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Pathology

Doctor 2018 | Medicine | JU

Sheet Slides

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Granule Enzymes

PMNs and **monocytes** contain granules packed with enzymes and anti-microbial proteins that degrade microbes and dead tissues and may contribute to tissue damage.

Neutrophils have two main types of granules:

1- Larger (or primary) azurophil granules.
2- Smaller (or secondary) granules.

These granules:

1- Are actively secreted and thus are distinct from classic lysosomes.

2- Undergo exocytosis (degranulation), leading to the extracellular release of the granule contents.

3- Contain:
   - **MPO* and other enzymes in** primary granules
   - **lysozyme, and other enzymes in** secondary granules.

***MPO(**Myeloperoxidase): An important intracellular killing agent, especially when it's coupled with a halide (such as chlorine).

Neutrophils only release their enzymes at certain times and for certain amounts, to avoid causing collateral damage to the cell.
The released neutrophil proteases are normally regulated by a system of anti-proteases ex: α1-anti-trypsin, which is the major inhibitor of neutrophil elastase. A deficiency in these inhibitors causes sustained action of leukocyte proteases, as is the case in patients with α1-anti-trypsin deficiency.

Neutrophil Extracellular Traps (NETs)

Neutrophil extracellular traps (NETs) are extracellular fibrillar networks that concentrate anti-microbial substances at sites of infection and prevent the spread of the microbes by trapping them in the fibrils.
They are produced by neutrophils (not monocytes or macrophages) in response to infectious pathogens (mainly bacteria and fungi) and inflammatory mediators (e.g., chemokines, cytokines, and complement proteins).

- This is a specific function of neutrophils, which occurs after the neutrophil dies.
- The extracellular traps consist of a viscous meshwork of nuclear chromatin that binds and concentrates granule proteins such as anti-microbial peptides and enzymes in order to facilitate phagocytosis by macrophages, after PMN death.
- In the process of NET formation, the nuclei of the neutrophils are lost, leading to the death of the cells, sometimes called NETosis, representing a distinctive form of cell death affecting neutrophils.

NETs also have been detected in the blood during sepsis. They may be a source of nuclear antigens in systemic autoimmune diseases, particularly lupus, in which individuals react against their own DNA and nucleoproteins. *This mainly affects young females, targeting joints and on a cellular level affecting organelle movement. It results in malar rash, red cheeks, joint pain and organ (specifically kidney) damage*.

