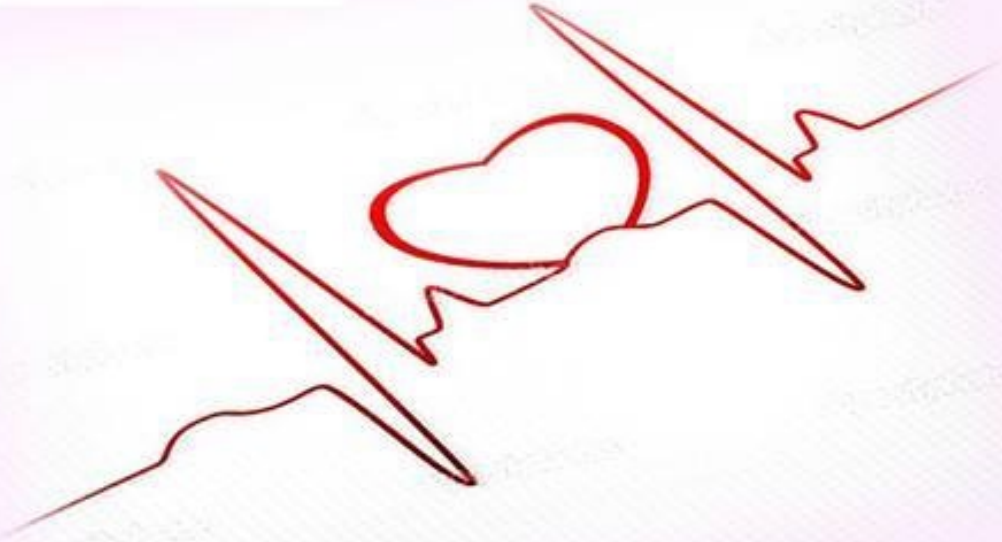
PATHOLOGY

Medical Committee
The University of Jordan

SHEET

SlIDE



Lecture Number: 9

Doctor: Dr. Heyam

DONE BY: Mai Ziad

Designed By: Majida Al-foqaraa'

Inflammation/chemical mediators ☺

Hello ☺

Hope you're all studying perfectly and you are all well-prepared for mid-term exams :D

ςFor this lecture I strongly suggest you check the figures in the book ☺

We are still talking about Inflammation *sigh* we are not done with it yet!

As you know Inflammation includes three things:

1. Cellular events : we already talked about these in the previous lectures
2. Vascular events: last lecture covered this..
3. Chemical mediators ☺

∞ In this lecture we are going to cover chemical mediators ☺

Now focus with me, these are the things that I want you to know about chemical mediators ☺ and they are more than enough for you to be an excellent doctor- Inshallah - ☺

Chemical mediators

So chemical mediators are divided into 4 groups:

1. Arachidonic acid metabolites
2. Vasoactive amines :amines from amino acids ☺
3. Cytokines: proteins
4. Complement system components: very important in inflammation and immunity

Now: the 1st groups group >>> **1.vasoactive amines**

The most important one is 1st. histamine :D

The 2nd one is serotonin ☺

Written by Mai Ziad

Histamine	**serotonin**
Vasodilatation and increases vascular permeability	Vasoconstrictor
Very important in inflammation, one of the earliest mediators that are secreted ☺	There is no experimental proof that serotonin is important in inflammation normally ,it has other effects in our body
Secreted mainly from mast cells, and many inflammatory cells ☺	

☆ How does histamine act?? It acts on receptors, (H1 receptor)*lock and key*

***** If you want to treat a patient that has effects due to histamine, YOU attack the receptor ☺

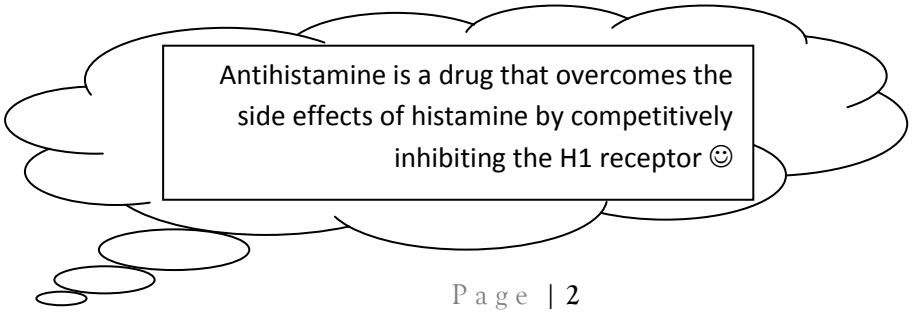
We already mentioned that: Inflammation is a protective mechanism to our bodies but it causes collateral damage.

