SHEET NO. 9

PATHOLOGY

DOCTOR 2019 | MEDICINE | JU

DONE BY : Doctor 2019

SCIENTIFIC CORRECTION : Dana Oshroq Laban

GRAMMATICAL CORRECTION :

DOCTOR : **Mousa Al-abbadi**

TERMINATION OF THE ACUTE INFLAMMATORY RESPONSE

(The 4th R of inflammation steps) → Regulation or termination the response.

After the immune system does its job, we need to minimize the damage that may happen from the inflammatory response itself such as tissue injury, so our system prepared to terminate, control, and decrease the impact of an inflammatory response by **seven mechanisms** : (HOW?)

1. **Mediators are produced in rapid bursts**

   These mediators are released mainly by the inflammatory cells, they are released quickly and not continuously being released into the system..we don't need them.

2. **Release is stimulus-dependent**

   The release of these mediators is stimulus-dependent, they're released if the stimulus is there and they're not released if the stimulus is not there.

3. **Short half-lives**

   These mediators have a short half-life (seconds, minutes, or maximum hours). So, this helps that if they're not due to the previous two mechanisms they will not have prolonged half-lives.

4. **Degradation after release**

   The tissue at the site of injury is equipped with certain enzymes that are ready and capable of destroying these mediators.

So, **mediators** are produced in rapid bursts and not continuously being released, they are stimulus-dependent, have short half-lives, and degrade after release by certain enzymes. (We will talk about mediators in details)

5. **PMNs short life (apoptosis)**

   The polymorph neutrophils cells -which are one of the major players in acute inflammation- have a short life (0- 24 hours) as they kill themselves by **Apoptosis**.

6. **Stop signals production (TGF-ß, IL-10)**

   By release certain mediators like **transforming growth factor-beta (TGF-ß)** or **interleukin-10 (IL-10)** toward the last phase of inflammation which capable to stopping the signals for the initial mediators to be released.

7. **Neural inhibitors (cholinergic): inhibits TNF**

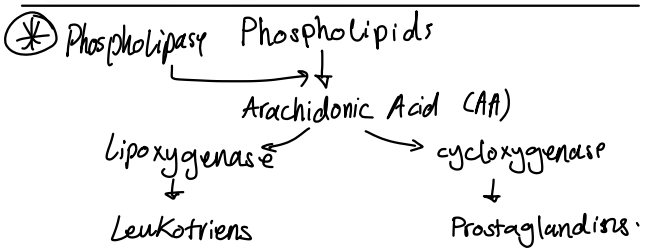
   Certain **neural** inhibitors which called **cholinergic inhibitors** can inhibit the release of certain mediators such as **tumor necrosis factor (TNF).** → Pro-inflammatory cytokine.

MEDIATORS OF INFLAMMATION

Substances that are produced by inflammatory cells, tissue macrophages, dendritic cells, and mast cells which are initiate and regulate inflammatory reactions.

*PGs: prostaglandins
*LTs: leukotriene

	MAJOR GROUPS	MOST IMPORTANT OF WHICH
1	Lipid products	PGs and LTs
2	Cytokines	IL, TNF, and chemokines → for chemotaxis
3	Complement activation	C1-9
4	Vasoactive amines	Histamine, → vasodilatation serotonin → CNS



Their functions in the next page :)

GENERAL FEATURES OF MEDIATORS

- **Cell-derived at the site of injury**

  Mediators are rapidly released from intracellular granules or are synthesized de novo in response to a stimulus (the cell machinery is ready to synthesize mediators upon stimulation). So, if there is no injury then no release of these mediators. (mediators → synthesized in granules and ready to be released. → have to be synthesized, when inflammation occurs. → may be in the liver like complement sys. / → or in their site.)

- **Plasma proteins: needs activation**

  The complement proteins which are present in small amounts in the plasma, don't exert any function unless they are activated, so they need stimulus to be active.

- **Active mediators need stimulation**

- **Most mediators have a short life span**

  We don't want the inflammatory process to be prolonged in order not to cause tissue injury.

- **One can activate the other**

  Each one of the mediators can activate or inhibit the release or the stimulation of others.