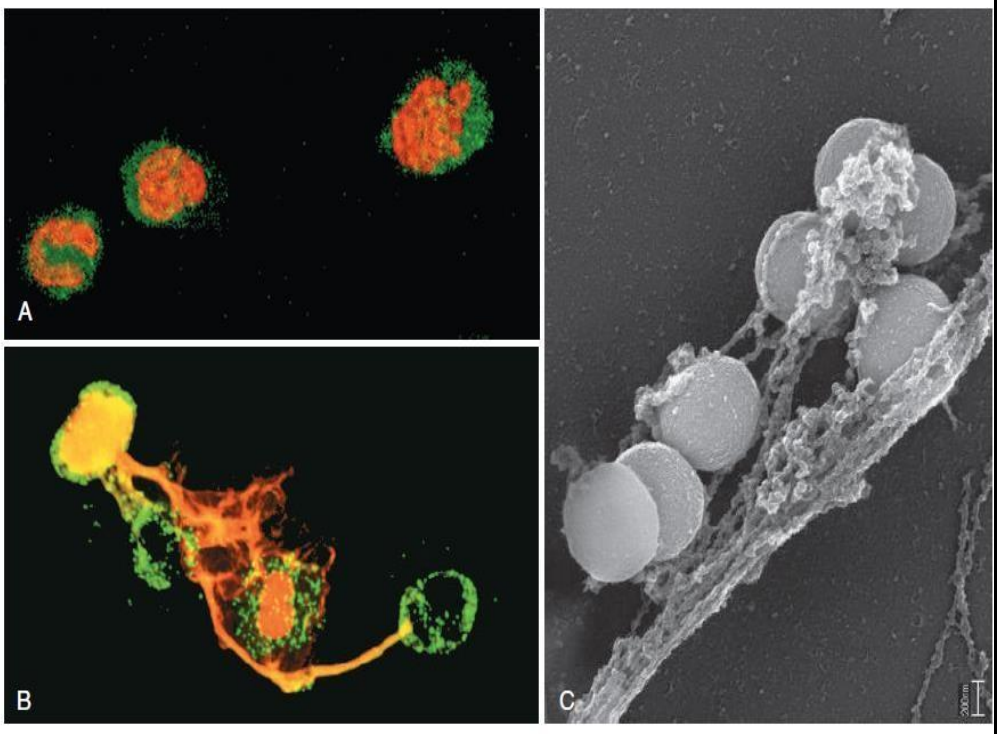


Fig. 3.8 Neutrophil extracellular traps (NETs). (A) Healthy neutrophils with nuclei stained red and cytoplasm green. (B) Release of nuclear material from neutrophils (note that two have lost their nuclei), forming extracellular traps. (C) An electron micrograph of bacteria (staphylococci) trapped in NETs. *(From*

LEUKOCYTE-MEDIATED TISSUE INJURY

A-Prolonged inflammation:

Happens in tough (virulent) infections like TB (caused by mycobacterium tuberculosis) and hepatitis c (viral disease which is the most common cause of chronic liver disease in our region). This mechanism causes injury by consistently stimulating local leukocyte production.

B-Inappropriate inflammatory response:

Ex: Autoimmune diseases - when inflammatory reactions damage normal tissues in the body.

C-Exaggerated response:

(Overreaction) certain reactions are exaggerated as what happens in severe acute allergic reactions (anaphylaxis) including asthma.

*Eosinophils infiltrate in allergic reactions and asthma.

Other functions of activated lymphocytes

Activated leukocytes play many roles in host defense, in addition to eliminating microbes:

1-Amplify or limit reactions by producing of cytokines. (4th R will be discussed later).
2-Produce growth factors (especially late mediators in repair) such as transforming growth factors beta and IL-10 ➔ *that stimulate the proliferation of endothelial cells and fibroblasts and the synthesis of collagen and the enzyme that remodel connective tissue*.
3-Although we had said that infiltration of T-lymphocytes happens in chronic inflammation, some of them have a role in acute inflammations such as: T-Helper-17 which produces IL-17 (Interleukin 17) in both acute and chronic disease, deficiency in it causes diseases.
*The Dr. said that there's an exam question about the 3rd one.

EXTRA INFO:(Book) In the absence of effective TH17 responses, individuals are susceptible to fungal and bacterial infections, and the skin abscesses that develop are "cold abscesses," lacking the classic features of acute inflammation, such as warmth and redness

Termination of the acute IR

In order to prevent collateral damage, clean up and regulation, inflammatory response is managed through 7 mechanisms:

1- Mediators are produced in rapid bursts (Not continuously getting released and produced), inflammation response decrease after microbes are removed.

2-Stimulus dependent: as long as the stimulus persists, mediators are released. That means no stimulus = no mediators.

3-Mediators have short life spans, such neutrophils, they die by themselves or via proteases.

4-They are degraded after being released.

5-PMNs short life: Mediators are mostly released by neutrophils, which have a very

short life span. When the source of the mediators dies, they are no longer released.