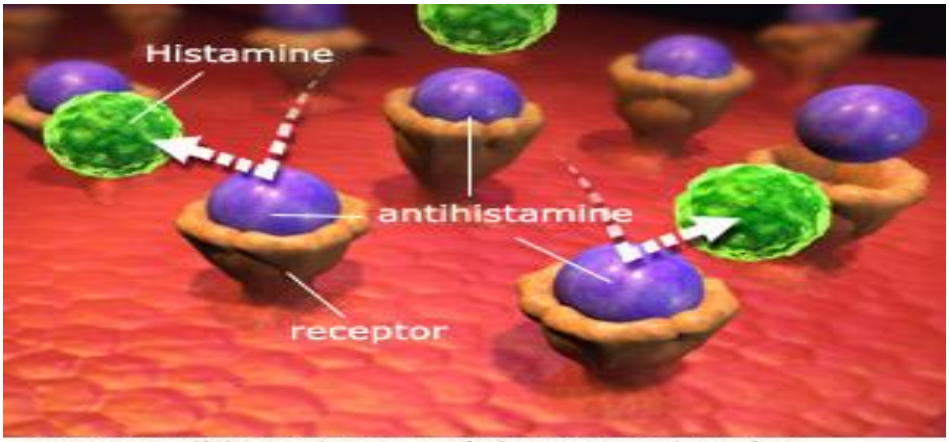
Histamines causes vasodilatation and increases vascular permeability..So it also causes edema, hotness, redness and Itching

So there are side effects/problems of histamine that you as a doctor will try to treat, especially in allergic conditions .but HOW and what drug you use? You use antihistamines

** How does this drug work? On the receptor! The H1 receptor .It's a competitive inhibitor of H1 receptor ☺

It attacks the receptor >> the histamine goes out >> the antihistamine takes its place





Many antihistamines work by occupying the receptors targeted by histamines. By blocking these receptors, antihistamines reduce or prevent allergic reactions.

Summary of what u need to know about vasoactive amines:

1. Serotonin: vasoconstrictor

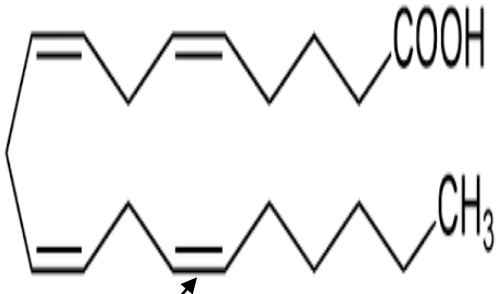
2. Histamine: vasodilator, increases vascular permeability, secreted from mast cells, acts on H1 receptors and we block the effects of histamine by antihistamines that blocks the receptor ☺

The second group of mediators the arcahadonic acid metabolites ☺

The structure in the figure represents a carboxylic acid (fatty acid) so it's a phospholipid ☺

How many carbons can u see? 20 carbons – anything that has twenty called EICOS in Greek.

So this is an eicosanoids…



This represents double bond so it's a poly unsaturated fatty acid.

Where are we going to find it? In the cell membrane!

So how does it work in inflammation??

*histamines were in granules so it's just released from granules ☺

But A.A? how ?

- Normally it's in the cell membrane
- During inflammation and due to the effect of mediators like cytokines microbial products and certain enzyme are activated.
- THIS ENZYME IS :**PHOSPHOLIPASE A2**
-

≅PHOSPHOLIASE A2: it acts on the A.A >it takes it from the cell membrane > to the cytoplasm > and now it's ready to act ^_^

--So the A.A is in the cytoplasm it can be acted on by different enzymes ☺

----A.A is a big molecule and it doesn't have any inflammatory prosperities, it needs to be changed to other things by other enzymes ….

And we have two families of enzymes!

