissue, accomplished by proliferation of small blood vessels (**angiogenesis**)

and, in particular, **fibrosis**.

# Cells of Chronic Inflammation

- Chronic inflammation is result of **local activation** of several cell types and production of mediator,
- 1) **Macrophages**
  - 2) **Lymphocytes**
  - 3) **Eosinophils**
  - 4) **Mast cells**

## **5) Neutrophils**



# Cells of Chronic Inflammation

## 1) Macrophages

➤ Contribute by;

- 1) **Secreting cytokines and growth factors that act on various cells.**
- 2) **by destroying foreign invaders and tissues.**
- 3) **by activating other cells, notably T lymphocytes.**

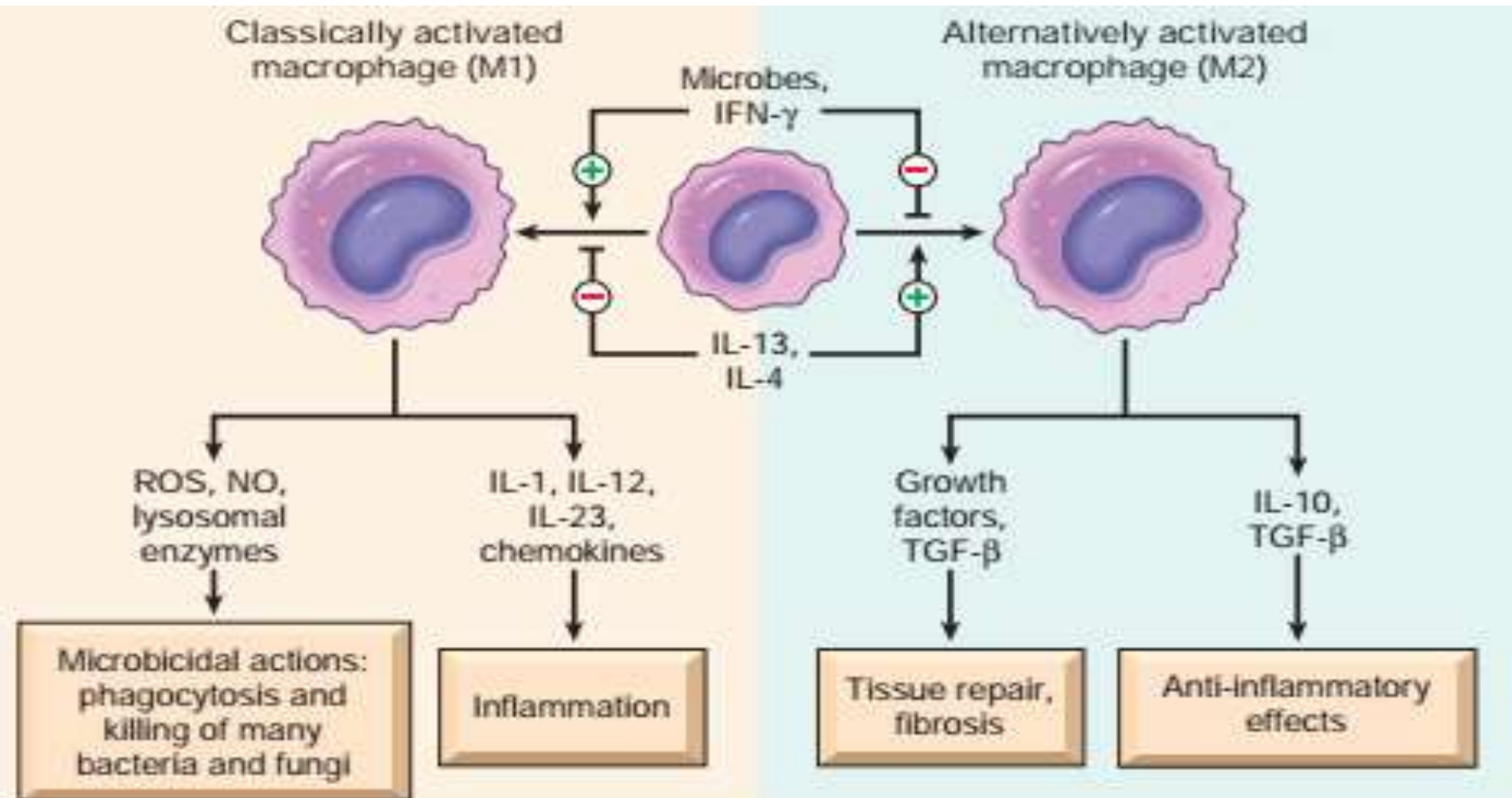
# Macrophages

- Diffusely scattered in most connective tissues.
- Also found in specific organs such as **liver** (called Kupffer cells), **spleen** and **lymph nodes** (called sinus histiocytes), **CNS** (microglial cells), and **lungs** (alveolar macrophages) ----- **mononuclear phagocyte system** (older name: **reticuloendothelial**

**system).**

# Macrophages activation pathways

- Endotoxin, T cell–derived signals (IFN- $\gamma$ ), immune responses; or by foreign substances including crystals and particulate matter.
- Cytokines other than IFN- $\gamma$ , such as IL-4 & IL-13, produced by T lymphocytes and other cells.



**Macrophages reside in various tissues**



**When macrophages**

**are inappropriately or excessively activated**



**Tissue destruction occurs which is  
one of the hallmarks of chronic inflammation.**

# Lymphocytes

- **Microbes and other environmental antigens activate T and B lymphocytes, which amplify and propagate chronic inflammation.**
- **When they are activated, inflammation tends to be persistent and severe.**
- **In granulomatous inflammation, autoimmune disorders & other hypersensitivity diseases play**

major role.

# Lymphocytes

- **TH1 cells produce IFN- $\gamma$ ---- activates macrophages by classical pathway.**
- **TH2 cells secrete IL-4 IL-5 and IL-13---- recruit and activate eosinophils ---- activates macrophages by alternative pathway.**
- **TH17 cells secrete IL-17 and other cytokines, ---- secretion of other chemokines ---- neutrophils &**