PRINCIPAL MEDIATORS OF INFLAMMATION

Unfortunately, you have to memorize this table and you will be questioned about it :)

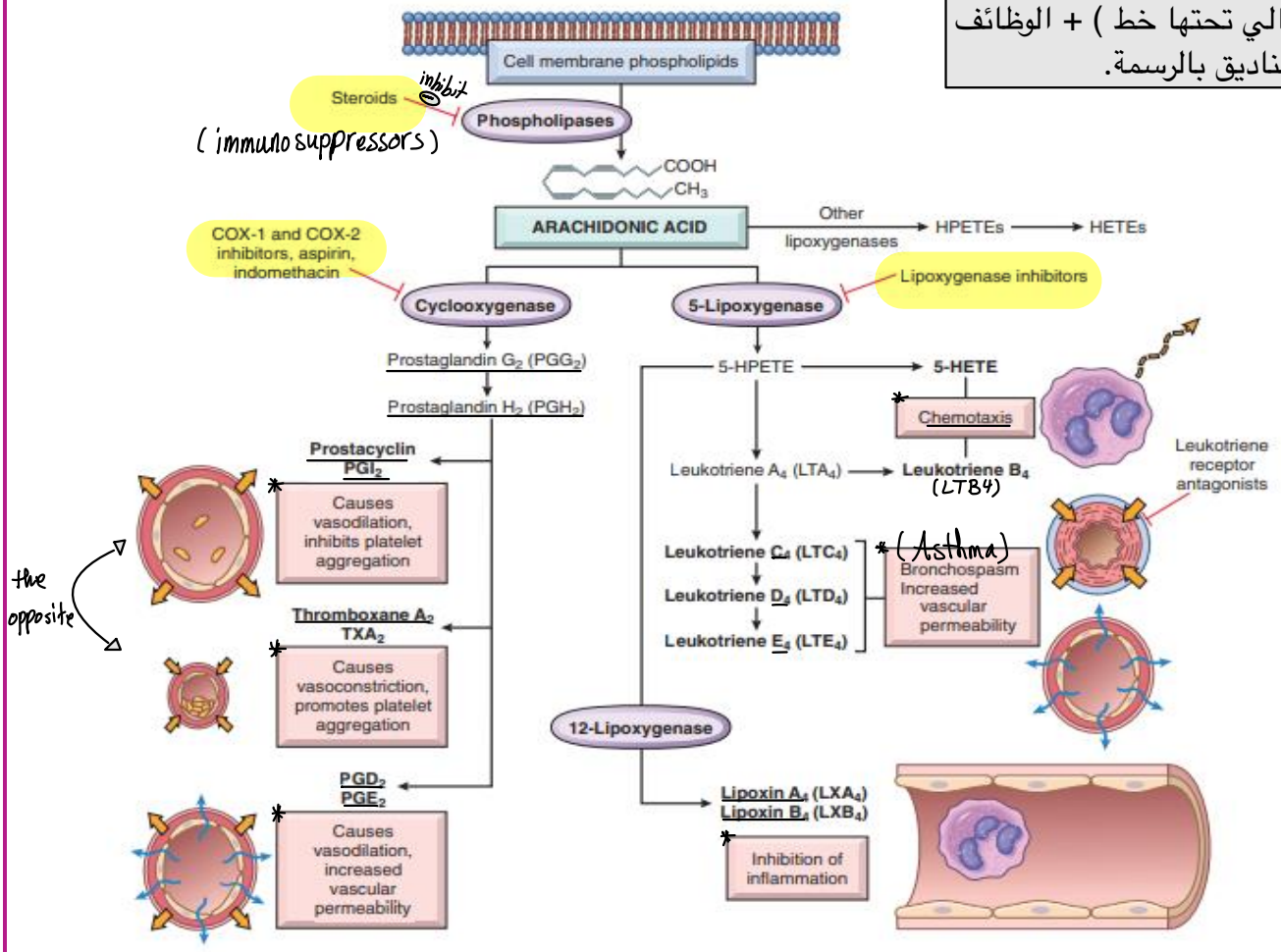
Mediator	Source	Action
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion, 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 the liver)	Leukocyte chemotaxis and activation, direct target killing (membrane attack complex), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in the liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain

1st big group of mediators of inflammation

ARACHIDONIC ACID METABOLITES (EICOSANOID)

- **Arachidonic acid** is a 20-carbon polyunsaturated fatty acid that is derived from dietary sources. It present in membrane phospholipids.
- When the cell membrane phospholipids are degraded, they will produce multiple products that have important and critical chemical inflammation function. (like mediators)

الدكتور مر على الرسمة كاملة ، اهم الاشياء (الي تحتها خط) + الوظائف الي بالصناديق بالرسمة.