ς Cyclooxygenase: produces prostaglandins

ς Lipoxygenase: produces lipoxins and leukotrienes

Summary:

A.A is moved from cell membrane to cytoplasm by phospholipase A2

↓

Now since it's in the cytoplasm we have two enzymes:

Cyclooxygenase: Change A.A to prostaglandins	lipooxygenase: gives two byproducts :lipoxins and leukotrienes

From where do we get A.A? From food ☺ *shocking *

Anything that contains fat can have A.A.and then it's digested and integrated in the cell membrane ☺

NOW, a closer look at what prostaglandins, lipoxins and leukotriens do:

Prostanglandins:

I need you to know four types of prostaglandins

PGD2, PGE2, thromoboxane A2, prostacyclin PG12

!PGD2 , PGE2 have same effects as histamines : vasodilators and increase membrane permeability ☺

The other two are just the opposite of each other *enemies*...

PROSTACYCLIN PG12	*THROMOBOXANE A2*
Vasodilator and inhibits platelet aggregation ☺ رايق:P	Vasoconstrictor , increases platelet aggregation ☺
Endothelial cells ☺	Platelets ☺

Question!!

If both of them come from A.A, the same precursor... why do we have in the endothelial cells prostacyclin and in platelets we have thromoboxane A2?

Different enzymes act on each, that's why we said FAMILY of cyclooxygenase ☺ so we have specific enzymes for prostacyclin which is found in endothelial cells AND specific enzymes for thromoboxane A2 which is found in platelets :D

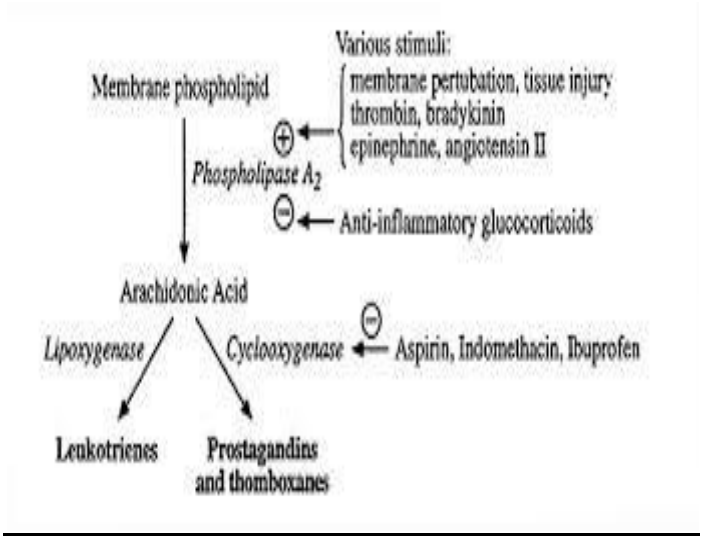
IS IT CLEAR?

.....

Cyclooxygenase ...big family of enzymes ☺ consists of two main groups

Cyclooxygenase 1 –COX1: it produces a group of prostaglandins, some of them have inflammation and some have protective effects on our body ((especially in the stomach

Cyclooxygenase 2 –COX 2: it produces a group of prostaglandins that are only involved in inflammation; they don't have any protective effect ☺



Note that: prostaglandins COX2 cause fever and pain.. So anyone with inflammation > they have fever and pain ☹ why? DUE TO PROSTAGLANDINS.

