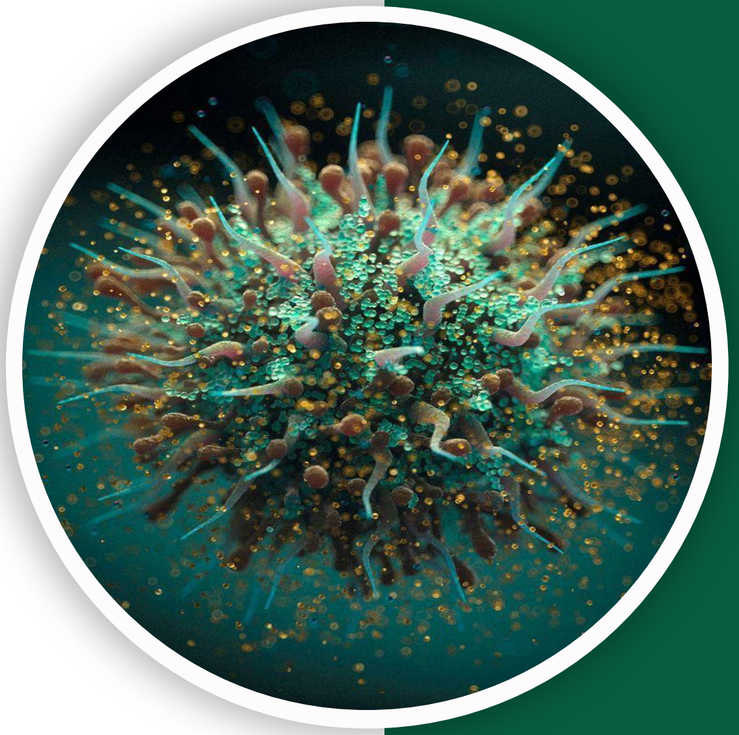
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pathology | Lecture 9

Inflammation pt.4



Written by : Leen Jarah
Leen Abukhalaf

Reviewed by : Rasha AlHamra

Lecture 4

We said that R1 is the recognition of foreign bodies
R2 is chemotaxis – cellular phase
R3: get rid of the response .
And after they we do not need more mediators or inflammation, as we have already killed the enemy so I need to slow down and terminate inflammatory response.

The next seven mechanisms is how we go to R4 :
termination and slowing down of inflammatory response.

TERMINATION OF ACUTE IR

Mediators are produced in rapid bursts

That's why the mediators don't have a sustaining long term impact

Release is stimulus dependent

The enemy is gone -> there is no stimulation

Short half-lives

Seconds-minutes, some may stay for hours

Degradation after release

Some of mediators when released they stimulate the release of their digestive enzymes. (For eg: NO and NOase)

PMNs short life (apoptosis)

In initial phase most of PMNs are produced by polymorphs nuclear cells or neutrophils (has a short life then make nets)

Stop signals production (TGF-ß, IL-10)

Some of these mediators will stimulate other mediators that will inhibit their production

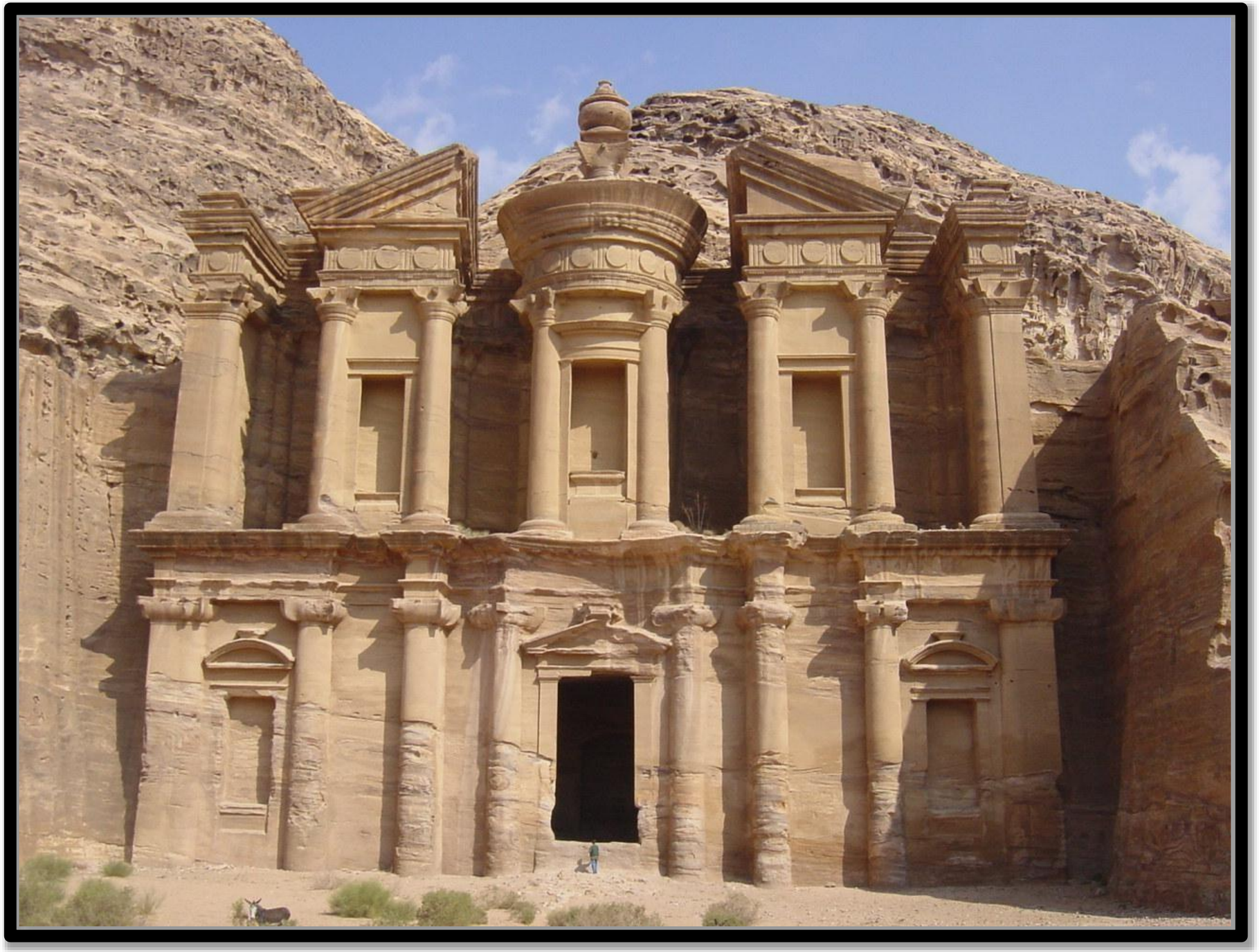
Transforming growth, factor(inhibit previous mediators)

