PATHOLOGY

◉ Sheets ○ Slides

Number: 9

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In the previous lectures we started talking about the **chemical mediators** that aid in t he inflammatory process, and we will continue now :D
We have mentioned vasoactive amines (histamine and seretonin) and arachidonic ac id metabolite we will cover the rest of the list in this lecture ^^

1- Platelet activating factor (PAF) :

One of the most important mediators
Why is it called so?
Because as the name implies at first it was discovered for its function on the plat elets, it **causes aggregations and activation of platelets.**
How is it generated?
From the membrane phospholipids by the action of phospholipase A2 (PL A2) ,, (r emember the arachidonic acid ;))
*its generated from many cells, neutrophils and others.

"The doctor said that it's not imp to know what mediator is generated from whic h cell, because in general speaking each mediator can be generated from many c ells."

What effect does it have?
It's effect is similar to leukotrienes, it's a :
A- **vasodilator** , increase the vascular permeability
B- **bronchoconstrictor >.<**

"Those who read the book :D will notice a strange number, indicating that the PA F is 100-1000 times more potent vasodilator than histamine"
*we know that the main vasodilator in inflammatory response is histamine! How ever, PAF is more potent.
C- it **stimulates the synthesis of other mediators** like cytokines

2- cytokines :

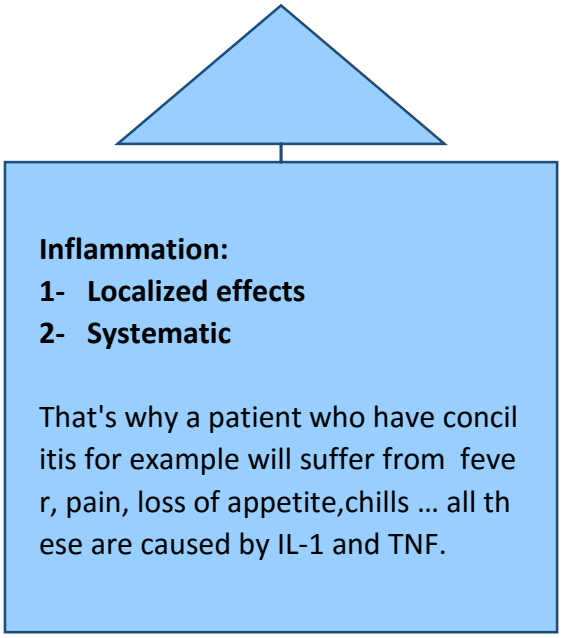
What are these?
They are small polypeptides (include a big group of mediators)
What are the most important ones?

TNF: tumor necrosis factor
IL-1
IL-6 (responsible for protein synthesis during inflammation)
Chemokines (small family of chemo-attracting agents)

So..what is the effect of *TNF and IL-1* ??!
A- These two mediators are very important, they **cause endothelial activation** (remember they stimulate adhesion molecules expression, allowing the firm adhesion of WBC :D)

B- They **increase the production of other mediators** like cytokines and arachido nic acid metabolites.

C- Responsible for the **systematic effect of inflammation**



Chemokines : **they attract** neutrophils and other WBCs and they **activate the leuko cytes** (increase integrins -on leukocytes- affinity to their ligands -on endothelium-)
What is the most important chemokine?
IL-8

3- Neuropeptides :

What is the most important one?
Substance P "**transmits pain signals**"
So if the patient is suffering from pain, it could be one of the mediators causi ng it.

***your neighbor who's 50 years old , has pancreatitis التهاب البنكرياس ,and suffer from abdominal pain, this pain is caused by which of these chemical mediator s :p :

A-substance P
b- kinin
c- cytokines
d- prostaglandins
e- all of the above (the right answer)

** if u hate your neighbor, these are enough to cause him pain :p

4- Nitric oxide :

Another mediator of inflammation, it's a free radical gas, similar to ROS.
It also causes **vasodilatation**.
Is nitric oxide found randomly and continuously in our cells?
(This wouldn't make sense because we know that free radicals are toxic to our bo dies if present always)
So the answer is NO! It's synthesized by the use of an enzyme called *nitric oxide s ynthase.*

***Nitric oxide synthase:*
Type1: present in the neurons, has no role in inflammation.
Type2: the most important, inducible nitric oxide synthase, in macrophages and endothelial cells
Type3: in the endothelial cells, causes vasodilatation.

* So nitric oxide in inflammation is synthesized from type2 (the inducible one)
Effects: **microbicidal, vasodilator, it reduces leukocytes recruitment** (anti-inflam matory effect - like lipoxins)

By this we know the mediators present in cells, now let's talk about

Plasma protein-derived mediators :

We have three main systems:
1- *Complement* system
2- *Coagulation* system
3- *Kinin* system

We will talk about the complement and kinin systems!