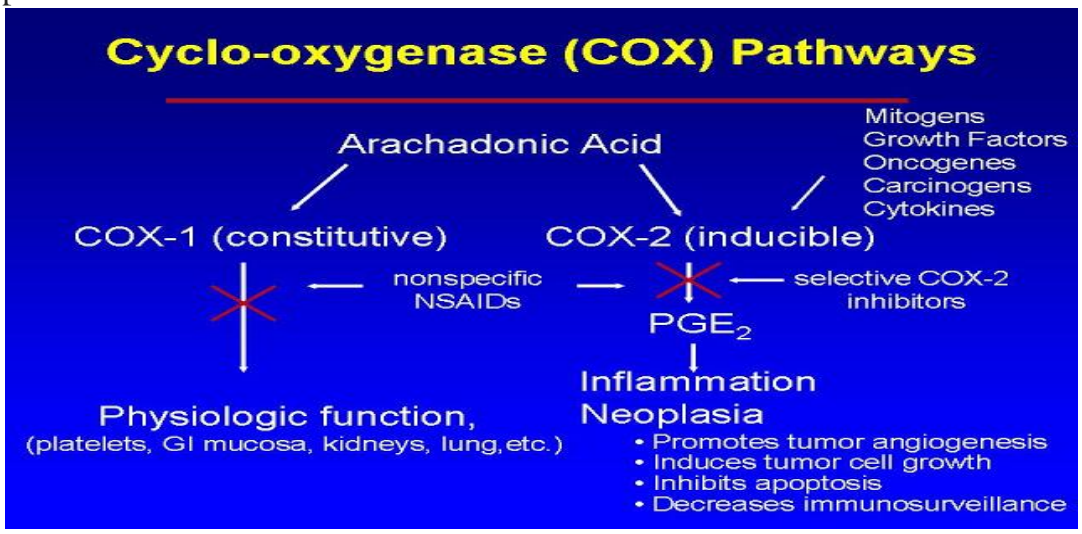
So if you want to decrease these effects, collateral damage, symptoms..You need to inhibit the production of prostaglandins …

BUT HOW?!!! The traditional way by ASPIRIN and NSAIDs. (Non steroidal anti-inflammatory drugs) Ex: ibuprofen ☺

#These drugs inhibit both COX 1 and COX 2, so NO PROSTAGLANDINS
! produced and no FEVER NO EDEMA
? ??!BUT
We are losing the protective effects from certain prostaglandins that are produced by COX 1 …that's why people who have been taking aspirin for a long time suffer from GASTRIC ULCERs☹
Because of this we started thinking of a new family of drugs! Called COX2
(: !inhibitors
They selectively inhibit the production of prostaglandins from COX 2
. So we are decreasing the pain and fever ⇦
Two groups of drugs that decrease the pain and fever by acting on prostaglandins :production which are

1. Not selective (ASPIRIN AND NSAIDs) that will inhibit cox2 and cox1..so a side effect is caused which is GASTRIC ULCER.

2. Selective ,,COX2 inhibitors..this act only on COX2 ,they decrease pain and fever but we don't have the reduction of prostaglandins from COX1 which protect the stomach .. ☺

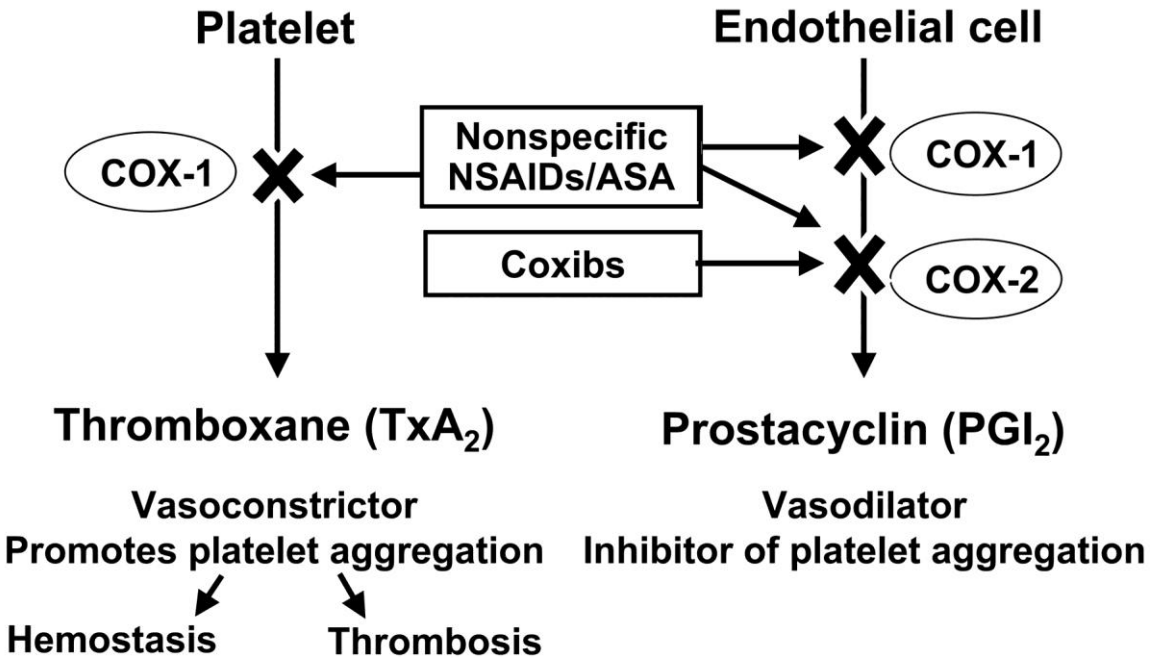
3. 