Neural inhibitors (cholinergic): inhibits TNF

Summary

Leukocyte Activation and Removal of Offending Agents

- Leukocytes can eliminate microbes and dead cells by phagocytosis, followed by their destruction in phagolysosomes.
- Destruction is caused by free radicals (ROS, NO) generated in activated leukocytes and by granule enzymes.
- Neutrophils can extrude their nuclear contents to form extracellular nets that trap and destroy microbes.
- Granule enzymes may be released into the extracellular environment.
- The mechanisms that function to eliminate microbes and dead cells (the physiologic role of inflammation) also are capable of damaging normal tissues (the pathologic consequences of inflammation).
- Anti-inflammatory mediators terminate the acute inflammatory reaction when it is no longer needed.



MEDIATORS OF A. INFLAMMATION:

Tissue macrophages, dendritic cells & mast cells

Histamine is The major vasodilator in human and mediator of edema, transudate vascular phase

Metabolites of digestion of the cell membrane (arachidonic acid-lipid) ones are digested-> gives metabolites- discussed later

Vasoactive amines	Histamine, serotonin
Lipid products	PGs and LTs Prostaglandins and leukotrienes (chemotaxis)
Cytokines Kine = motor. Cytokines are major lymphocytes products	IL, TNF and chemokines
Complement activation (Proteins)	C1-9

GENERAL FEATURES OF MEDIATORS:

These features will overlap with how the inflammatory response will be terminated

- **Cell derived at the site: from granule release or synthesized upon stimulation**
- **Plasma proteins: needs activation** They are already present, but they need activation
- **Active mediators needs stimulation**
- **Most mediators have short life span**
- **One can activate the other** Or inhibit(previous mediators)

Complementary proteins are synthesized in the liver. In case of liver failure, -> proteins deficiency (compliment deficiency)

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

كل الجدول حفظ

We use steroids as drugs/medications. They are strong anti-inflammatory agents that inhibits phospholipase , and decrease the production of all the below.

Nonsteroidal anti-inflammatories that inhibit COX and decrease the production of all prostaglandins(does not affect LT)

PGI2: Useful in case of strokes(anti-stroke)