- So, at first >> enzyme called **phospholipase** destroys phospholipids producing Arachidonic acid, then the arachidonic acid goes into two different pathways: Check the pic above..

1. **Cyclooxygenase pathway (left arm)**: the two cyclooxygenases enzymes called COX-1 and COX-2 will destroy arachidonic acid, producing a big group of mediators called **prostaglandins.**

2. **5-lipoxygenase pathway(right arm):** lipoxygenase enzyme will destroy arachidonic acid, producing another big group of mediators called **leukotrienes.**

Inhibitors involved in AA metabolism :

1. **Steroids** → very strong and potent anti-inflammatory drugs that function mainly to inhibit physical phosphor lipase. So, if you give a patient steroids, this drug will inhibit phospholipase which will inhibit the production of **ALL** the **leukotrienes** and the **prostaglandins**.

2. **cox-1 and cox-2 inhibitors** → non-steroidal inflammatory drugs, inhibit the cyclooxygenase pathway which will inhibit only the production of all **prostaglandins.** So they are called **anti-prostaglandins**. Ex. aspirin and indomethacin

3. **lipoxygenase inhibitors** → inhibit only the production of all the **leukotrienes.**

cox-1,cox-2, and lipoxygenase inhibitors less potent and less critical than steroids.

let's go through some of these mediators specifically. Prostaglandins and Leukotrienes:

Prostaglandins (PGs)

Produced by mast cells, macrophages, or endothelial cells by the actions of **two cyclooxygenases** enzyme in response to inflammatory stimulis. They are produced one by one:

1. **Prostaglandin G2 (PGG2)**

2. **Prostaglandin H2 (PGH2)**

3. **Prostacyclin (PGI2)**
   Is an important chemical mediator of inflammation because of its functions as a **vasodilator** -similar to histamine- and also it **inhibits platelet aggregation**.

4. **Thromboxane A2 (TXA2)'**
   Has the opposite function of Prostacyclin, it causes **vasoconstriction** and **stimulates platelet aggregation.**

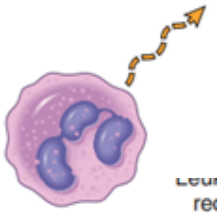
(PGI2, TXA2) are very important, the imbalance between them is thought to be involved in the development of **atherosclerosis** and **ischemic heart diseases.**

5. **PGD2/PGE2**
   They have a less critical function but they can cause vasodilation which leads to increased vascular permeability (similar to PGI2).

Leukotrienes

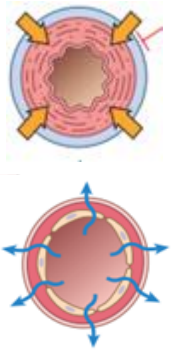
Produced by leukocytes and mast cells by the action of **lipoxygenase** enzyme**.**

1. **5-HPETE → 5-HETE / Leukotriene A4 (LTA4)→ Leukotriene B4**
   5-HETE and Leukotriene B4 are strong chemotactic agents, the function of leukotriene B4 is chemotaxis and recruitment of white blood cells into the site of injury.

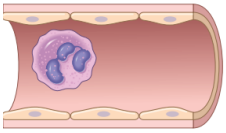


2. **Leukotriene C4 (LTC4) /Leukotriene D4 (LTD4) /Leukotriene E4 (LTE4)**
   Chemical mediators of inflammation are thought to play a major role in the **bronchospasm** (induce constriction of the bronchial diameter and cause bronchial asthma) and increase vascular permeability causing more edema.

   The antagonists of these products are utilized as a targeted therapy to control acute attacks of bronchial asthma.



3. **Lipoxin A4 (LXA4) / Lipoxin B4 (LXB4)**
   They are major inhibitors of inflammation.