Prostaglandins are made by two different enzymes, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). The prostaglandins made by the two different enzymes have slightly different effects on the body. COX-2 inhibitors are NSAIDs that selectively block the COX-2 enzyme and not the COX-1 enzyme. Blocking this enzyme impedes the production of prostaglandins by the COX-2 enzyme that often causes the pain and swelling of inflammation and other painful conditions. Because they selectively block the COX-2 enzyme and not the COX-1 enzyme, these drugs are uniquely different from traditional NSAIDs which usually block both COX-1 and COX-2 enzymes.-from internet.

COX 2 inhibitors have been developed with the expectation that they will inhibit harmful inflammation but will not block the protective effects of CONSTITUTIVELY produced prostaglandins (from COX 1) ☺-from robbins-

#We were very happy that a new drug with no side effects, but any drug is a poison, any drug will have side effects. What is the problem with COX 2 inhibitors??
For example
COX 1 produces among other things: thromoboxane TxA2
COX2 produces among other things: Prostacyclins PGI2
So when we have COX2 inhibitors we are decreasing prostacyclin! But TxA2 is the same!
#The thing is in normal situation they work in contrary to each other, they have two different actions! they keep the balance in the blood, because when you have a mediator that causes aggregation and the other one decreases it in the blood ,the blood maintain its fluidity :D so when you have a drug that decreases the

production of platelets aggregation inhibitor (COX 2 decreases prostacyclin) when the TxA2 is the same. The balance is disturbed.. it can cause SIDE EFFECTS with time ! it can cause thrombosis...it can hurt the brain and heart ..
So Any drug should be experimented for a long time!! Not like كفته عبد العاطي:3



NOTE THAT when we say prostaglandins P2 ,I2 .. The letter refers to a name so we can differentiate between them... BUT the number refers to the number of DOUBLE bonds...☺
Now since we finished the prostaglandins.. let's move to LEUKOTRIENES and LIPOXINS ☺

Leukotrienes

LEUKOTRIENES B4 it's a chemotactic agent (chemotaxix) and has 4 double bond ☺

The other ones:
LTC4, LTD4, LTE4...they cause –-BRONCHOSPASM (that's why they are important in reactions like ASTHMA) AND increase VASCULAR PERMEABILITY.

***That's what you need to know only :')

Lipoxins :

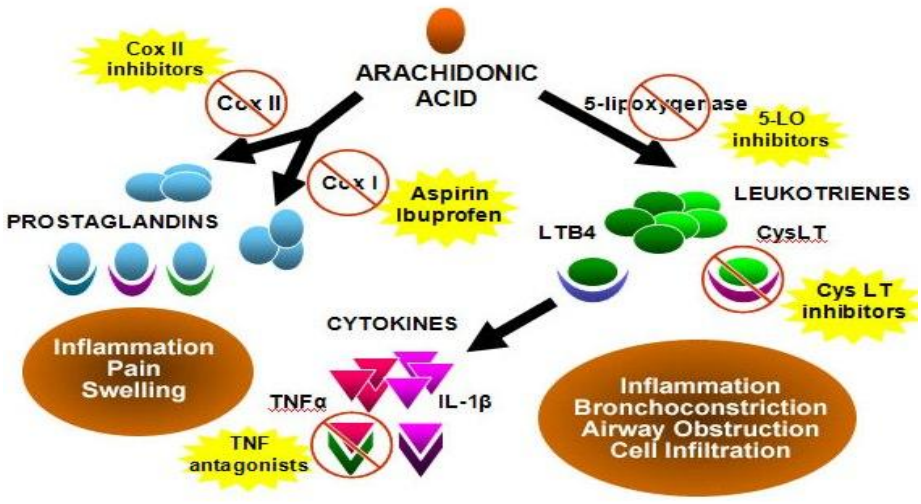
The doctor only said that arachadonic acid gives leukotriens and prostaglandins and in the lipoxygenase pathway it produces lipoxin ☺ :