TXA2: The total opposite of PGI2

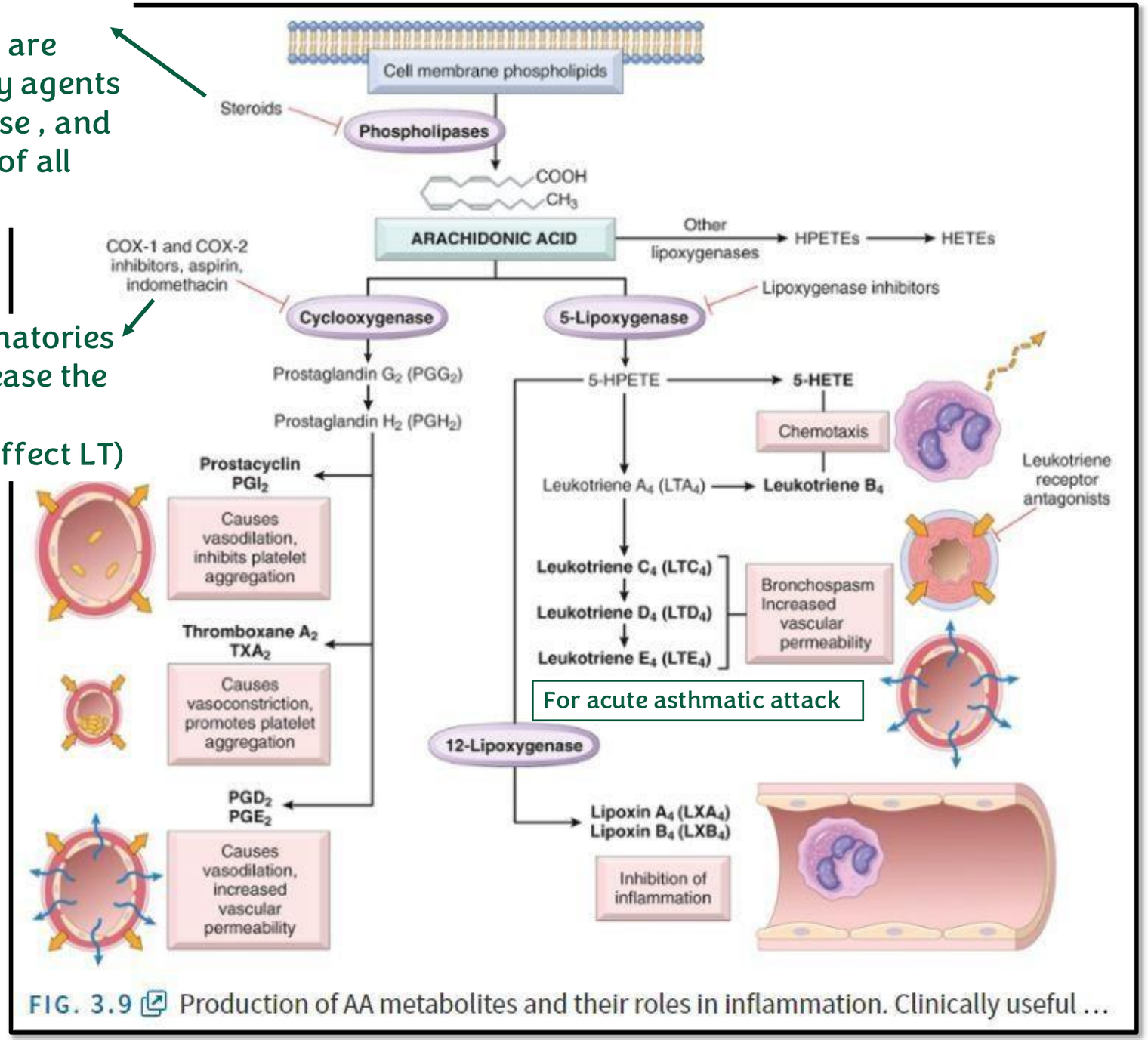


FIG. 3.9 Production of AA metabolites and their roles in inflammation. Clinically useful …

الجدول حفظ

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 (asthma)	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotriene B_4 Strong chemotaxis agents
Smooth muscle contraction	Prostaglandins PGC4, PGD4, PGE4

Eicosanoids = metabolites of AA

At delivery : in cases of premature labor we might give anti-prostaglandins for postponing baby delivery .

POINTS TO REMEMBER ABOUT AA METABOLISM:

– : inhibits

+ : stimulates

- Aspirin – cycloxygenase
- Steroids – phospholipase and anti inflamm
- Prostacyclin (PGI2): vasodilator and – Pl aggreg platelet aggregation
- Thrombaxane A2: vasoconstrictor and + pl aggreg
- TXA2-PGI2 imbalance: IHD & CVA
- PG (PGE2): pain & fever

IHD: Ischemic heart disease

CVA : Cerebrovascular accident (الجلطة)

CYTOKINES:

- **Proteins secreted by many cells (activated lymphocytes, macrophages and dendritic cells)**
- **Mediate and regulate immune and inflammatory response**

Activated lymphocytes, are the major producers of cytokines

The whole table is required
Notice that cytokines are important players in both acute and chronic inflammation
IL- 17 that come from T lymphocytes has a role in both chronic and acute inflammation

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.