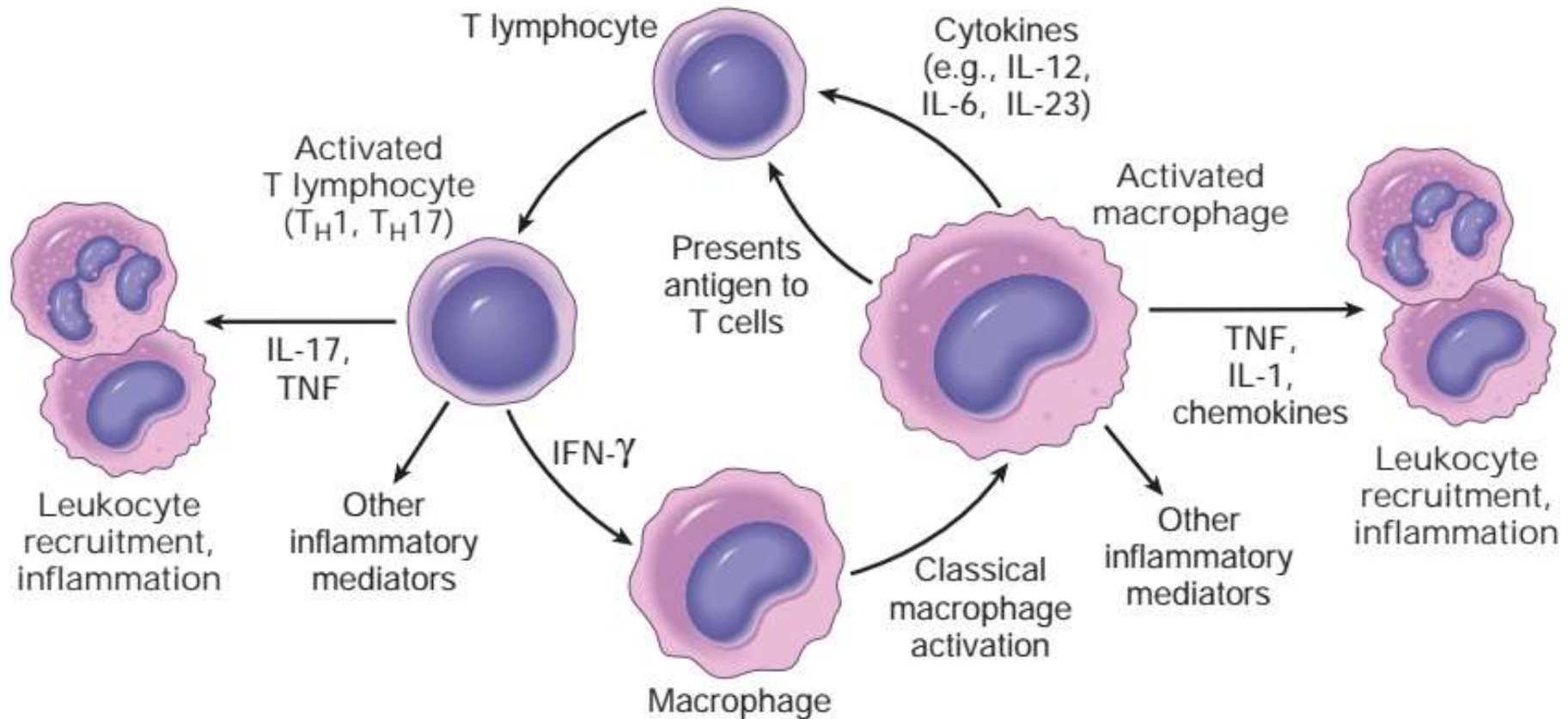
**monocytes recruitment.**

# Lymphocytes

- **Lymphocytes and macrophages interact in a bidirectional way, and these interactions play an important role in propagating chronic inflammation.**
- **Macrophages display antigens to T cells, express membrane molecules (called costimulators), and produce cytokines (IL-12 and others) that stimulate T-**

**-cell responses.**

# Lymphocytes, macrophages interaction



# Lymphocytes

- **Activated T lymphocytes**, in turn, produce **cytokines**, which **recruit** and **activate macrophages**, promoting more antigen presentation and cytokine secretion leading to **cycle of cellular reactions** that **fuel** and **sustain chronic inflammation**.

# Lymphocytes

- In some chronic inflammatory reactions, **accumulated lymphocytes, antigen-presenting cells, and plasma cells** cluster together to form **lymphoid tissues** resembling lymph nodes. These are called **tertiary lymphoid organs**
- Lymphoid organogenesis is often seen in **synovium of patients** with long-standing **rheumatoid arthritis**

and in thyroid in **Hashimoto thyroiditis**.

# Eosinophils

- Abundant in **immune reactions** mediated by **IgE** and in **parasitic infections**.
- Have **granules** containing **major basic protein**, (highly cationic protein) that is **toxic to parasites** but also **causes lysis of mammalian epithelial cells**.
- Also contribute to tissue damage in immune reactions



such as allergies.

# Mast cells

- Widely distributed in **connective tissues** and participate in both **acute** and **chronic inflammation**.
- Have **surface receptor** (FceRI) that binds **Fc portion** of **IgE antibody** and **degranulate** and **release mediators**, such as **histamine** and **prostaglandins** (immediate hypersensitivity reactions).

# Mast cells

- Present in **chronic inflammatory reactions**, and secrete a **plethora of cytokines**, they may **promote inflammatory reactions**.

# Neutrophils

- Many forms of **chronic inflammation**, lasting for months, continue to show large numbers of neutrophils, **induced** either by **persistent microbes** or by **mediators** produced by **activated macrophages** and **T lymphocytes**.
- For example, in **chronic bacterial infection of bone (osteomyelitis)**, **neutrophilic exudate** can persist for

many months.

# Neutrophils

- Neutrophils play important role in **chronic damage** of **lungs** induced by smoking and other irritant stimuli.
- This pattern of inflammation has been called **acute on chronic**

# Granulomatous Inflammation

- A form of chronic inflammation characterized by **collection of activated macrophages**, often with **T lymphocytes**, and sometimes associated with **central necrosis**.
- Granuloma formation is a cellular **attempt to contain** an **offending agent** that is **difficult to eradicate**.

# Granulomatous Inflammation

- Leads to strong activation of **T lymphocytes** ---- **macrophage activation** ---- injury to normal tissues.
- **Activated macrophages** may **develop abundant cytoplasm** and begin to **resemble epithelial cells**, and are called **epithelioid cells**.
- Some **activated macrophages** may **fuse**, forming



**multinucleate giant cells.**

# Types of Granulomas

- Two types of granulomas, which differ in their pathogenesis.

## 1) Foreign body granulomas

- Caused by relatively **inert foreign bodies**.
- T cell-mediated **immune responses** are **absent**.

# Types of Granulomas

## 1) Foreign body granulomas

- Formed around materials such as **talc** (associated with intravenous drug abuse), **sutures**, or **other fibers** which are **large enough** to **preclude phagocytosis** by a **macrophage** and **do not incite** any **specific inflammatory** or **immune response**.

# Types of Granulomas

## 1) Foreign body granulomas

- **Epithelioid cells and giant cells are apposed to surface of foreign body. The foreign material can usually be identified in the center of granuloma.**

## 2) Immune granulomas

- Caused by **variety of agents** that are capable of inducing a **persistent T cell-mediated immune response**.
- When **inciting agent** is **difficult to eradicate**, such as **persistent microbe** or **self antigen**.

## 2) Immune granulomas

- In such responses, **macrophages activate T cells** to produce cytokines (**IL-2** ---- activates other T cells, perpetuating the response, and **IFN- $\gamma$**  which **activates macrophages**).

# Caseous vs Noncaseous granulomas

1) **Caseous granulomas** ----- Central necrosis zone ---  
---- caused by a combination of hypoxia and free radicals.

- Cheesy in appearance
- Examples **granulomas** associated with certain **infectious organisms** (most classically

*Mycobacterium tuberculosis*)



# Caseous vs Noncaseous granulomas

## 1) Caseous granulomas

- Granuloma formed in **tuberculosis** is referred to as a **tubercle**.

## 2) Noncaseous granulomas

- Central necrosis zone absent.
- No cheesy appearance.

**Table 3-8** Examples of Diseases with Granulomatous Inflammation

Disease	Cause	Tissue Reaction
Tuberculosis	<i>Mycobacterium tuberculosis</i>	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	<i>Mycobacterium leprae</i>	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	<i>Treponema pallidum</i>	Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; central cells are necrotic without loss of cellular outline
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against intestinal bacteria, possibly self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