> lipoxins are Anti inflammatory and this is one of the mechanisms that Inflammation can stop ! In which we can cause inhibition of inflammation or regulation of inflammation; by production of lipoxins ☺

this pathway which forms the leukotriens and prostanglandins with time –maybe after few days – the balance will switch to produce lipoxins !which will result in decreasing the inflammatory responses and increasing the anti inflammatory responses and this will stop the inflammation ☺ it is clear ? :D

This figure that shows us the anti inflammatory drugs (COX 1 inhibitors COX 2 inhibitors, aspirin and ibuprofen which act on both COX 1 and COX 2) and also we have anti-lipoxygenase some drugs that acts as lipoxygenase inhibitors ☺ and inhibitors for leukotrienes receptors and we have anti-prostaglandins ! So you can block this Pathway at any point by a drug which will decrease the side effects of these mediators (either leukotriens or prostaglandins..)

Figure 2. Arachidonic acid is metabolized to produce inflammatory mediators. Many current anti-inflammatory and pain medicines are inhibit some portion of the arachidonic acid pathways.



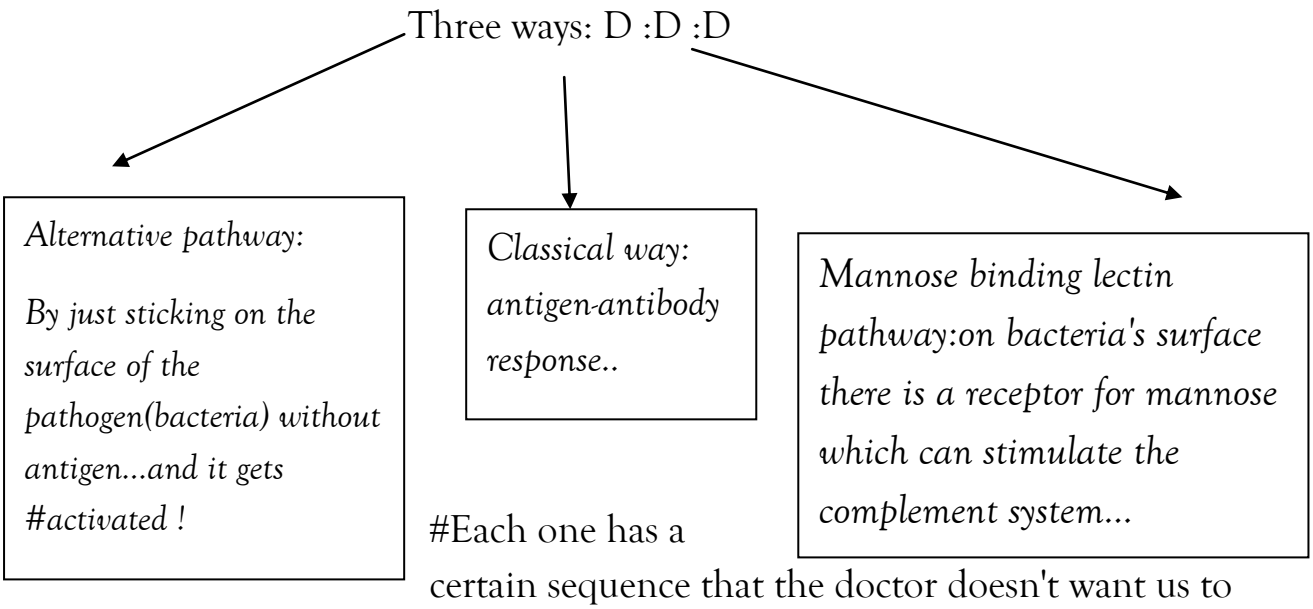
COMPLEMENT SYSTEM ☺YOU SHOUD KNOW THE BASICS ONLY

1. Basically it consists of proteins.(plasma proteins :book says so ☺)

2. Circulating in the blood doing NOTHING :')

3. They are inactive and in need to be activated..When they are activated, they have certain effects

HOW ARE THEY ACTIVATED?