حفظ

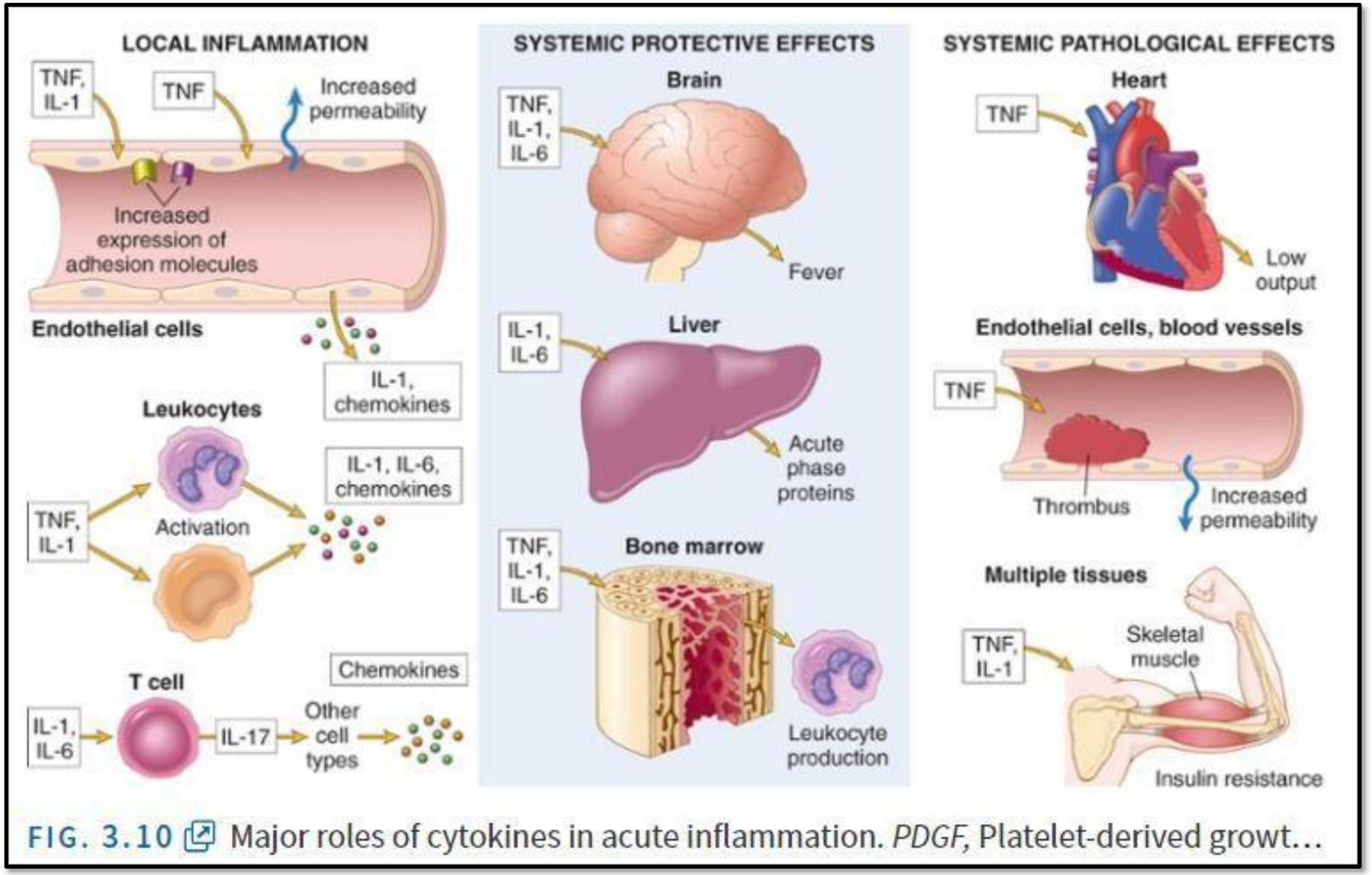


FIG. 3.10 Major roles of cytokines in acute inflammation. *PDGF,* Platelet-derived growt…

Cytokines can cause both local and systemic effects.
Locally, they produce signs and symptoms limited to the affected area. For example, in tonsillitis, the inflammation and pain occur specifically in the tonsils.

Systemic effects, on the other hand, occur when cytokines enter the bloodstream and act throughout the body—from the brain to the toes. These are called systemic manifestations and can be divided into protective and severe (sometimes fatal) responses. The severe systemic effects are responsible for life-threatening conditions seen in diseases such as severe COVID-19,

Local manifestations include increased vascular permeability, edema (swelling), and chemotaxis—which is the attraction of immune cells to the site of infection.
Cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6) also play a key role locally by activating T cells, which in turn release interleukin-17 (IL-17) to recruit even more immune cells and amplify the inflammatory response.

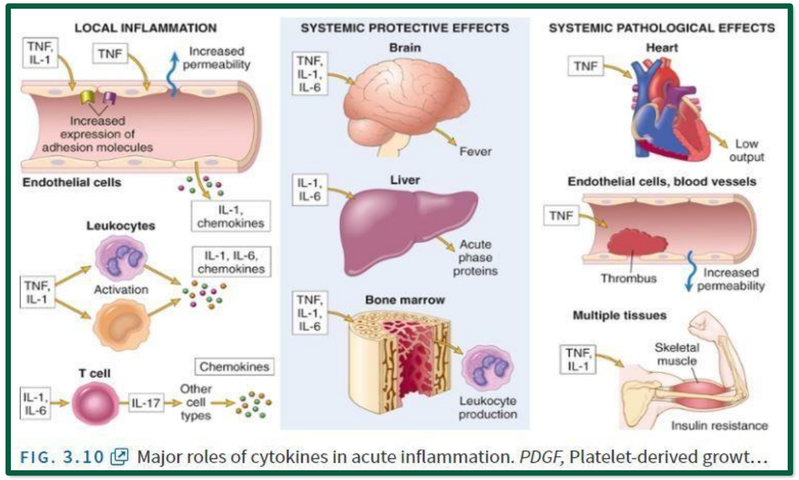


FIG. 3.10 Major roles of cytokines in acute inflammation. *PDGF,* Platelet-derived growt…