# **Mediators of Inflammation**

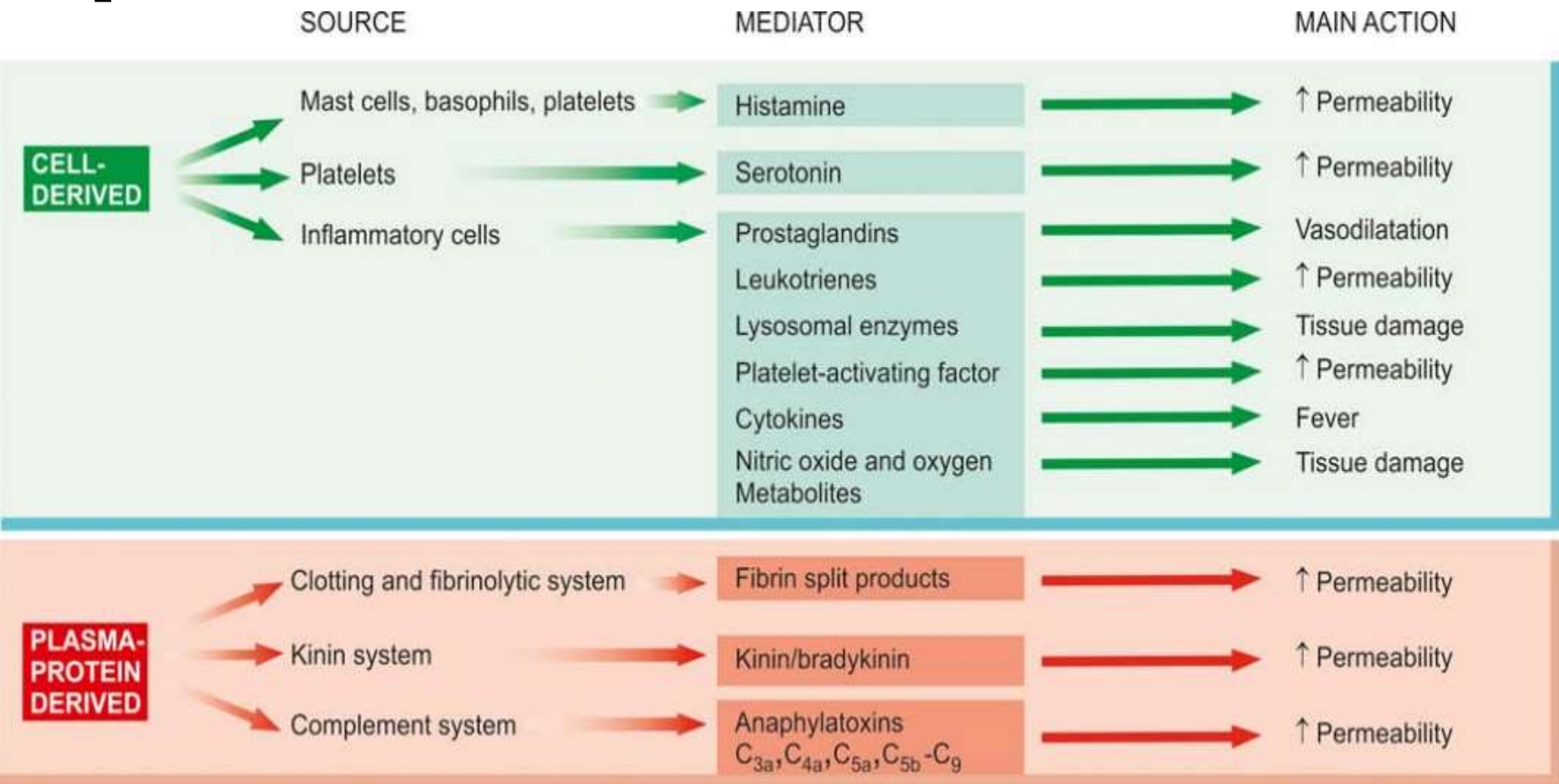
# Mediators of Inflammation

- Substances that **initiate** and **regulate** inflammatory reactions.
- Mediators are either **secreted by cells** or **generated from plasma proteins**.
- Active mediators are **produced** only in response to **various stimuli**.

# Mediators of Inflammation

- **Most** of the mediators are **short-lived**.
- One mediator can stimulate release of other mediators.

➤ Either secreted by cells or generated from plasma proteins.



# Mediators of Inflammation

**1) Cell-derived mediators are sequestered in intracellular granules.**

- Rapidly secreted by granule exocytosis (histamine in mast cell granules).
- Synthesized *de novo* (prostaglandins and leukotrienes, cytokines).

# Cell-derived mediators

## 1) Vasoactive Amines: Histamine and Serotonin.

- So named because they have important actions on blood vessels.
- Stored as **preformed molecules** in cells.
- Are among the **first mediators** to be released during **inflammation**



# Cell-derived mediators

## 1) Vasoactive Amines: Histamine

- **Richest sources** of histamine are **mast cells** that are normally **present** in **connective tissue** adjacent to **blood vessels**.
- Also found in **blood basophils** and **platelets**.
- Causes **dilation** of **arterioles** and **increases**

**permeability of venules.**

# Cell-derived mediators

## 1) Vasoactive Amines: Histamine

- Its vasoactive effects of histamine are mediated mainly via binding to **H1 receptors** present on **microvascular endothelial cells**.

# Cell-derived mediators

## 1) Vasoactive Amines: Serotonin

- **5-hydroxytryptamine**
- Present in **platelets** and certain neuroendocrine cells, such as in **gastrointestinal tract**, and **in mast cells** in **rodents** but **not humans**.
- Role in inflammation is unclear.

## 2) Arachidonic acid metabolites (Eicosanoids)

- Arachidonic acid metabolites or eicosanoids (20 carbon atom) ----- **most potent mediators of inflammation.**
- Constituent of phospholipid cell membrane.  
Released from cell membrane by phospholipase A<sub>2</sub>.
- Activated to form AA metabolites by one of the

following 2 pathways

## **2) Arachidonic acid metabolites (Eicosanoids)**

- Eicosanoids bind to G protein coupled receptors on many cell types and **can mediate virtually every step of inflammation.**

# Cyclo-oxygenase Pathway

- Prostaglandins
- Thromboxane A<sub>2</sub>
- Prostacyclin

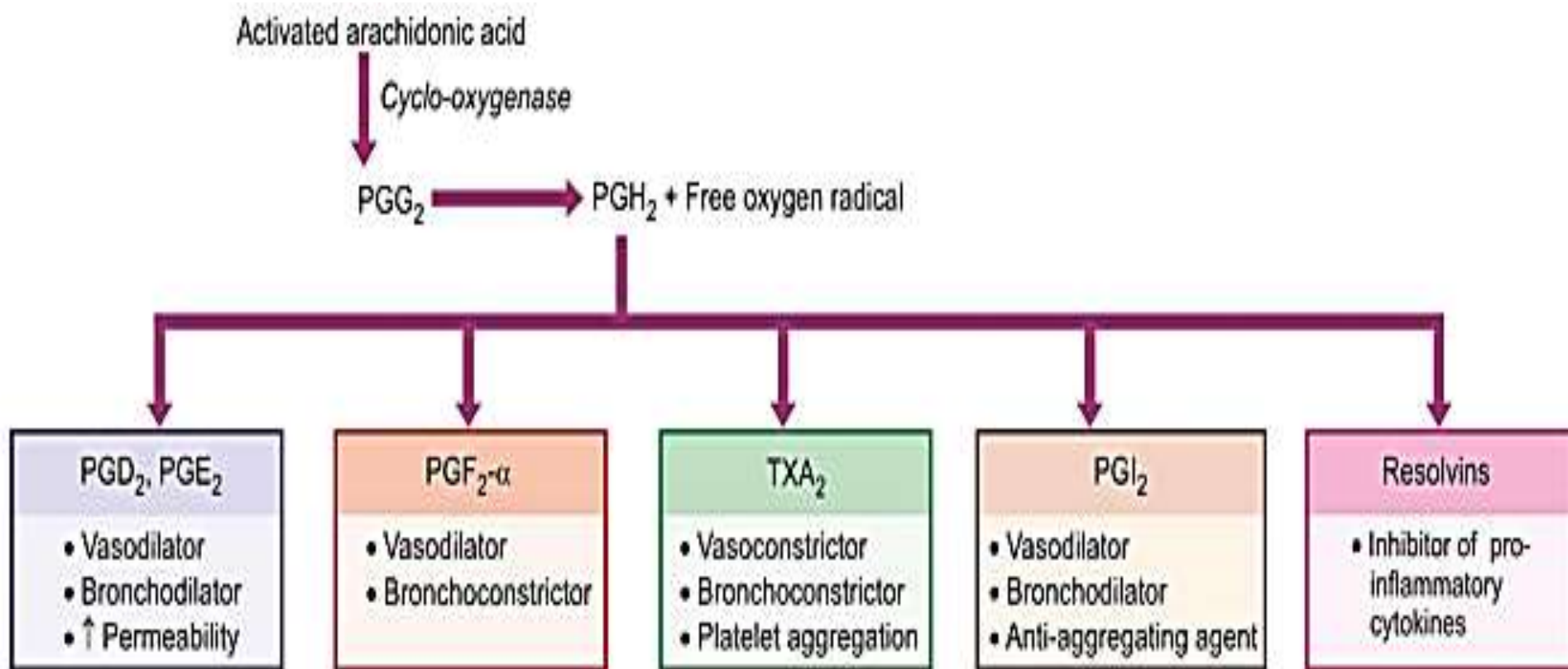


Figure 5-6 Arachidonic acid metabolism: cyclooxygenase pathway



## 2) Arachidonic acid metabolites (Eicosanoids)

- **Prostaglandins**
- Produced by **mast cells, macrophages, endothelial cells**, and many other cell types, and are involved in the vascular and systemic reactions of inflammation.
- Generated by actions of COX-1 and COX-2

## 2) Arachidonic acid metabolites (Eicosanoids)

- **Prostaglandins**
- Divided on the basis of structural features as PGD, PGE, PGF, PGG, and PGH and a subscript numeral (e.g., 1, 2), which **indicates number of double bonds** in compound.
- Inflammation ----- **PGE2, PGD2, PGF2a, PGI2**

(prostacyclin), and **TxA<sub>2</sub>** play major role.