#Each one has a certain sequence that the doctor doesn't want us to know :'))

The main effect is to stimulate an enzyme called C3 convertase ☺

ς C3 convertase: an enzyme that converts C3 into two components..C3A and C3 B

ς C3A along with C5A stimulates an inflammatory response ☺

ς C3B can cause two things: 1) lysis of microbe /bacteria

2) Acts as an opsonin ...opsonize the bacteria so it can be phagocytosed ...>> killing the bacteria by opsonization ☺

> ***Opsonin: is any molecule that enhances <u>phagocytosis</u> by marking an <u>antigen</u> for an immune response***
>
> ***From wiki :D***

Are you bored? :P

Link of the video: http://www.youtube.com/watch?v=vbWYz9XDtLw

Doctor showed us a video of how the complement system works. And the goal of this video is to see how complicated the processes are, when each substrate is acted on by an enzyme and that enzyme forms two things that we call A and B…the word an aflatoxin means in the video: INVOLVED IN INAFFLAMATION ☺

-details are not required of this video just to see the mechanism ☺ mac attack complex ☺ and the steps *_^

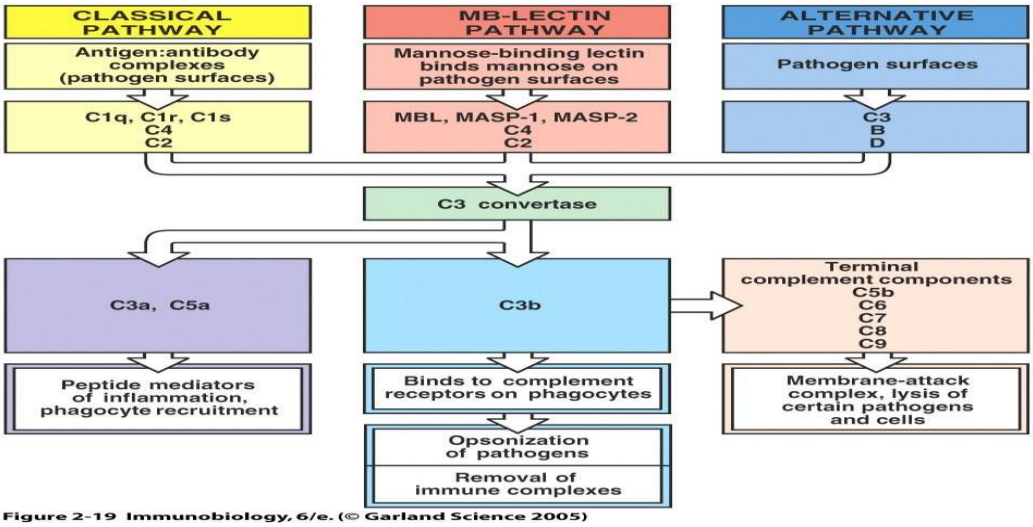
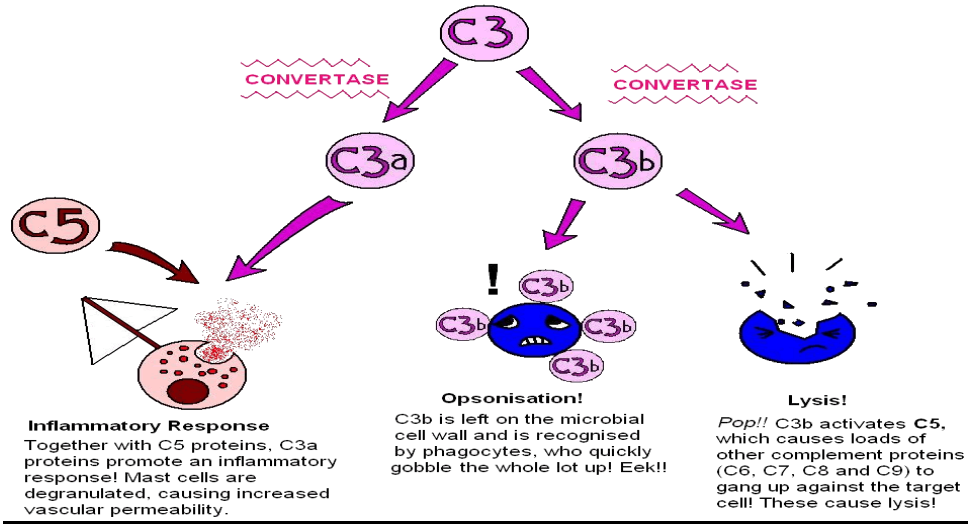


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)



Cytokines:

≅Are also important mediators ☺

≅ They are proteins

≅ major kinds are :interleukins(IL and numbered ☺ IL 1) ,chemokines and tumor necrosis factor TNF .