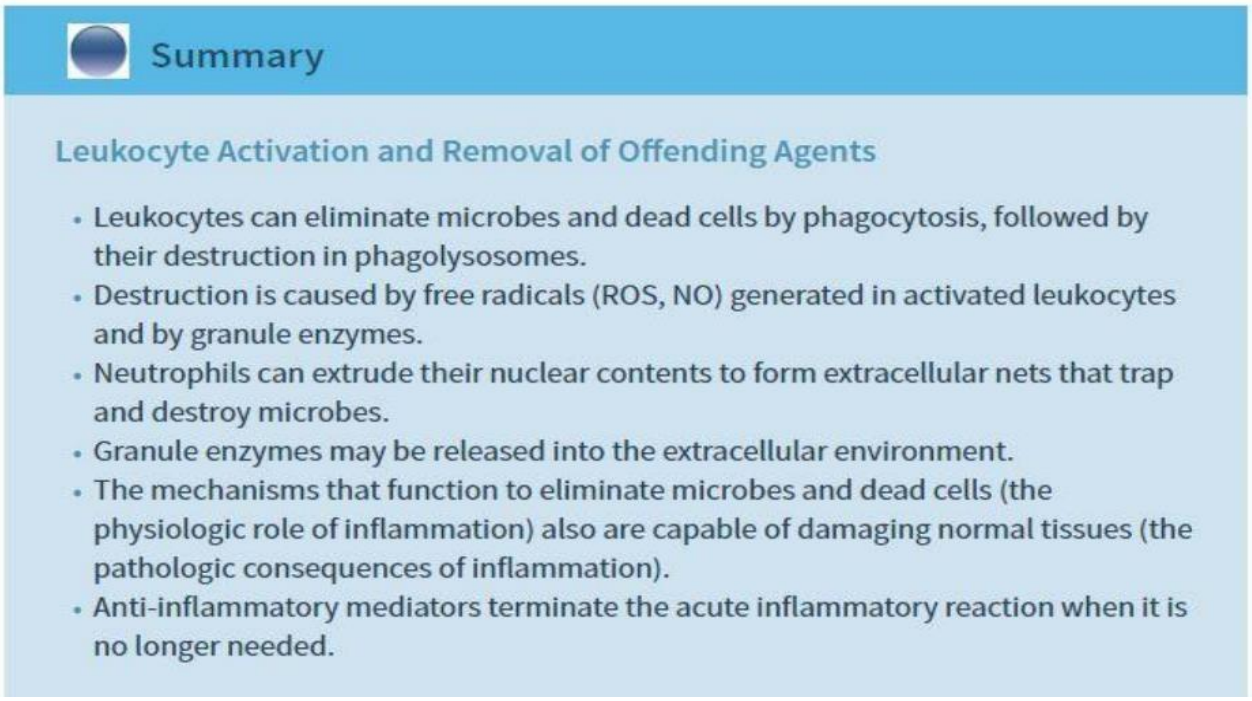
NOTES:

*After 3rd and 4th Rs, repair mediators are released.

*There is overlapping between the Rs, however step 3 can't come before step 1.

6- Stop signals production (TGF-BETA, IL-10) which are late mediator that inhibit the release of earlier mediators.

7- Neural cholinergic inhibitors can inhibit TNF (Tumor Necrosis Factor, a cytokine involved in acute inflammation).



Mediators of Acute Inflammation

Vasoactive amines	Histamine, serotonin
Lipid products	PGs and LTs
Cytokines	IL, TNF and chemokines
Complement activation	C1-9

Notes about the table:

*Vasoactive amine groups are important in the early vascular phase of inflammation (edema, swollen, redness…).

*Lipid products consist of 2 groups:

1-Prostaglandins

2-Leukotrienes

These come from arachidonic acid metabolism. (will be discussed later in details Insha'Allah)

General Features of Mediators

1-Most of them are cell derived at the site of infection: either released from granules or synthesized upon stimulation.

2-Plasma proteins (such as complement proteins) need activation.

3-Active mediators also need activation by other mediators.

4-Most mediators have short life spans.

5-Mediator can activate and inhibit each other (late mediator inhibits early one)