## 2) Arachidonic acid metabolites (Eicosanoids)

- **Prostaglandins**
- Derived by action of a **specific enzyme** on an **intermediate in pathway**.
- Some of these enzymes have restricted tissue distribution.

## 2) Arachidonic acid metabolites (Eicosanoids)

### ➤ Prostaglandins

- Platelets ---- **thromboxane synthase** ----- **TxA<sub>2</sub>** ----  
potent platelet -aggregating agent &  
vasoconstrictor.
- **PGD<sub>2</sub>** is major prostaglandin made by **mast cells**;  
along with **PGE<sub>2</sub>** ---- **vasodilation** and **increases**  
**permeability** of **postcapillary venules** ----

**potentiating edema formation.**

## **2) Arachidonic acid metabolites (Eicosanoids)**

- **PGD2 is a chemo-attractant for neutrophils.**
- **Vascular endothelium ---- prostacyclin synthase -  
--- PGI2 & its stable end product PGF1a ----  
vasodilator and potent inhibitor of platelet  
aggregation ---- markedly potentiates  
permeability -increasing and chemotactic effects of**

other mediators.

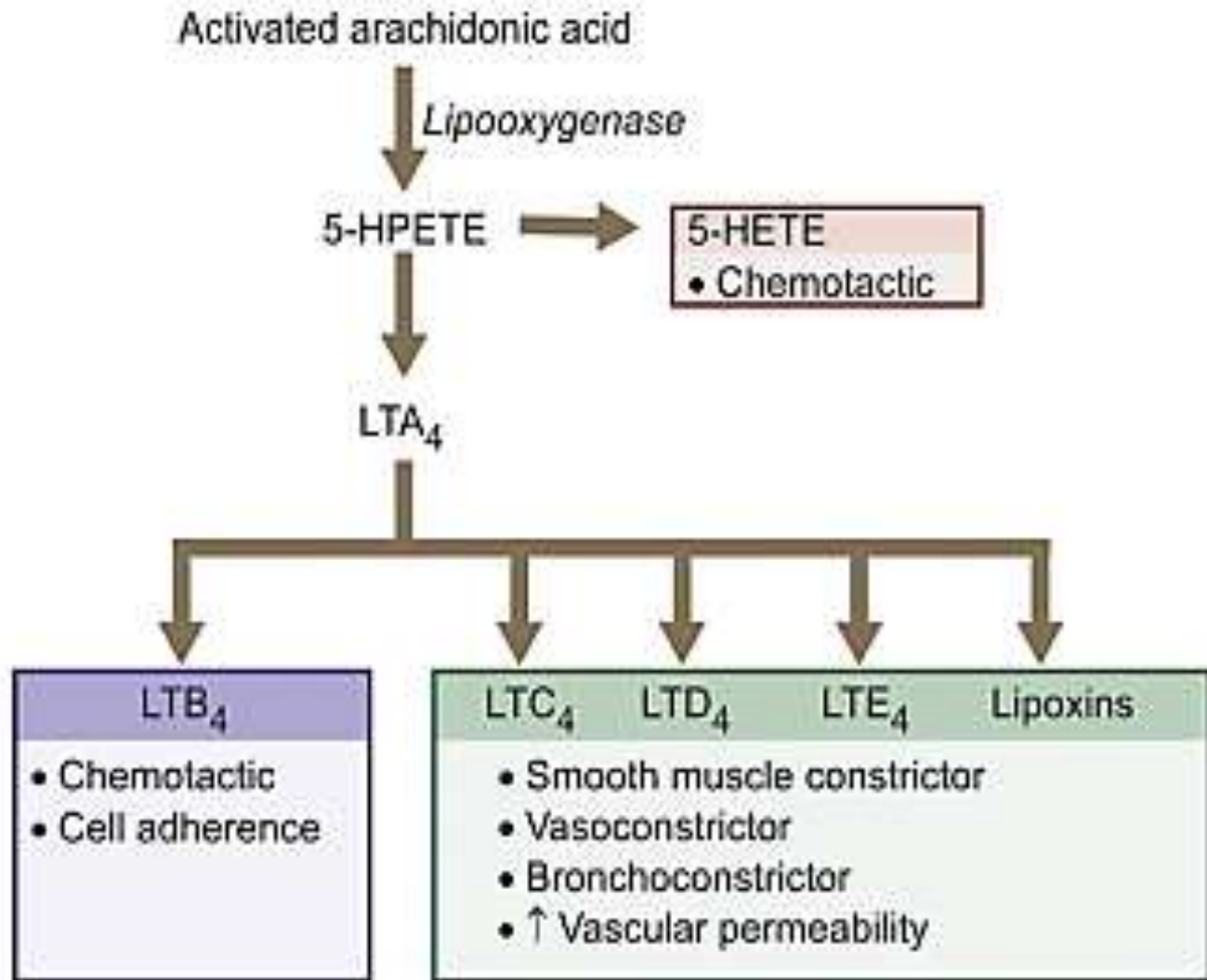


## 2) Arachidonic acid metabolites (Eicosanoids)

- Prostaglandins are involved in pathogenesis of **pain** and **fever** in inflammation.
- Like, **PGE2** is **hyperalgesic** and makes **skin hypersensitive to painful stimuli**.

## 2) Lipo-oxygenase pathway

- 5-HETE
- Leukotrienes
- Lipoxins



**Figure 5.9** Arachidonic acid metabolites via lipoxygenase pathway.

# Leukotrienes

- **Produced by leukocytes and mast cells by action of lipoxygenase.**
- **Involved in vascular and smooth muscle reactions and leukocyte recruitment.**
- **Three different types of lipoxygenases.**
- **5-lipoxygenase being the predominant one in**

neutrophils.

# Leukotrienes

- 5-lipoxygenase converts AA to **hydroxyeicosatetraenoic acid (5HETE)**
- **5HETE** is chemotactic for neutrophils, and is **precursor of other leukotrienes.**
- **LTB4** ---- **potent chemotactic agent & activator of neutrophils** ---- **aggregation** and adhesion of the cells to **venular endothelium**, generation of **ROS**,

**and release of lysosomal enzymes.**

# Leukotrienes

- **LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> cause intense vasoconstriction, bronchospasm (important in asthma), and increased permeability of venules.**
- **More potent than histamine in increasing vascular permeability and causing bronchospasm.**

# Lipoxins

- Generated from AA by **lipoxygenase pathway**.
- Suppress inflammation by **inhibiting recruitment of leukocytes**.
- **Inhibit neutrophil chemotaxis and adhesion** to endothelium.
- Two cell populations are required for transcellular



biosynthesis of lipoxins.