≅ **IL 1 and TNF** have the same functions: 1. They activate the endothelial cells which is important for adhesion of neutrohphils on endothelial cells, they increase/stimulates the expression of adhesive molecules on the endothelial cells.

≅They also act on other mediators ..:) * in some pathways ,mediators were activated by interleukins and TNF

≅They also cause leukocyte activation

≅For TNF AUGMENTS RESPONSE OF NEUTROPHIL TO OTHER STIMULI meaning it makes the neutrophil responsive to other stimuli ☺ and activates the microbicidal activity of macrophages.

≅IL1 ACTIVATES COLLAGEN SYNTHESIS BY FIBROBLASTS

≅And they cause the systemic effect of inflammation (FEVER)

≅TNF causes cachexia: wasting of muscles...: one of the malnutrition symptoms

≅Both can cause SEBSIS: s a potentially fatal whole-body inflammation

ςChemokines : a family of small (8 to 10 kDa)structurally related proteins that act primarily as chemoattractants.:book robbins : **IL 8 the most important one**

Chemoattractants act on specific cell type..IL 8 acts on neutrophil

And a specific chemokines acts on lymphocytes

There are other chemokines for each cell type, chemokines include small, big proteins that acts specifically on certain cell type ☺

There are also some other mediators rather than the previous ones in this lecture

~OTHER MEDIATORS: platelet activating factor PAF, it causes platelet aggregation and vasoconstriction ...like???Thromboxane TxA2

~~bronchoconstriction like LEUKOTRIENES C4 , D4 , E4..

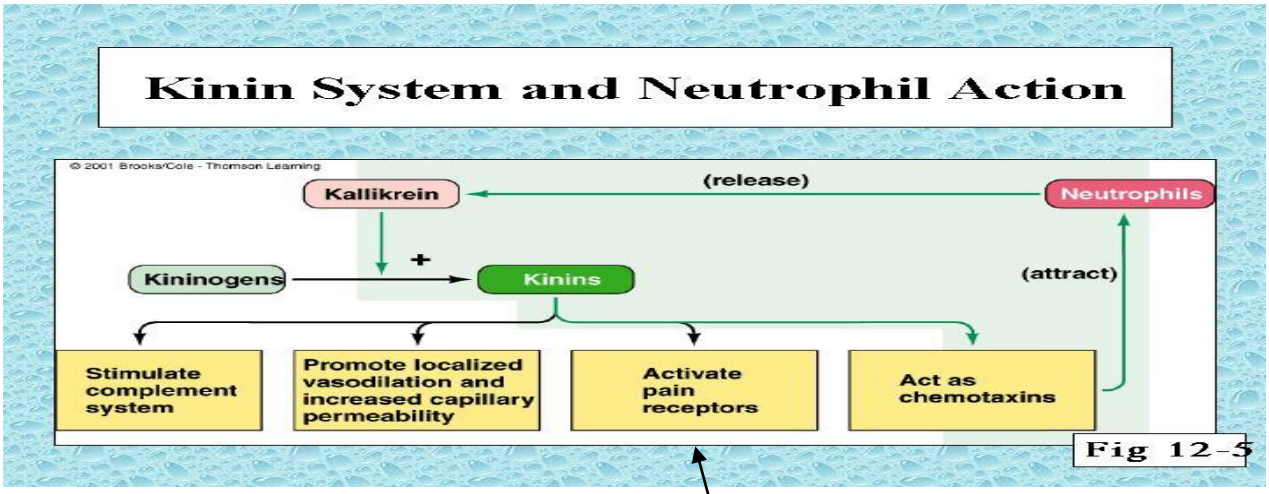
kinin system: It's very important

~~we have a material in the blood called kininogen ..

Like the complement system..DOING NOTHING, it's in active...it can be activated by an enzyme

Called kallekrien .. ☺

ς Kininogen is stimulated by kallerien to form Kinin and KININ is very important for inflammation as u can see in the figure :D



Causes pain ☺

Good luck ☺