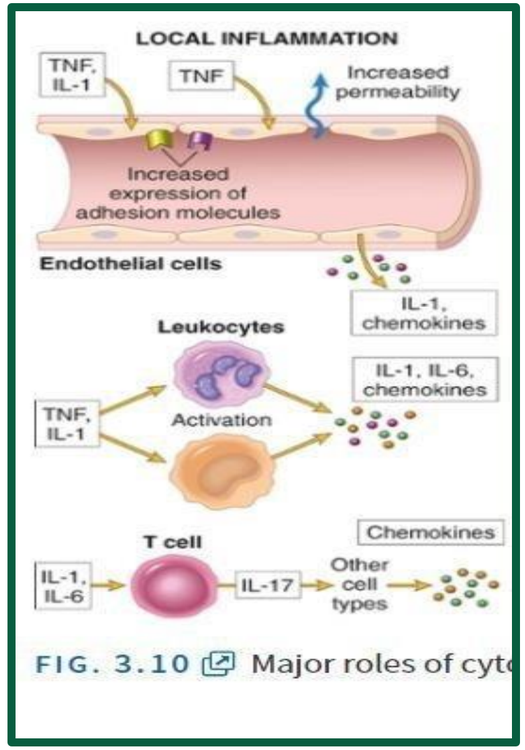


FIG. 3.10 Major roles of cyt

Protective systemic manifestations are body-wide responses that help the body fight infection or injury. For example, fever is considered a protective response because it signals that something is wrong, prompting you to seek medical attention

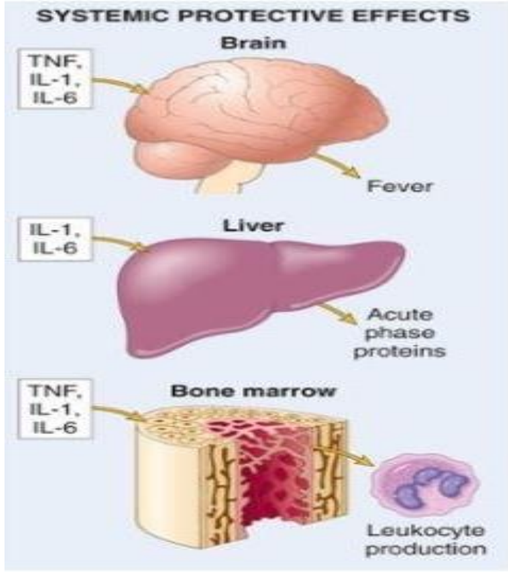
The liver plays a major protective role by producing important serum proteins, such as those of the complement system, which help defend against infection.
If the liver is damaged, it can lead to hypoproteinemia (low blood protein levels)

Liver produces non-specific serum reactants, such as C-reactive protein (CRP), which increase significantly during severe inflammation. They are called non-specific because their levels rise in all types of inflammation, regardless of the cause.

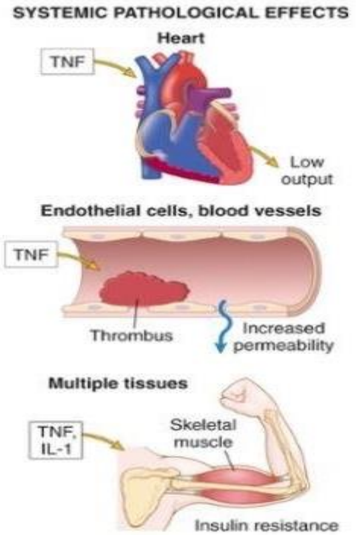
Additionally, tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) stimulate the bone marrow to produce more white blood cells through a process called hematopoiesis, helping the body fight infection more effectively.

1.TNF can affect the heart, reducing cardiac output and potentially leading to cardiogenic shock, which is a major cause of death in severe inflammation.
2.TNF can contribute to vascular injury, increasing the risk of strokes and heart attacks.
3.TNF and IL-1 promotes insulin resistance, which worsens the condition, especially in patients with diabetes.

These effects are part of the dangerous systemic manifestations of inflammation



kines in acute inflammation. *Pl*



GF, Platelet-derived growt…

CHEMOKINES:

Chemokines are a small group of cytokines. The name means chemoattractants, which means they mainly act in R2, the cellular phase, by directing chemotaxis.