This table summarizes the major function produced by arachidonic acid metabolites in inflammation : (**Eicosanoid** is another name for AA metabolites)

ACTION	EICOSANOID
VASODILATION	Prostaglandins PGI2 (prostacyclin), PGE1, PGE2, PGD2
VASOCONSTRICTION	Thromboxane A2, leukotrienes C4, D4, E4
INCREASED VASCULAR PERMEABILITY	Leukotrienes C4, D4, E4
CHEMOTAXIS, LEUKOCYTE ADHESION	Leukotriene B4
SMOOTH MUSCLE CONTRACTION	Prostaglandins PGC4, PGD4, PGE4

One example is delivery , there is an increase of PG so there is continuous contractions in smooth muscles of uterus, so we give an anti-prostaglandins and that may cause a delay in delivery .

POINTS TO REMEMBER ABOUT AA METABOLISM:

Don't worry .. nothing new!

الدوك ركز عليهم

- **Aspirin – cyclooxygenase**

  Aspirin and cox1,cox2 inhibitors can inhibit cyclooxygenase, then they inhibit the production of **prostaglandins** (in the cyclooxygenase pathway).

(cortisol)

- **Steroids – phospholipase and anti inflame**

  Steroids are a major inhibitor to the major enzyme which is **phospholipase** and it will inhibit the production of **all prostaglandins and all leukotriene**, this is why steroid is a very potent, strong and sometimes it's a dangerous anti-inflammatory drug.

opposite

- **Prostacyclin (PGI2): vasodilator and – Pl aggregate**

  PGI2 is a strong **vasodilator** and **inhibits platelet aggregation**.

- **Thromboxane A2: vasoconstrictor and + Pl aggregate**

  TXA2 is a major **vasoconstrictor** and **stimulator of platelet aggregation**.

- **TXA2-PGI2 imbalance: IHD & CVA**

  PGI2, TXA2 have opposite functions and the imbalance between those two prostaglandins is thought to play a major role in the pathogenesis of ischemic heart disease and cerebrovascular accident strokes in the brain.

- **PG (PGE2): pain & fever**

  Is a major mediator for the production of pain and fever.

2nd big group of mediators of inflammation

CYTOKINES

Cyto → are produced by cells kines→they make a kinetic function

CYTOKINES are proteins secreted by minicells, predominantly activated lymphocytes, activated macrophages, and dendritic cells. They are a big group of chemicals that mediate and regulate the immune and inflammatory response.

They are targeted by thousands of studies to help produce some effective medications in the role of cancer angiogenesis and the spread of metastasis of certain cancers.

CYTOKINES IN INFLAMMATION

another table and you have to memorize it ..:)

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; a 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 T helper cells (CD4+)	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

IL17 acts in acute AND chronic inflammation .