1- Complement system:

_What are these?
Small proteins named C1-C9
They circulate in the plasma in their inactive form; they need to be activated to p erform the function.
_How is this system activated?
By three pathways:
A- Classical pathway: antigen-antibodies complexes
b- Alternative pathway: by pathogens, when the complement becomes intact wit h the surface of the pathogen, it becomes stimulated.
c- Lectin pathway: stimulated by certain sugars
_What do we stimulate exactly??
An enzyme called (**C3 convertase**)
_Why?
This enzyme cleaves C3 to: C3a and C3b (activation).
"C3 is present in the blood in an inactive form, when cleaved by the convertase it gives C3a and C3b each one has effect. This is a cascade, so it doesn't only cleave C3, C3 when activated cleaves C4, C5….etc "not necessarily in order" "

The cascade ends with activation of all 9 components.
C3a and C5a : cause **vascular changes** we talked about these are called (anflatoxi ns- cause classic inflammatory response)

C5a: has **chemotactic activity** (complement component that has chemotactic acti vity)

C3b and C4b: act as **opsonins**, target for phagocytosis.

When all the complement components are activated (especially C9): this will **cau se a pore in the membrane of the cell, the osmosis is now different, water will enter the cell, the cell lyses, and rupture occurs!**
This is called **MAC "membrane attack complex"**

2- kinin system :

Hageman factor (factor12) in coagulation cascade stimulate 4 systems, 3 were m entioned
This when activated will activate:
1- Clotting system
2- Anti clotting system (fibrinolytic system)
3- Kinin system

The kinin system is very important in inflammation,
How can we get the activated kinin?
It's present as kininogen (inactive)
Kallikrein (enzyme that cleave kinin) this stimulated by hageman factor

Kininogen + kallikrein >>>>kinin

Kinin is a very important mediator:
1- Acts as a **chemotactic agent**
2- Causes **pain**
3- **Activates the complement system**
4- **Vaso dilation** and increased vascular permeability

By now we finished talking about the inflammatory mediators :)

** systematic effect of inflammation:

All the previous cellular changes, vascular changes, and the mediators, happened locally,
How? Activation of intigrins, secretion of mediators only when needed, migration of the cells and aggregation..etc
However, in any inflammatory response, we have systematic effect, but the main is the local effect

Why do we have this effect?
Because chemical mediators can circulate in the blood and cause systemic effects .

Vasodilatation, increased permeability, activation of WBCs, phagocytosis >>**local**

The mediators are secreted locally at first, but some of them circulate and caus e systematic effect.

What are these effects?
*these are also acute phase reaction
Fever, elevated acute-phase proteins,leukocytosis and increased heart rate and blood pressure

What are the most important mediators that cause them?
Cytokines (IL-1 ,IL-6 ,TNF)

*** Fever

Now, why a patient suffering from inflammation has fever??
It's caused by small substances called ***pyrogens***, which stimulate the production of prostaglandins around the hypothalamus!
Notice that we have prostaglandins at the site of the injury too!

These prostaglandins around hypothalamus stimulate neurotransmitters to incre ase body temperature,
To sum up:
The fever is caused by prostaglandins produced around the hypothalamus not t hose at the site of injury,
These are produced by the action of pyrogens.

What are pyrogens?
One of them is cytokines, notice that cytokines are not directly related to the fev er, these when travel through the blood activate cells to produce prostaglandins, prostaglandins around the hypothalamus are directly related to fever!
So cytokines are pyrogens, internal pyrogens because it's from the cells there are external pyrogens from bacterial products

***** elevated acute phase proteins**

Certain proteins produced during inflammation mainly by the effect of ***IL-6***
We use these proteins for diagnosis, as they increase in number during inflammation!

We can by following these proteins level, know if the Inflammation is under contr ol or not

What are the proteins we are talking about? (remember biochem :p)
CRP (C-reactive proteins) ,, ***SAA (serum amyloid A)***

Why are these proteins elevated?
(Msh 3ashan sawad 3yona tab3an :p)
These act as opsonins , but we use them clinically to diagnose and follow up treat ment.

Another protein is ***fibrinogen***, this bind the RBCs, and cause aggregations (loose not thromboses)These are called rouleaux, that sediment quickly if we cyto-spin them "centrifugation" ,so the sedimentation rate increases, this is called **ESR (ery throcytes sedimentation rate)**this is used for diagnosis and indicate if there is an inflammation.

IL-6 affects the liver >> more fibrinogen synthesis >> ESR

***** leucocytosis**

Another systematic effect is leucocytosis, increased WBCs ,this is different from t he activation we talked about before (margination, ….)
This effect means **increase the *number of WBCs* in the whole blood**, but they are not activated.(this is called **leukomoid reactions**)

Note: if a patient comes with high number of WBCs you should put leukemia into your consideration!

Other effects are increased heart rate, sweating,…

Forgive me for any mistakes ^_^