- **Small proteins, mainly chemoattractants**
- **40 different and 20 receptors** . All mediators have specific receptors.
- **4 groups: C-X-C; C-C; C; CX_3-C**
- **They have G-protein coupled receptors**
- **2 main functions: A inflammation & maintain tissue architecture**

They maintain tissue architecture. For example, in pneumonia(التهاب الرئة), tissue can be damaged, but these mechanisms preserve the cytoskeleton, so that after inflammation, the tissue is approximately the same as it was before the injury.

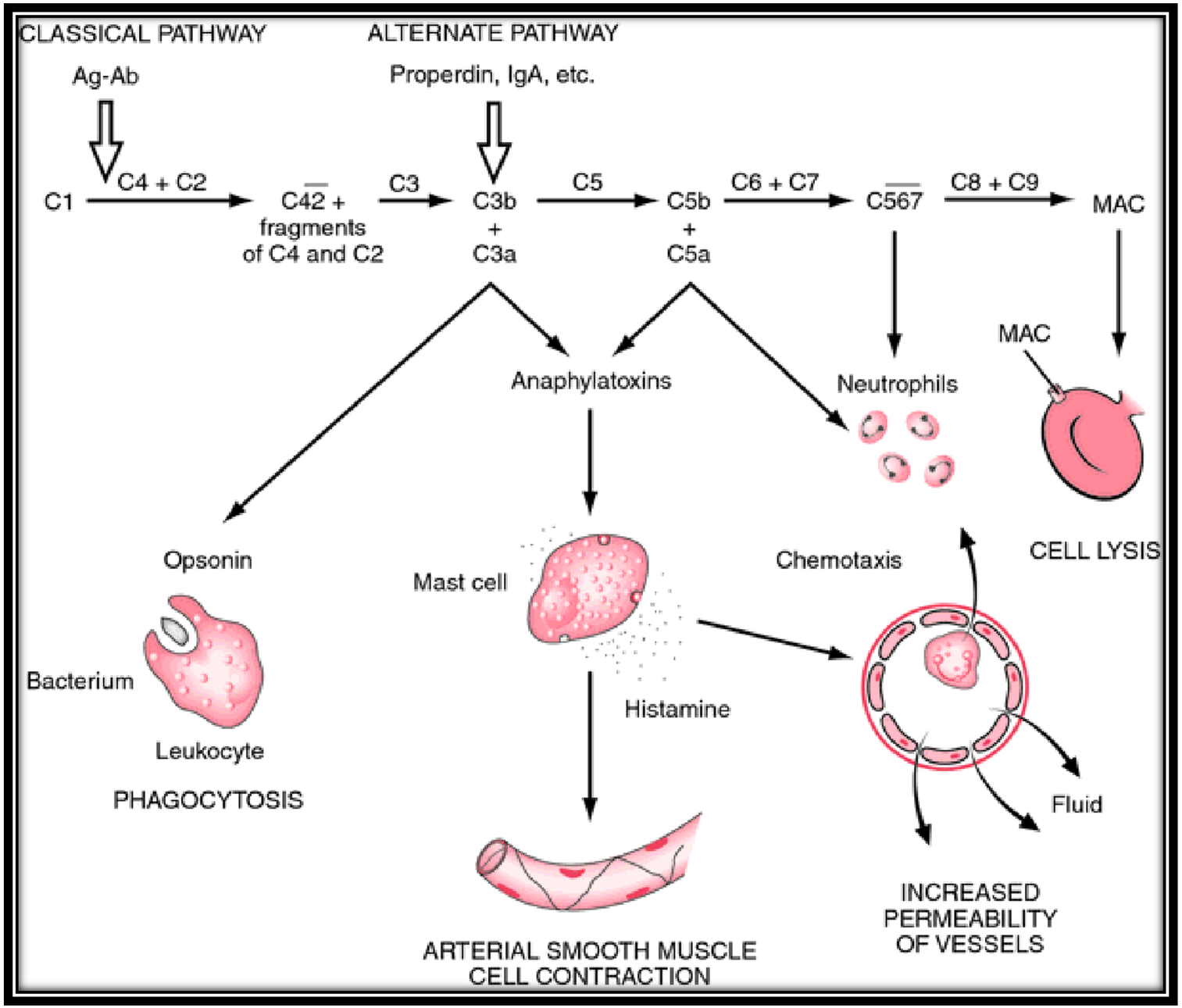
So far, we have talked about histamine, lipid mediators (AA derivatives), cytokines, and chemokines. The fourth group of inflammatory mediators is the complement system.

COMPLEMENT SYSTEM:

- **Soluble proteins (inactive) needs activation**
  - •small
  - •circulate in the serum in an inactive form, and are produced by the liver
- **More than 20, C1-C9**
  - •The most important components are C1 to C9.
- **Innate & adaptive immunity**
  - •innate (non-specific) and adaptive (specific) immunity
- **Functions: vascular permeability, chemotaxis & opsonization**
  - •Opsonization is the process of coating a virus or bacterium to enhance phagocytosis.
- **C3 is most abundant**(in serum)**; cleavage of which is the critical in all pathways**

•C3 is considered the(main gate) of the complement system.
•Cleavage of a complement protein means its activation, and fixing complement also refers to activation.