Endothelial adhesion molecules: selections,integrins,…

MAJOR ROLES OF CYTOKINES IN ACUTE INFLAMMATION

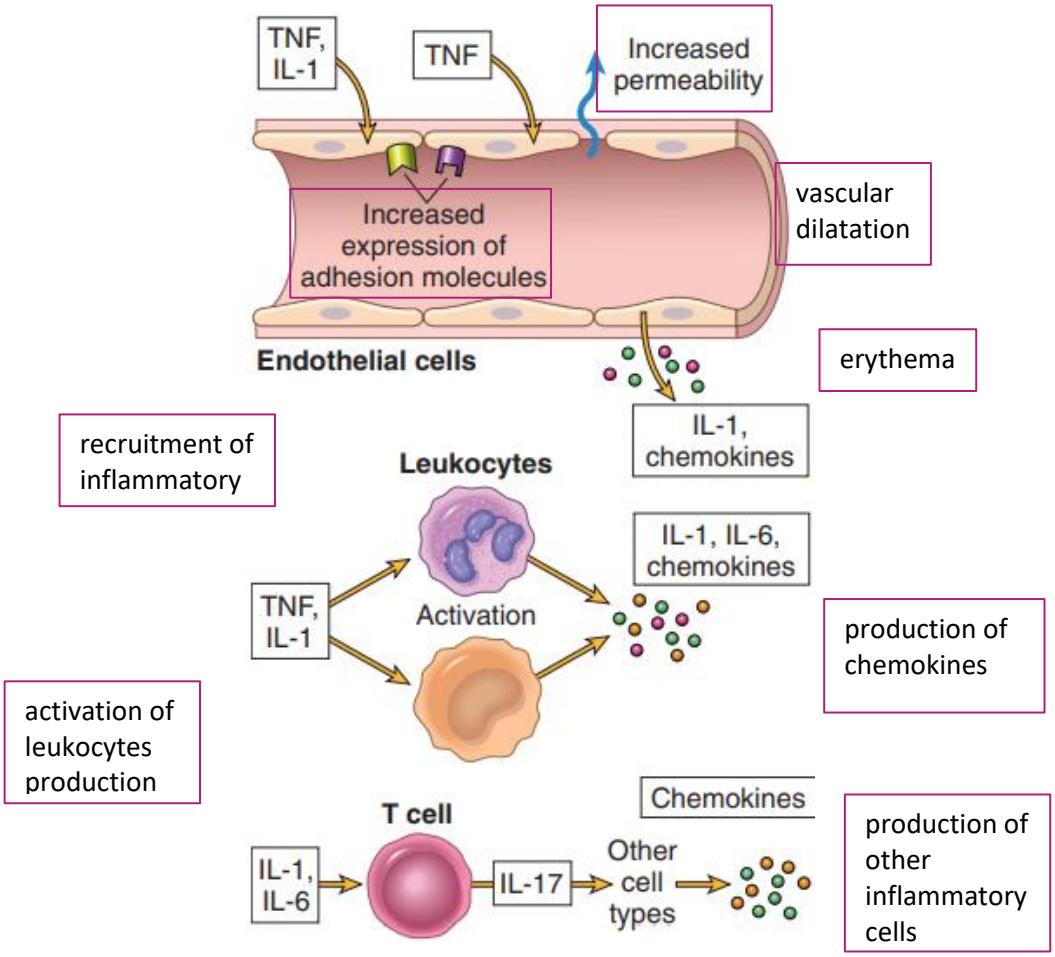
Whenever we have an inflammatory response, we have local signs, symptoms, or effects of inflammation (**Local inflammation)**, and we have also distant non-local functions (**Systemic manifestations of inflammation)** which happened because of the release of many of these mediators to the bloodstream. **Systemic manifestations of inflammation** can be either protective or pathological.

1. Local inflammation

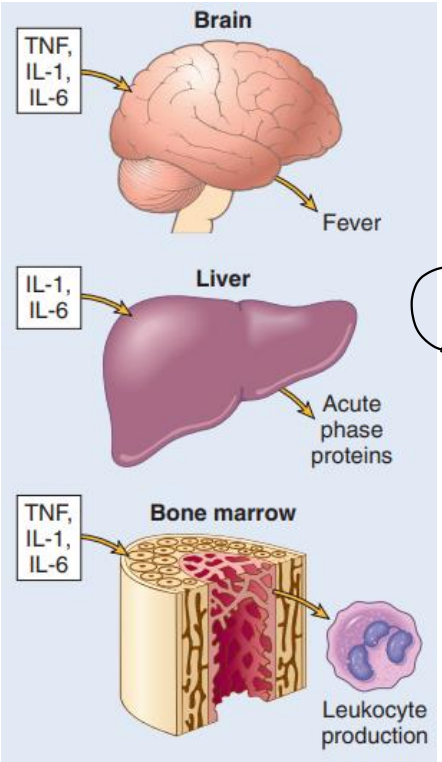
The local inflammatory changes from :

- increased permeability
- increased expression of endothelial cells
- vascular dilatation
- erythema
- recruitment of inflammatory cells
- activation of leukocytes
- production of chemokines
- production of other inflammatory cells

So locally, there will be swelling, edema, and redness which are induced by chemical mediators at the local level.



2. Systemic protective effects



Many of the cytokines (such as TNF, IL-1, IL-6) will have systemic protective mechanisms, they go to the brain and produce **fever** which could be sometimes dangerous but it's beneficial because it brings the patient to the clinician where it will be treated.

C - reactive Proteins.

Cytokines (like IL-1, IL-6) can stimulate the production of **acute-phase proteins** which have a protective effect. Sometimes we can measure those proteins in the blood to determine if the patient is in acute distress or not.

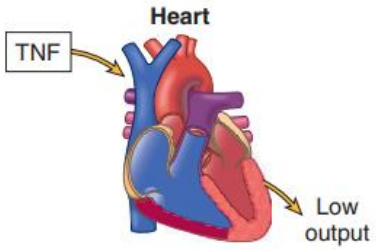
Other cytokines (such as TNF, IL-1, IL-6) will go to the bone marrow and stimulate the production of more **hematopoietic cells** which help in the fight against inflammation.