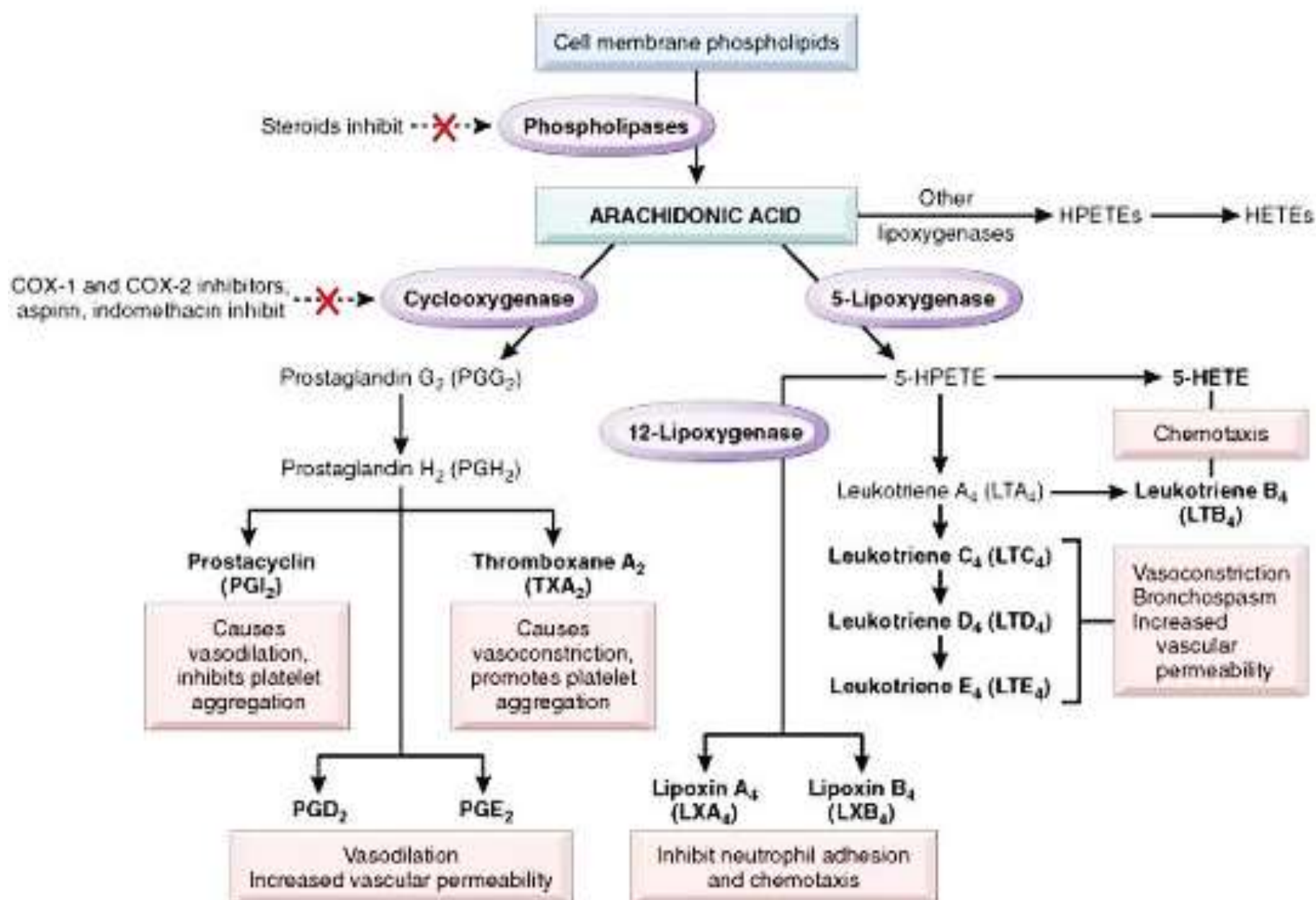
# Lipoxins

- Leukocytes, particularly **neutrophils**, produce **intermediates in lipoxin synthesis**, and these are converted to **lipoxins** by **platelets** interacting with **leukocytes**.

**Table 3-5** Principal Actions of Arachidonic Acid Metabolites in Inflammation

Action	Eicosanoid
Vasodilation	Prostaglandins $\text{PGI}_2$ (prostacyclin), $\text{PGE}_1$ , $\text{PGE}_2$ , $\text{PGD}_2$
Vasoconstriction	Thromboxane $\text{A}_2$ , leukotrienes $\text{C}_4$ , $\text{D}_4$ , $\text{E}_4$
Increased vascular permeability	Leukotrienes $\text{C}_4$ , $\text{D}_4$ , $\text{E}_4$
Chemotaxis, leukocyte adhesion	Leukotrienes $\text{B}_4$ , HETE

HETE, Hydroxyeicosatetraenoic acid.



### 3) Cytokines

- **Cytokines** are **proteins** produced by many cell types, principally **activated lymphocytes, macrophages, and dendritic cells**, but **also endothelial, epithelial, and connective tissue cells**)
- **Mediate and regulate immune and inflammatory reactions.**

# **A) Tumor Necrosis Factor (TNF) and Interleukin-1 (IL-1)**

- Serve critical roles in **leukocyte recruitment** by **promoting adhesion** of **leukocytes** to endothelium and their **migration through vessels**.
- Produced mainly by **activated macrophages** and **dendritic cells**.
- **TNF** is also produced by **T lymphocytes** and **mast**

**cells.**

# TNF and IL-1

- Secretion is stimulated by **microbial products, immune complexes, foreign bodies, physical injury**, and a **variety of other inflammatory stimuli**.
- Actions of TNF and IL-1 contribute to **local and systemic reactions** of inflammation.



# **TNF and IL-1**

## **1) Endothelial activation.**

➤ Spectrum of changes including;

- a) Increased expression of endothelial adhesion molecules, (E-- and P-selectins and ligands for leukocyte integrins).**
- b) Increased production of other cytokines and**

**chemokines, growth factors, and eicosanoids.**

# TNF and IL-1

## 1) Endothelial activation.

c) Increased procoagulant activity of endothelium.

## 2) Activation of other cells

- **TNF** augments **responses** of **neutrophils** to other stimuli such as **bacterial endotoxin**.
- Stimulates **microbicidal activity** of **macrophages**, in

part by inducing production of NO.

# **TNF and IL-1**

## **2) Activation of other cells**

- **IL-1** activates **fibroblasts** to **synthesize collagen**.
- **IL-1** also stimulates **TH17 responses**, which in turn induce acute inflammation.

## **3) Systemic acute-phase response**

- **IL-1** and **TNF** induce systemic acute-phase responses

associated with infection or injury.

# **TNF and IL-1**

## **3) Systemic acute-phase response**

- Implicated in **syndrome of sepsis**, resulting from disseminated bacterial infection.

# TNF and IL-1

- **TNF regulates energy balance by promoting lipid and protein mobilization and by suppressing appetite.** Therefore, sustained production of TNF contributes to **cachexia**, a pathologic state characterized by weight loss and **anorexia** that accompanies some **chronic infections** and **neoplastic**



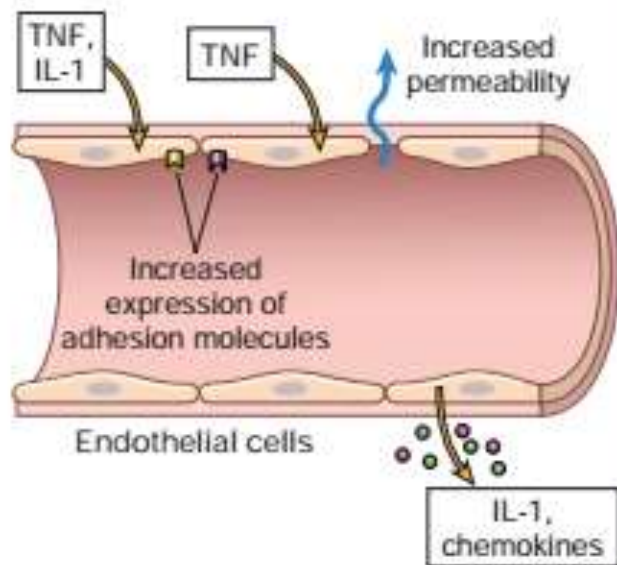
**diseases.**

**Table 3-6** Cytokines in Inflammation

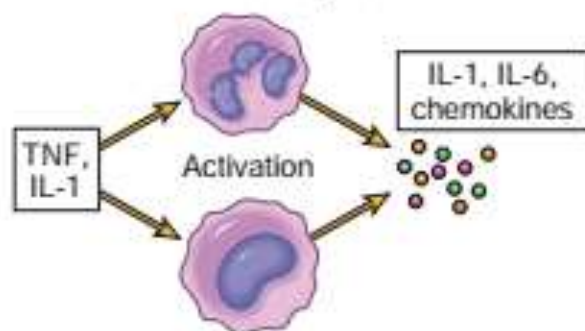
Cytokine	Principal Sources	Principal Actions in Inflammation
In Acute Inflammation		
TNF	Macrophages, mast cells, T lymphocytes	Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effects
IL-1	Macrophages, endothelial cells, some epithelial cells	Similar to TNF; greater role in fever
IL-6	Macrophages, other cells	Systemic effects (acute phase response)
Chemokines	Macrophages, endothelial cells, T lymphocytes, mast cells, other cell types	Recruitment of leukocytes to sites of inflammation; migration of cells in normal tissues
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes
In Chronic Inflammation		
IL-12	Dendritic cells, macrophages	Increased production of IFN- $\gamma$
IFN- $\gamma$	T lymphocytes, NK cells	Activation of macrophages (increased ability to kill microbes and tumor cells)
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes

IFN- $\gamma$ , Interferon- $\gamma$ ; IL-1, interleukin-1; NK cells, natural killer cells; TNF, tumor necrosis factor.  
The most important cytokines involved in inflammatory reactions are listed. Many other cytokines may play lesser roles in inflammation. There is also considerable overlap between the cytokines involved in acute and chronic inflammation. Specifically, all the cytokines listed under acute inflammation may also contribute to chronic inflammatory reactions.