Explanation regarding this illustration
· Previously, there were only two ways to activate the complement system:
1 The classic pathway: By antigen-antibody complex, that stimulates the complement (fixing it) and activation of C3 (the main driver).
2 The alternate pathway: Activated by various
substances, such as IgA, secretions, properdin and some cell membrane components from bacteria and viruses.



Now we have three different stimulants for the activation of the complement system via activation C3

1

2

3

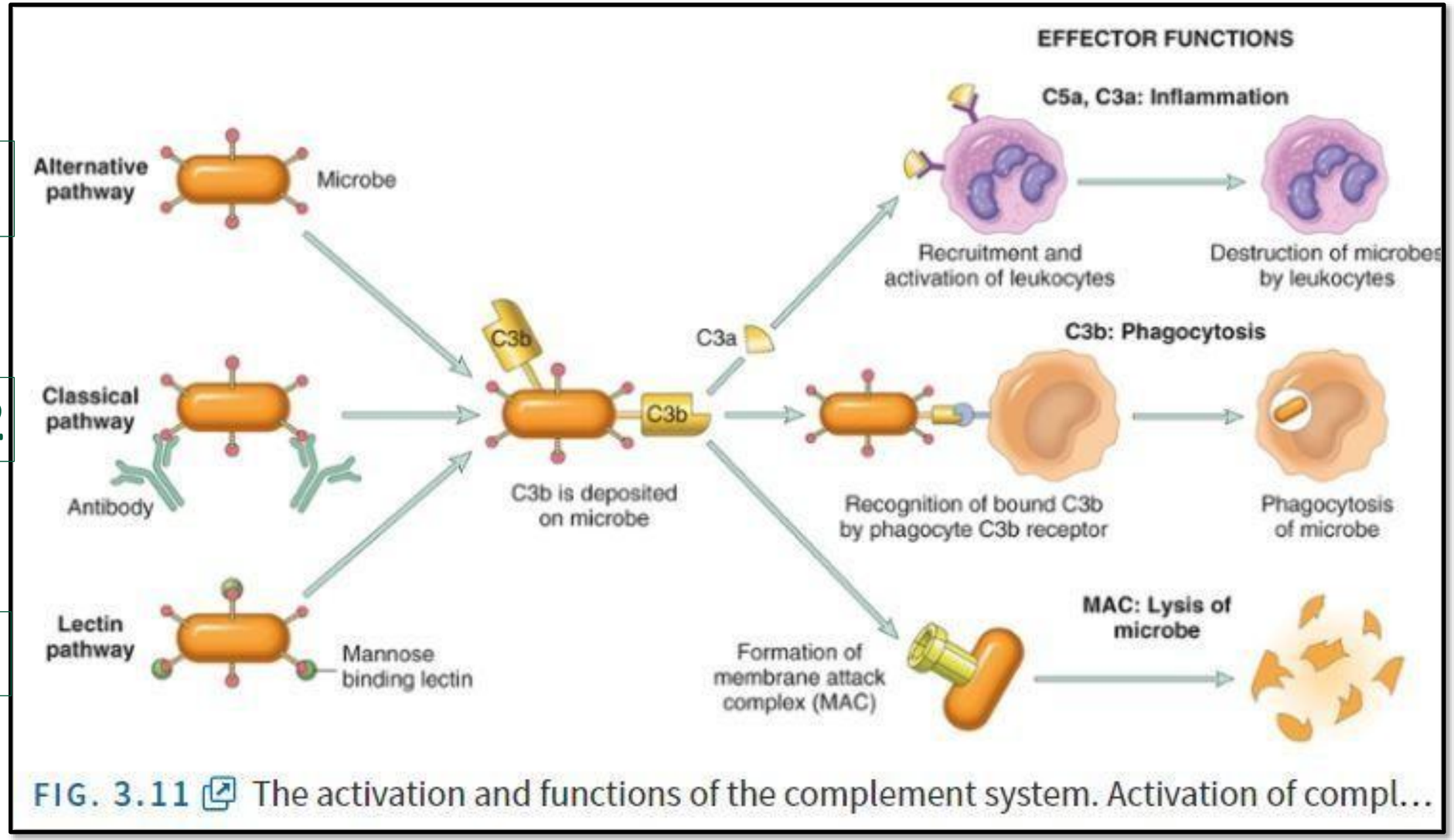
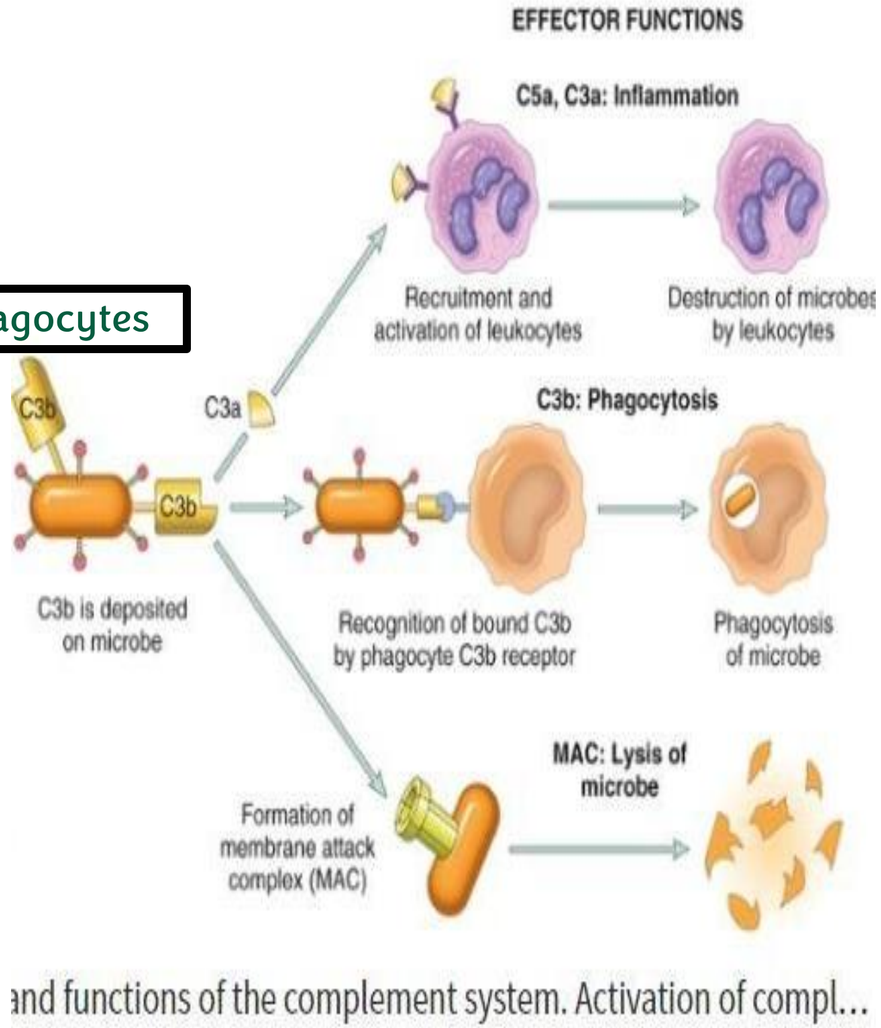