TABLE 3.5 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

******This table is a gift from the Dr. so memorize it Allah ys3edkom.***

Arachidonic Acid Metabolites

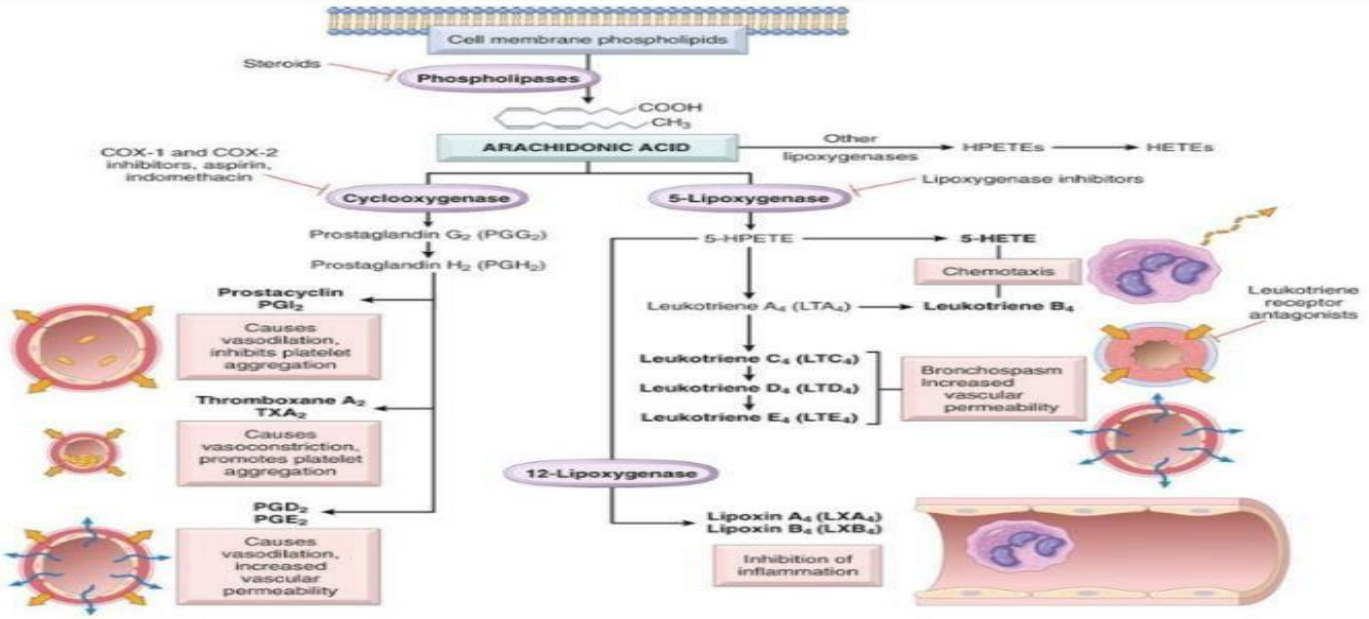


FIG. 3.9 Production of AA metabolites and their roles in inflammation. Clinically useful ...

-Cell membrane phospholipids are degraded by an enzyme called phospholipase to give Arachidonic acid.

-Arachidonic Acid is a 20 carbon polyunsaturated fatty acid.

-When it is released from the membrane it gets converted into mediators called Eicosanoids (Eicosa=20 in GREEK).

-These mediators are synthesized by 2 enzymes in different pathways:

1-Cyclooxygenase:

It is the generator of prostaglandins.

-There are a lot of prostaglandins but we don't have to know all of them so we will only mention the important ones:

1) Prostacyclin PGI2.

It is a vascular dilator and inhibitor of platelet aggregation so it prevents thrombosis and stroke of brain.

2) Thromboxane A2.

It induces vascular constriction and stimulates platelet aggregation. Since it minimizes the lumen's diameter it ⟶ causes **thrombus** ⟶ **acute ISCHEMIA** ⟶ **Cerebrovascular accident.**

**The function of prostacyclin completely opposes that of Thromboxane A2, so the balance between them is very important. If there's an imbalance, tipping more towards TA2, the risk of stroke and cerebrovascular accident increases.

3)PGD2+PGE2.

They are vascular dilators that increase vessel permeability.

2)Lipoxygenase:

Generates multiple mediators called **leukotrienes** (leuko = white blood cells, triene = motor), which are strong chemotactic agents. Some of these are involved in inflammatory reactions, especially in the acute attack of asthma, edema….

*Lipoxin A4 and b4 are **Anti-inflammatory mediators.**

Extra info:

Unlike prostaglandins and leukotrienes, lipoxins suppress inflammation by inhibiting the recruitment of leukocytes. They inhibit neutrophil chemotaxis and adhesion to endothelium. Leukocytes, particularly neutrophils, produce intermediates in lipoxin synthesis, and these are converted to lipoxins by platelets interacting with the leukocytes.

Inhibitors involved in AA metbolism

1) Inhibitors of phospholipase (steroids).

It is a strong, potent, dangerous anti-inflammatory drug that you can't get without a doctor's consult, commonly used in autoimmune diseases and cancer (we will take it in detail in pharmacology).

Taking steroids ⟶ inhibition of phospholipase ⟶ decreasing all AA products

2) Inhibitors of cyclooxygenase: (inhibit the production of prostaglandins)

e.g. NSAIDs (Cox1 and Cox2 inhibitors, aspirin).