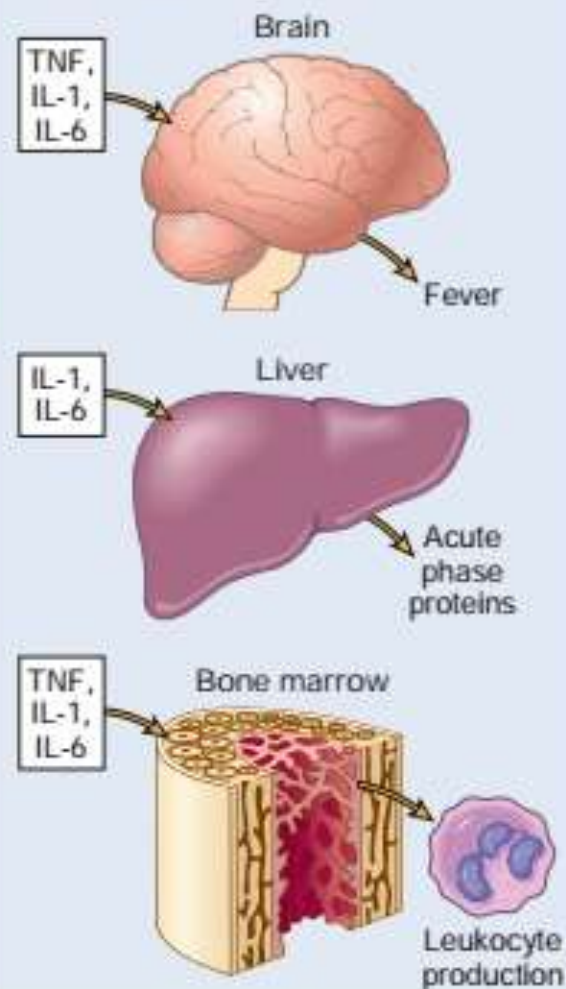
### LOCAL INFLAMMATION



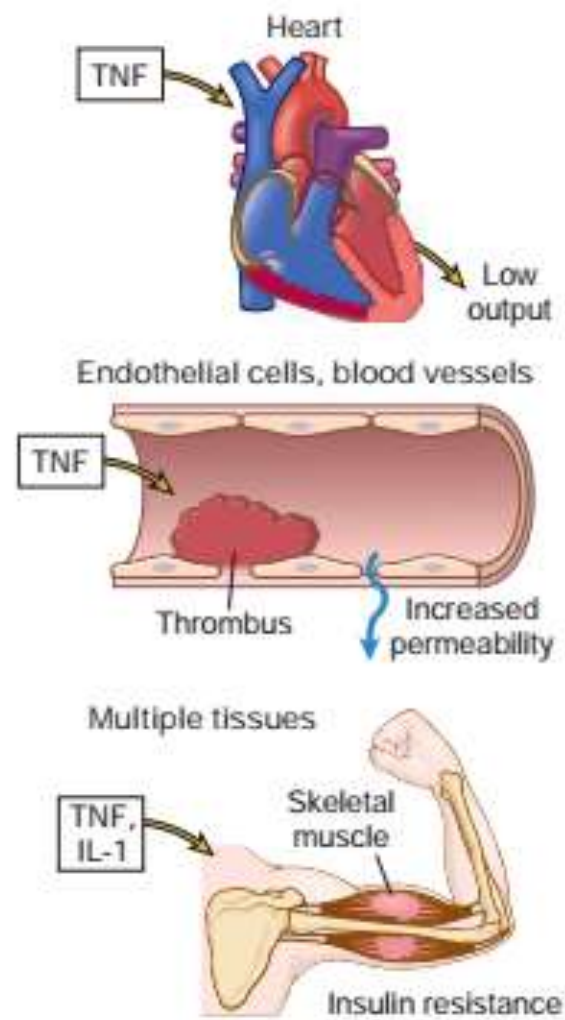
Leukocytes



### SYSTEMIC PROTECTIVE EFFECTS



### SYSTEMIC PATHOLOGICAL EFFECTS

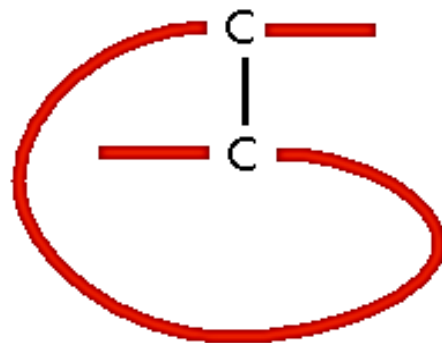


# Chemokines

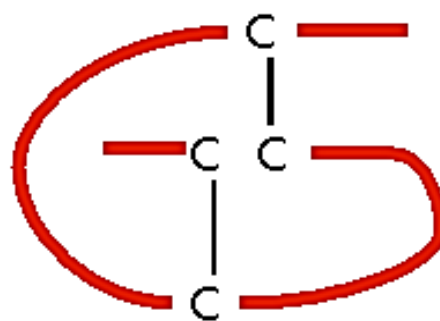
- A family of **small** (8 to 10 kD) **proteins** that act **primarily** as **chemoattractants**.
- About 40 different chemokines and 20 different receptors for chemokines have been identified.
- Classified into **four groups**, according to **arrangement of cysteine (C) residues in proteins**.

# Chemokines

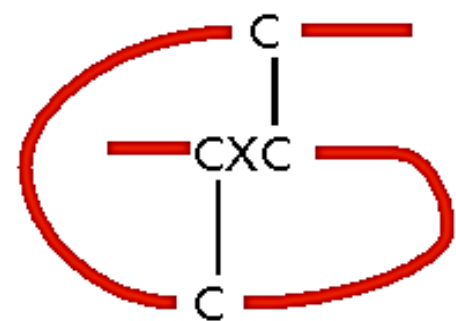
## Structure of chemokine classes



C chemokines

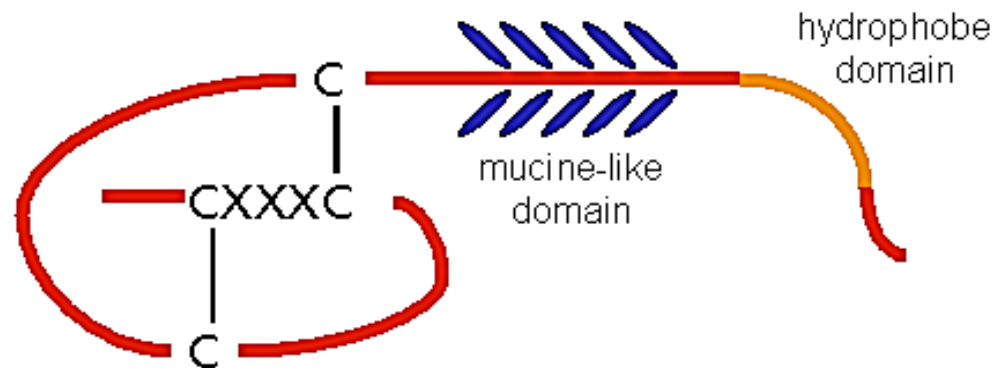


CC chemokines



CXC chemokines

peptide chain  
—  
disulphide bridge  
—



CX<sub>3</sub>C chemokines

# Chemokines

## 1) C-X-C chemokines

- Have one amino acid residue separating first two of four conserved cysteine residues.
- **Act primarily on neutrophils.**
- **IL-8** is typical member of this group.