So, all these considered protective systemic effects of inflammation via the production of mediators, which go to the blood vessels and have effects on the systemic body.

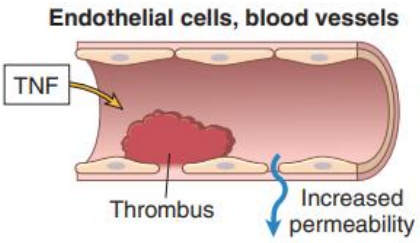
3. Systemic pathological effects

On the other hand, these systemic impacts can be pathological

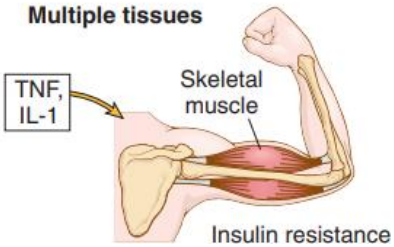
Some cytokines (like TNF, the major cardiogenic function inhibitors) can go to the heart and depress the cardiogenic function which could lead to heart failure from just severe acute inflammation.



The same cytokines (TNF) could cause endothelial cell injury. We said before that the vascular compartment is an important part of the initial phase of inflammation so, TNF can induce platelet aggregation, thrombus formation, and shooting emboli which will cause ischemia in the heart and other organs.



TNF, IL-1 may go to the skeletal muscle tissue and causes **insulin resistance** which is another systemic bad effect.



CHEMOKINES

- **Chemokines** are small proteins, they are many different their types and each one of them has receptors (more than 40 different and 20 receptors)
- Their major function as Chemoattractants.
- They are grouped in letters (C-X-C; C-C; C; CX3-C) you don't have to memorize them!
- They all have G-protein coupled receptors so, the major receptors of the chemokines is the G-protein.
- They have two main functions:
  - In maintain tissue architecture.
  - In Acute inflammation (they recruit white blood cells to the side of injury).

The doc finished the lecture here.

3rd big group of mediators of inflammation

COMPLEMENT SYSTEM (CS)

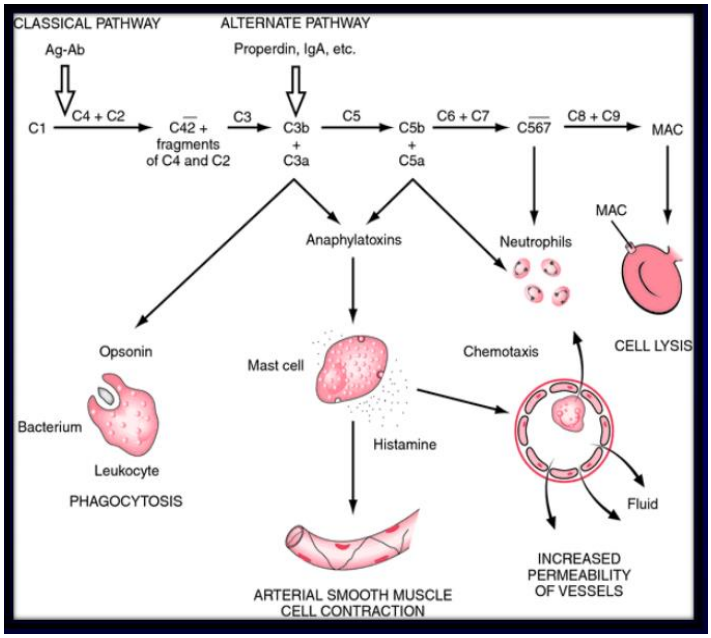
- the **complement system** is a collection of soluble proteins that are produced by the liver, their function mainly in host defense against microbes and in pathologic inflammatory reactions.
- These proteins present in the body in an inactive form, so they need stimulation or activation to do their functions.
- There are more than 20 complements. (the most important C1 - C9)
- They are important in **innate** and **adaptive** immunity.
- The major functions of the CS are vascular permeability, chemotaxis and also they are important in a process called **opsonization**.
- **C3 is the most abundant** in the CS. Besides, C3 cleavage of which is critical in all pathways, it will be the first gatekeeper so, when C3 cleaved that will induce the cascade critical pathways of all activation of the complement system.
- **Complement fixation** = complement system activation.
  So, when we said this drug fixes the complement, that's means this drug stimulates the cascade of the complement system.

complement system activation(Complement fixation):

In the **old days** there were only two ways to activate the complement system:

1. **The classic pathway**

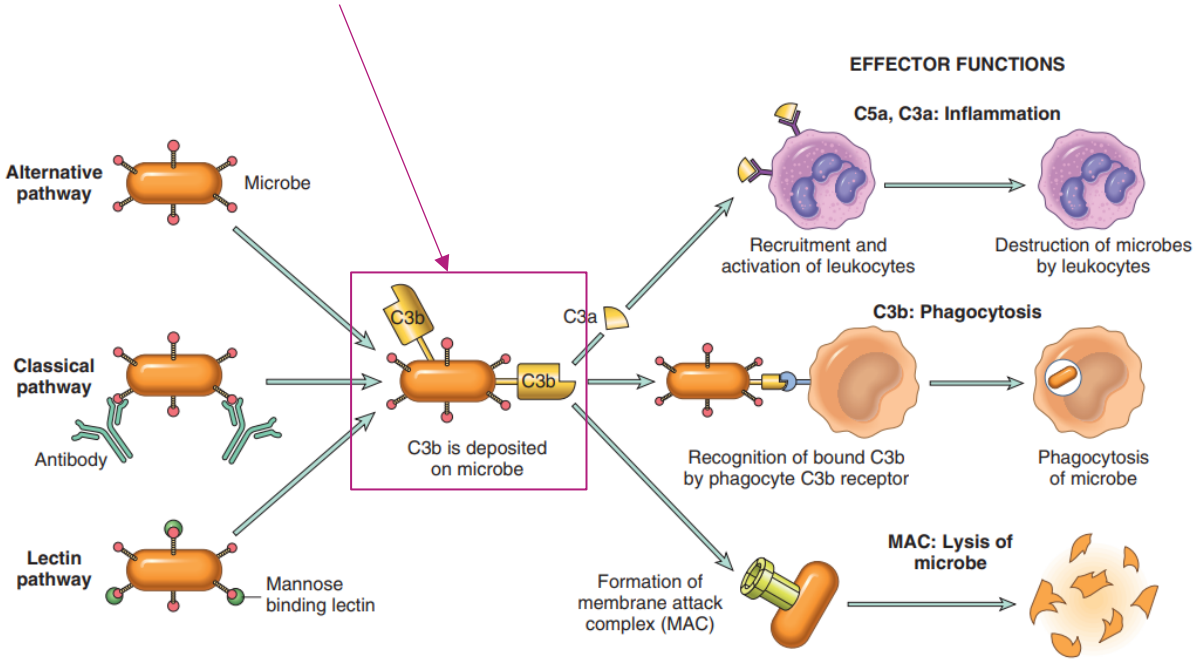
By antigen-antibody complex, an invader comes →produce antibodies→antibody will join the antigens→the antigen-antibody complex will start activating the complement system.



2. **The alternate pathway**

Through either **IgA** or other certain products. The cleavage starts at the activation C3 component and the cascade will continue inducing multiple functions.

BUT, this is stale knowledge. However, the current knowledge is that we have **three pathways** in which the C3 can be activated:

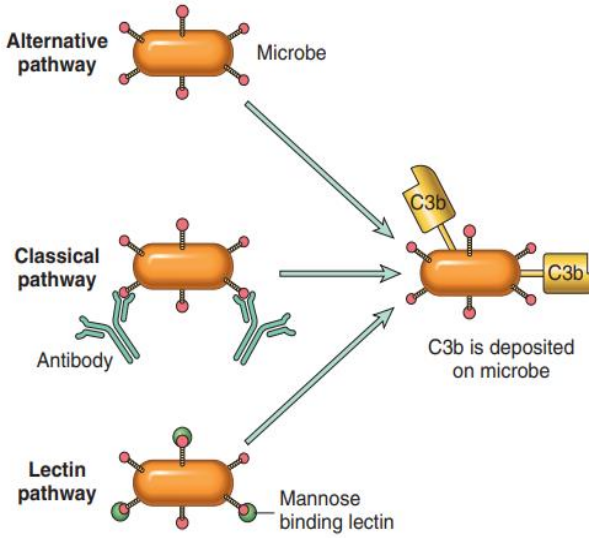


ALL details in this pic are important.