NSIDs: Non-steroidal anti-inflammatory drugs, which are a large group of common drugs e.g. (profen, ibuprofen, voltaren)

3) Inhibitors of lipoxygenase: Used to treat certain diseases like acute and chronic asthma.

This is another gift from the Dr. so memorize It also Allah ys3edkom.

TABLE 3.6 Principal Actions of Arachidonic Acid Metabolites in Inflammation

Action	Eicosanoid
Vasodilation	Prostaglandins PGI_2 (prostacyclin), PGE_1, PGE_2, PGD_2
Vasoconstriction	Thromboxane A_2, leukotrienes C_4, D_4, E_4
Increased vascular permeability	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotriene B_4
Smooth muscle contraction	Prostaglandins PGC4, PGD4, PGE4

***Clinical*:**

Doctors use muscle relaxants (prostaglandin synthetase inhibitors) to prevent premature labor, trying to delay delivery, in order to make sure that the baby matured completely before birth.

POINTS TO REMEMBER ABOUT AA METABOLISM:

- Aspirin and NSAIDs (nonsteroidal anti-inflammatory drugs) – inhibit cyclooxygenase (which inhibits prostaglandins production)
- Steroids – major anti-inflammatory drugs which inhibit phospholipase (that inhibits all arachidonic acid - including prostaglandin and leukotriene - production).
- Lipoxygenase inhibitors: Inhibit leukotriene production.
- Thromboxane A2: a potent platelet-aggregation agent and vasoconstrictor which promotes thrombosis, cerebrovascular accident and heart attack.
- Prostacyclin (PGI2): a vasodilator and a potent inhibitor of platelet aggregation, and thus serves to prevent thrombus formation on normal endothelial cells. (ischemic heart disease and cerebrovascular accident).

Two opposite mechanism of action
Both are prostaglandins
Both are produced by cyclooxygenase

***Thromboxane– prostacyclin imbalance has been implicated in ischemic heart disease (IHD) & cerebrovascular accident (CVA).*

- PG (PGE2): causes pain & fever
  This is why COX1 -such as ibuprofen and indomethacin- inhibitors are used as pain killers and antibiotics.

Cytokines

-Proteins secreted by many cells (activated lymphocytes, macrophages and dendritic cells.

-Mediate, regulate and control immune and inflammatory responses.

This is the third gift from the Dr. so memorize It also Allah ys3edkom.

TABLE 3.7 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-γ
IFN-γ	T lymphocytes, NK cells	Activation of macrophages (increased ability to kill microbes and tumor cells)
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes

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.
IFN-γ, Interferon-γ; *IL-1*, interleukin-1; *NK*, natural killer; *TNF*, tumor necrosis factor.

Have roles in acute inflammation and chronic inflammation.

Local inflammation (local tissue changes): involves vascular phase (transudate and exudate), edema, constrictions, chemotaxis, etc.., which will eventually cause redness, swelling, pain, tenderness.

Some of these mediators (especially cytokines) enter the blood's serum and reach different tissues, causing:

1- **Systemic protective effects:**

***** Cytokines (TNF, IL-1, IL-6) reach the thermo center of the brain, inducing fever, which is considered both a bad and a good sign!

A Good sign: As it is an indication of disease, which guides the patient to take the necessary treatment, thus preventing other complications. On the other hand, fever may cause systemic hyperthermia.

Malignant hyperthermia: The condition occurs when the body's heat-regulation system becomes overwhelmed by outside factors, causing a person's internal temperature to rise.

****** Cytokines (IL-1, IL-6) reach the liver and stimulate the synthesis and release of small amounts of proteins called acute phase proteins, such as C-reactive proteins (CRP), into the blood stream. When we test blood samples, we can identify CRPs and recognize that an acute inflammation occurred.

-These CRPs are non-specific markers of acute inflammation, meaning that they are not indicators for certain disease.

****** Cytokines (TNF, IL-1, IL-6) reach the bone marrow and stimulate leukocyte production, causing leukocytosis (the leukocyte count becomes above normal range in the blood)

Leukemic reaction: is exaggerated (sever) leukocytosis (the white blood count may reach 40000, instead of the white blood count for simple diseases 20000). This may be a sign of leukemia.