# Chemokines

- Secreted by **activated macrophages, endothelial cells**, and other cell types,
- Cause **activation** and **chemotaxis** of **neutrophils**, with **limited activity** on **monocytes** and **eosinophils**.
- Secretions are stimulated by **microbial products** and other **cytokines (IL-1 and TNF)**.

# Chemokines

## 2) C-C chemokines

- First two conserved cysteine residues adjacent.
- Include **monocyte chemoattractant protein** (MCP-1), **eotaxin**, **macrophage inflammatory protein-1 $\alpha$**  (MIP-1 $\alpha$ ), and **RANTES** (Regulated And Normal T-cell Expressed and Secreted).



# Chemokines

- Act as **chemoattractants** for **monocytes**, **eosinophils**, **basophils** and **lymphocytes**.
- **Not potent chemoattractants** for **neutrophils**.

## 3) C chemokines

- Lack first and third of four conserved cysteines.
- C chemokines (e.g., **lymphotactin**) are relatively

specific for lymphocytes.

# Chemokines

## 4) CX<sub>3</sub>C chemokines

- Contain three amino acids between two cysteines.
- Only known member of this class is called **fractalkine**.

# Chemokines

- Chemokines may be displayed at high concentration attached to **proteoglycans** on **surface of endothelial cells** and in **extracellular matrix**.
- They have two main functions;
  - 1) **In acute inflammation**
- **Inflammatory chemokines** are ones whose

production is induced by microbes and other stimuli.

# Chemokines

## 1) In acute inflammation

- Stimulate leukocyte attachment to endothelium.
- Increase affinity of integrins
- Stimulate migration (chemotaxis) of leukocytes in tissues to site of infection or tissue damage.

# Chemokines

## 2) Maintenance of tissue architecture.

- **Homeostatic chemokines.**
- **Organize** various cell types in different anatomic regions of tissues, such as **T** and **B lymphocytes** in discrete areas of **spleen** and **lymph nodes**.

# **Plasma derived Mediators**

## **1) Complement System**

- **Complement proteins are present in inactive forms in plasma.**
- **Activated to become proteolytic enzymes that degrade other complement proteins, thus forming an enzymatic cascade capable of tremendous**



amplification.

# **Plasma derived Mediators**

## **1) Complement System**

- **Collection of soluble proteins and membrane receptors that function mainly in host defense against microbes and in pathologic inflammatory reactions.**
- **Consists of more than 20 proteins, some of which**

are numbered **C1** through **C9**.

# Plasma derived Mediators

## 1) Complement System

- In process of complement activation, several cleavage products of complement proteins are **produced** that cause increased **vascular permeability, chemotaxis, and opsonization.**

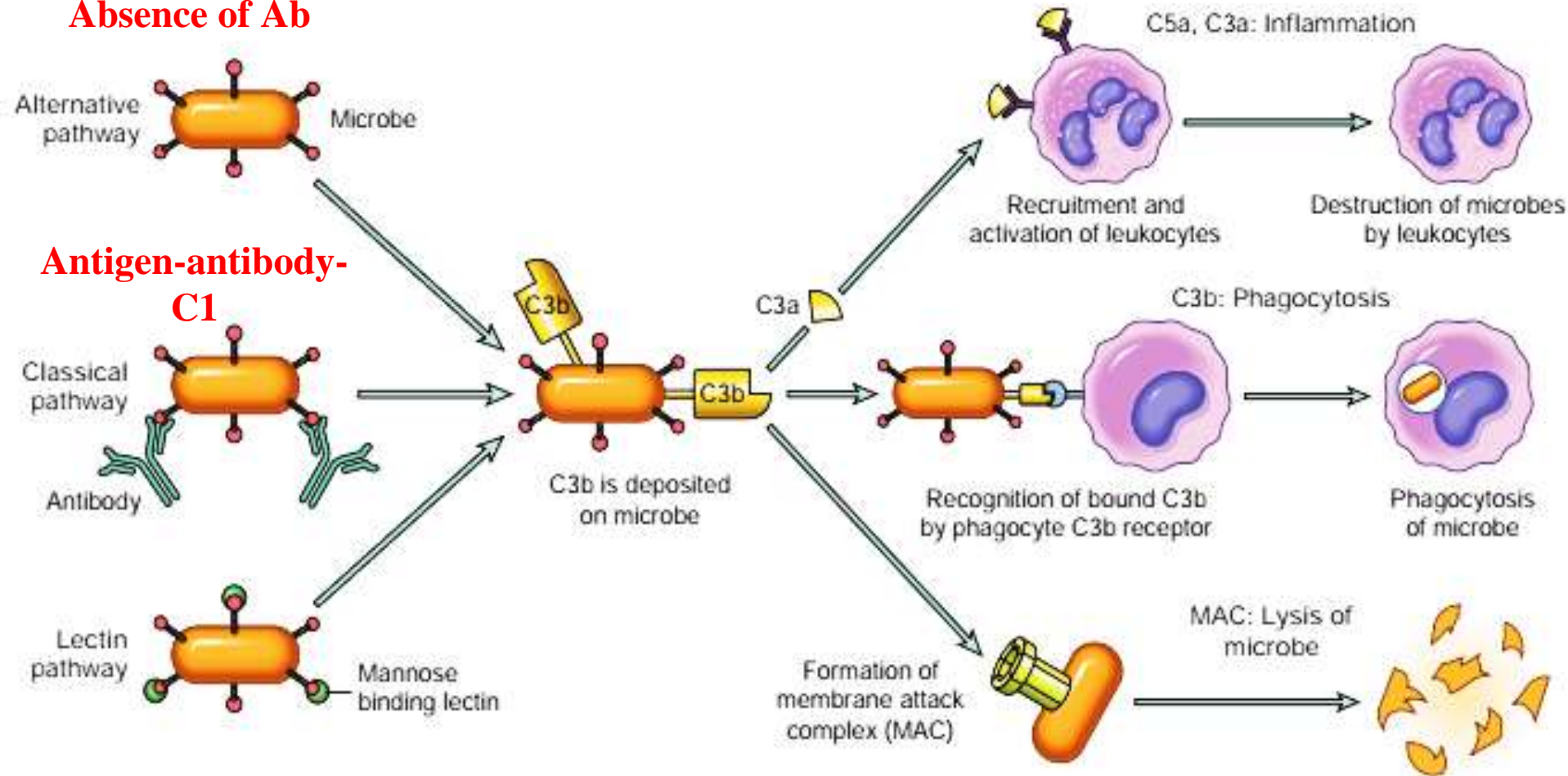
# Plasma derived Mediators

## 1) Complement System

- **Critical step in complement activation is proteolysis of 3<sup>rd</sup> (and most abundant) component, C3 which can occur by three pathways.**
- **All three pathways of complement activation lead to formation of membrane attack complex (MAC,**

composed of multiple C9 molecules).

## Absence of Ab



**Mannose binding lectins  
with microbial  
carbohydrates**

# Complement proteins

➤ The complement system has three main functions;

## 1) Inflammation

➤ **C3a**, **C5a**, and, to a lesser extent, **C4a** are major contributors.

➤ Stimulate **histamine release** from **mast cells** and thereby **increase vascular permeability** and cause



**vasodilation.**

# Complement proteins

## 1) Inflammation

- They are called **anaphylatoxins** because they have effects similar to those of mast cell mediators that are involved in reaction called **anaphylaxis**.

# Complement proteins

## 1) Inflammation

- **C5a** is also a **chemotactic agent** for **neutrophils**, **monocytes**, **eosinophils**, and **basophils**.
- **C5a** **activates lipoxxygenase pathway** of **AA** metabolism in **neutrophils** and **monocytes**, causing further **release of inflammatory mediators**.