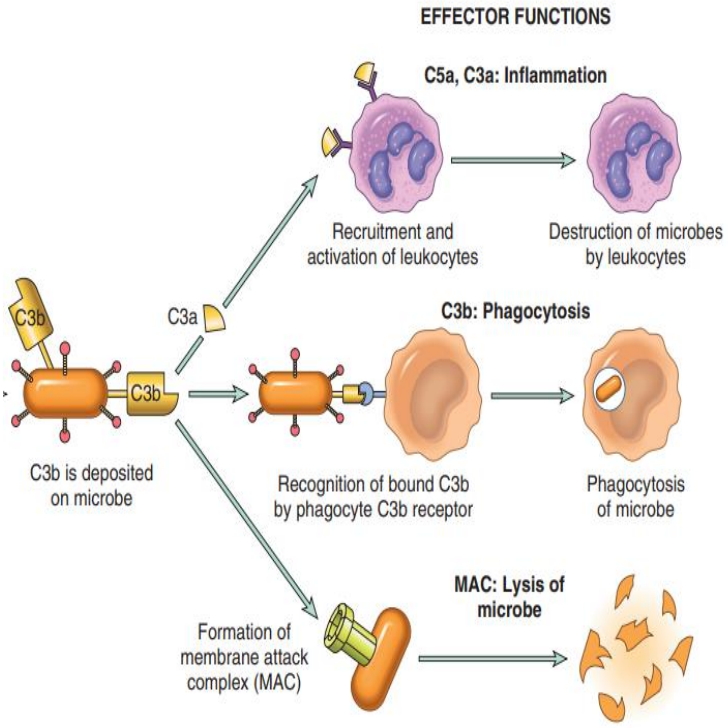
1. **The alternative pathway**
   By certain receptors in the microbial products, activate C3 directly.

2. **The classical pathway**
   By antigen-antibody complex on the surface of bacteria or viruses, the antigen-antibody complex will activate C3.

3. **Lectin pathway**
   In which there a **Mannose receptor** binding to lectin inducing the activation of C3.



After that, **activated C3** goes into 3 pathways:



The active part **C3a** will work as a chemotactic agent (recruitment and activation of leukocytes), this will induce the production of C5a and C3a which are also chemotactic agents.

The **C3b** which is a very important stimulator of phagocytosis helps the macrophage and neutrophil in the phagocytosis process.

The continuous stimulation of the cascade leads to the activation of C5, C6, C7, and then they will produce something called MAC (membrane attack complex)

MAC (membrane attack complex): certain products of the complement system, in the past it used to be a combination of C5, C6, C7, and sometimes C8 or C9 but, nowadays it is recognized that it is multiple of nines (C9s). MAC is important to lice and attacks directly without going through the phagocytosis.

COMPLEMENT SYSTEM FUNCTIONS:

- **Inflammation**
  CS have histamine like-function such as **anaphylatoxins (C5a).** C5a is a strong anaphylatoxin which is an important mediator in acute inflammation.
- **Opsonization & phagocytosis**
  Opsonization→ helping the phagocytes, macrophages, and neutrophils to enhance their function (phagocytosis function) by **C3b**.
  C3b is the strongest opsonizing in the CS, it makes the phagocytosis more efficient, faster, and active. (without the opsonizing agents such as the C3b the phagocytosis would be slow and slightly inefficient)
- **Cell lysis**
  Membrane Attack Complex (MAC) can make small holes in the membrane of the microbial wall which leads to killing them.

REGULATORY PROTEINS FOR CS

whenever we have a strong activated response we need to regulate, maintain, terminate, and decrease the impact of these processes.
So, as we mentioned before there were **seven mechanisms** to control the inflammatory response BUT there are also other four mechanisms to regulate the functions, the release, and the activation of the complement system:

- **C1 inhibitor**
  Is normally present to control and decrease the amount of inactivating C1, so the cascade will be decreased.
  If the C1 inhibitor is deficient, that will cause **hereditary angioedema**.
- **Decay accelerating factor (DAF)**
  DAF inhibits C3 convertases and CD59 inhibits MAC.
  Irregularities in those factors are the major cause of a disease called **Paroxysmal nocturnal hemoglobinuria (PNH).**
- **Factor H**
  proteolysis of C3 convertase, mutations of this factor cause **hemolytic uremic syndrome.**
- **CS protein deficiencies**
  Can occur leading to **infection susceptibility.**

Sorry for errors, If there was :)

HAVE FUN ♥