2- **Systemic pathological effects.**

^ Too much TNF decreases cardiac output causing cardiogenic shock, hypotension and bradycardia.

^^ TNFs and A thromboxane– prostacyclin imbalance, can induce endothelial cell injury and platelet aggregation causing ischemia (local thrombosis) and heart attack.

^^^Production of TNF contributes to myalgia, a pathologic state characterized by weight loss, muscle atrophy, and anorexia (***General fatigue***) which accompanies some chronic infections and cancers.

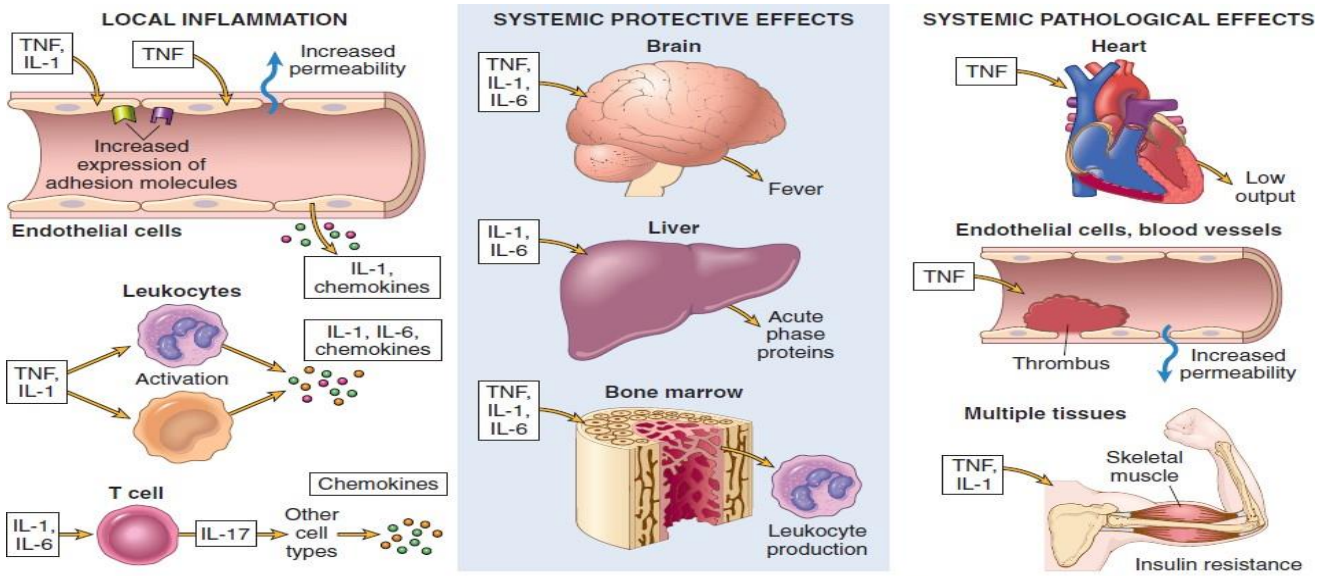


Fig. 3.10 Major roles of cytokines in acute inflammation. *PDGF*, Platelet-derived growth factor; *PGE*, prostaglandin E; *PGI*, prostaglandin I.

Chemokines

- Small proteins, mainly chemo-attractants
- 40 different and 20 receptors
- 4 groups: C-X-C; C-C; C; CX_3-C
- They have G-protein coupled receptors
- 2 main functions: Acute inflammation (chemo-attractants) & maintain tissue architecture (by inhibiting proteases in order to inhibit the digestion and prevent tissue damage).

COMPLEMENT SYSTEM

- Group of small proteins produced by the liver upon stimulation.
- Soluble proteins are normally present in inactive forms in the plasma, and many of them are activated (***fixation***) to become proteolytic enzymes that degrade other complement proteins, thus forming an enzymatic cascade capable of tremendous amplification.
- More than 20, most important ❼C1-C9
- Innate & adaptive immunity
- Functions: vascular permeability, chemotaxis & opsonization (C3b)
- C3 is most abundant; cleavage of which is critical in all pathways.

Activation of complement proteins by cleavage