# Complement proteins

## 2) Opsonization and phagocytosis.

- **C3b and its cleavage product iC3b (inactive C3b) --  
--fixed to a microbial cell wall ---- act as opsonins --  
--promote phagocytosis by neutrophils and  
macrophages.**

# Complement proteins

## 3) Cell lysis

- Deposition of **MAC** on cells makes these cells **permeable** to **water** and **ions** and results in death (lysis) of the cells.
- Plays an important role killing of microbes with thin cell walls, such as *Neisseria* bacteria ----- deficiency

leads to *Neisseria* infections.

# Complement proteins

- The activation of complement is tightly controlled by cell-associated and circulating regulatory proteins.
- **C1 inhibitor** (C1 INH) blocks the activation of C1 ---  
----- inherited deficiency of this inhibitor is the cause of **hereditary angioedema**.

# Complement proteins

- **Decay accelerating factor (DAF) and CD59** -----  
linked to plasma membranes by a **glycophosphatidyl (GPI) anchor**.
- **DAF prevents** formation of **C3 convertases** and **CD59 inhibits** formation of membrane attack complex (**MAC**).



# Complement proteins

- An **acquired deficiency** of enzyme that creates **GPI anchors** leads to **deficiency of these regulators** and excessive complement activation and **lysis of red cells** (which are sensitive to complement mediated cell lysis) in disease called **paroxysmal nocturnal hemoglobinuria (PNH)**.

## 2) Kinins

- **Vasoactive peptides** derived from plasma proteins, called **kininogens**, by action of specific **proteases** called **kallikreins**.
- **Bradykinin** increases **vascular permeability** and causes **contraction** of **smooth muscle**, **dilation** of **blood vessels**, and **pain** when **injected** into **skin**.

### **3) Other mediators**

#### **1) Platelet-Activating Factor (PAF)**

- **A phospholipid- derived mediator ----- cause platelet aggregation.**
- **Have multiple inflammatory effects.**
- **Secreted by platelets, basophils, mast cells, neutrophils, macrophages, and endothelial cells.**

### **3) Other mediators**

#### **1) Platelet-Activating Factor (PAF)**

- In addition to platelet aggregation, PAF causes **vasoconstriction** and **bronchoconstriction**
- At low concentrations it induces **vasodilation** and **increased permeability**.

# 3) Other mediators

## 2) Neuropeptides

- Small peptides (**substance P** and **neurokinin A**)
- Secreted by **sensory nerves** and various **leukocytes**.
- May play a role in **initiation** and **regulation** of **inflammatory responses**.
- **Nerve fibers** containing **substance P** are prominent

**in lung and gastrointestinal tract.**

# 3) Other mediators

## 2) Neuropeptides

- Substance P has many biologic functions, including **transmission of pain signals, blood pressure regulation, stimulation of hormone secretion by endocrine cells, and increasing vascular permeability.**

**Table 3-4** Principal Mediators of Inflammation

Mediator	Source	Action
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion, and activation
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	Local: endothelial activation (expression of adhesion molecules). Systemic: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (membrane attack complex), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain



# Mediators of Inflammation

**Table 3-7** Role of Mediators in Different Reactions of Inflammation

Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine Prostaglandins
Increased vascular permeability	Histamine and serotonin C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Leukotrienes C <sub>4</sub> , D <sub>4</sub> , E <sub>4</sub>
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1 Chemokines C3a, C5a Leukotriene B <sub>4</sub>
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes Reactive oxygen species

**Table 5.2****Mediators of inflammation.****I. CELL-DERIVED MEDIATORS**

1. Vasoactive amines (Histamine, 5-hydroxytryptamine, neuropeptides)
2. Arachidonic acid metabolites (Eicosanoids)
  - i. Metabolites via cyclo-oxygenase pathway (prostaglandins, thromboxane A<sub>2</sub>, prostacyclin, resolvins)
  - ii. Metabolites via lipo-oxygenase pathway (5-HETE, leukotrienes, lipoxins)
3. Lysosomal components (from PMNs, macrophages)
4. Platelet activating factor
5. Cytokines (IL-1, IL-6, IL-8, IL-12, IL-17, TNF- $\alpha$ , TNF- $\beta$ , IFN- $\gamma$ , chemokines)
6. Free radicals (Oxygen metabolites, nitric oxide)

**II. PLASMA PROTEIN-DERIVED MEDIATORS (PLASMA PROTEASES)**

Products of:

1. The kinin system
2. The clotting system
3. The fibrinolytic system
4. The complement system

# Mediators of Inflammation

## KEY CONCEPTS







### **Actions of the Principal Mediators of Inflammation**

- Vasoactive amines, mainly histamine: vasodilation and increased vascular permeability
- Arachidonic acid metabolites (prostaglandins and leukotrienes): several forms exist and are involved in vascular reactions, leukocyte chemotaxis, and other reactions of inflammation; antagonized by lipoxins
- Cytokines: proteins produced by many cell types; usually act at short range; mediate multiple effects, mainly in leukocyte recruitment and migration; principal ones in acute inflammation are TNF, IL-1, and chemokines
- Complement proteins: Activation of the complement system by microbes or antibodies leads to the generation of multiple breakdown products, which are responsible for leukocyte chemotaxis, opsonization, and phagocytosis of microbes and other particles, and cell killing
- Kinins: produced by proteolytic cleavage of precursors; mediate vascular reaction, pain

# **Cells of Inflammation**



**Table 5.4** Morphology and functions of inflammatory cells.

MORPHOLOGY	FEATURES	MEDIATORS
 <b>A, POLYMORPH</b>	<ul style="list-style-type: none"> <li>i. Initial phagocytosis of bacteria and foreign body</li> <li>ii. Acute inflammatory cell</li> </ul>	<ul style="list-style-type: none"> <li>i. Primary granules (MPO, lysozyme, cationic proteins, acid hydrolases, elastase)</li> <li>ii. Secondary granules (lysozyme, alk. phosph, collagenase, lactoferrin)</li> <li>iii. Tertiary granules (gelatinase, cathepsin)</li> <li>iv. Reactive oxygen metabolites</li> </ul>
 <b>B, MONOCYTE/MACROPHAGE</b>	<ul style="list-style-type: none"> <li>i. Bacterial phagocytosis</li> <li>ii. Chronic inflammatory cell</li> <li>iii. Regulates lymphocyte response</li> </ul>	<ul style="list-style-type: none"> <li>i. Acid and neutral hydrolases (lysosomal)</li> <li>ii. Cationic protein</li> <li>iii. Phospholipase</li> <li>iv. Prostaglandins, leukotrienes</li> <li>v. IL-1</li> </ul>
 <b>C, LYMPHOCYTE</b>	<ul style="list-style-type: none"> <li>i. Humoral and cell-mediated immune responses</li> <li>ii. Chronic inflammatory cell</li> <li>iii. Regulates macrophage response</li> </ul>	<ul style="list-style-type: none"> <li>i. B cells: antibody production</li> <li>ii. T cells: delayed hypersensitivity, cytotoxicity</li> </ul>
 <b>D, PLASMA CELL</b>	<ul style="list-style-type: none"> <li>i. Derived from B cells</li> <li>ii. Chronic inflammatory cell</li> </ul>	<ul style="list-style-type: none"> <li>i. Antibody synthesis</li> <li>ii. Antibody secretion</li> </ul>
 <b>E, EOSINOPHIL</b>	<ul style="list-style-type: none"> <li>i. Allergic states</li> <li>ii. Parasitic infestations</li> <li>iii. Chronic inflammatory cell</li> </ul>	<ul style="list-style-type: none"> <li>i. Reactive oxygen metabolites</li> <li>ii. Lysosomal (major basic protein, cationic protein, eosinophil peroxidase, neurotoxin)</li> <li>iii. PGE<sub>2</sub> synthesis</li> </ul>
 <b>F, BASOPHIL/MAST CELL</b>	<ul style="list-style-type: none"> <li>i. Receptor for IgE molecules</li> <li>ii. Electron-dense granules</li> </ul>	<ul style="list-style-type: none"> <li>i. Histamine</li> <li>ii. Leukotrienes</li> <li>iii. Platelet activating factor</li> </ul>