FIG. 3.11 The activation and functions of the complement system. Activation of compl…

C3b→ Major opsonizing agent it enhances phagocytes

The complement system always activates at C3, which starts a chain reaction that continues until C9. The end result is the Membrane Attack Complex (MAC), made from C9 fragments, which forms holes in the membranes of bacteria or viruses, causing them to break apart and die.



and functions of the complement system. Activation of compl...

MAC is the final product of the series of activation of the complement system

C S FUNCTIONS:

Vasodilation (initial vascular phase)

- **Inflammation: histamine like, anphylatoxins (C5a)**"one of the strongest anaphylactic agents"**.**

Anaphylaxis: means allergic reaction

- **Opsonization & phagocytosis: enhance phagocytosis (C3b)**
- **Cell lysis: Membrane Attack Complex (MAC), C9 multiples. Makes small holes in thin membrane of microbial wall**

REGULATORY PROTEINS FOR CS:

- **C1 inhibitor: if deficient hereditary angioedema**
- **Decay accelerating factor (DAF), which inhibit C3 convertases and CD59 inhibits MAC Abnormalities cause PNH**

Paroxysmal Nocturnal Hemoglobinuria

•Paroxysmal → "sudden" or "attack" (refers to sudden episodes)
•Nocturnal → "at night" (episodes often happen at night or early morning)
•Hemoglobinuria → "hemoglobin in the urine" (from red blood cell breakdown)

So a simple way to remember: "Sudden night attacks of hemoglobin in the urine

- **Factor H: proteolysis of C3 convertase; mutations cause hemolytic uremic syndrome**
- **CS protein deficiencies can occur leading to infection susceptibility**

**(the enzyme C3 convertase is the enzyme that breaks down C3, so inhibition of this enzyme leads to increase C3)

رسالة من الفريق العلمي:

دَواؤُكَ فيكَ وَما تُبصِرُ

وَدَاؤُكَ مِنكَ وَما تَشعُرُ

أَتَزعُمُ أَنَّكَ جُرمٌ صَغير

وَفيكَ اِنطَوى العالَمُ الأَكبَرُ

فَأَنتَ الكِتابُ المُبينُ الَّذي

بِأَحرُفِهِ يَظهَرُ المُضمَرُ

وَما حاجَةٌ لَكَ مِن خارِجٍ

وَفِكرُكَ فيكَ وَما تُصدِرُ

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			