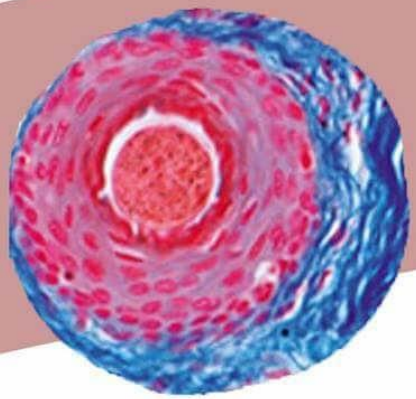
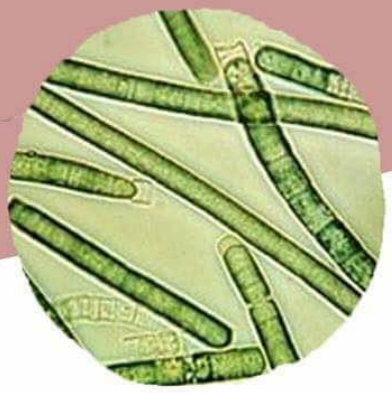
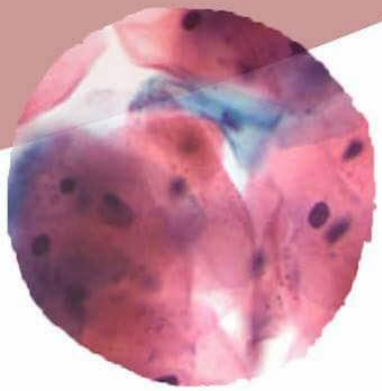
INTRODUCTION TO PATHOLOGY

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Sheet# 10

In the last lecture we started talking about some **inflammatory mediators** and we'll continue in this sheet talking about others, including:

1) Cytokines: they are polypeptides. Cytokines are a big family of mediators and the most important cytokines to know are:
a) interleukin 1 (IL1)
b) interleukin 6 (IL6)
- "inter" means between and the word "leukin" is derived from leukocytes(WBCs)and they are called so as they regulate the function of leukocytes in general(the **talk**(communication) between leukocytes is regulated by them).
c) tumor necrosis factor (TNF)
d) chemokines

-Firstly we will talk about **TNF and IL1** as they have **the same effect**. Their main roles are:
1)activating the endothelial cells so adhesion molecules (their 3 main families) are then expressed on the endothelial cells and as you remember those adhesion molecules are important for 3 things (rolling, firm adhesion and transmigration).

2)increasing the production of other cytokines and arachidonic acid metabolites.

3) they are both important for systemic effects of inflammation, mainly fever and lethargy (losing strength), cachexia also losing appetite.

- **Source**: activated macrophages, mast cells and endothelial cells.

NOTE: fever and lethargy are caused by many mediators, mainly TNF and IL1.

-Another family of cytokines is **chemokines**: they are small peptides which are very important for chemotaxis.
-REMEMBER IL8 is the most important chemotactic agent from chemokine family.
-finally we have **IL6** family which we will discuss in systemic effects of inflammation.

2) Neuropeptides (which include Substance P family), they are important because they transmit pain signals.

3)Nitric oxide(NO)

remember when we talked about phagocytosis we said there are lysosomal enzymes, oxygen radicals and nitrogen radicals.

How are these nitrogen radicals synthesized? Nitric oxide (NO) is a free radical gas and is synthesized by an enzyme called (Nitric oxide synthase **NOS**) from arginine, this NO is the source of nitrogen free radicals which are important during phagocytosis.

The enzyme (NOS) -that synthesizes Nitric oxide mediators- has 3 types, each one is secreted and present in a certain site and thus has a certain effect:

-Type 1 is in neurons and isn't involved in inflammation

-Type 2 is called inducible NOS (INOS), it's in macrophages and important in inflammation

-Type 3 is secreted in endothelial cells and is important in vasodilation ,in other words , **(1) nitric oxide mediator causes vasodilation**.

-NO mediator is **(2) microbicidal** (it kills microbes), How?
that's by nitrogen free radicals which are derived from nitric oxide.
-NO mediator also **(3) reduces leukocyte recruitment**, in other words, it works as anti-inflammatory mediator.

TO SUM UP, what are the **mediators that cause vasodilation**?
1)histamine 2) platelet activating factor 3) prostaglandins E2 and D2
4) prostacyclin 5) nitric oxide

TO SUM UP, what are the **mediators that cause anti-inflammation**?
1)Nitric oxide (it has both inflammatory and anti-inflammatory effects)

2)lipoxanes

So all the previously mentioned mediators (in this sheet and the previous one) are synthesized in the cells. We also have mediators that circulate in the blood and aren't going out of cells.

- ✓ **Plasma Protein–Derived Mediators:**

1)coagulation system mediators
2)Kinin system mediators (K mediators)
3)complement system mediators (C mediators)

These mediators are synthesized in the liver under the influence of **IL6** (IL6 isn't normally present just as a mediator of inflammation)and they are normally present and circulate in the blood but in an inactive form, when inflammation happens they become activated.

1) Coagulation system mediators
what do we need to know here? One of the coagulation system mediators is **Hageman factor**, it's factor 12 in coagulation system, it stimulates:
a) clotting system which makes clot by fibrin.
b) The anti-clotting(fibrinolytic)system by plasmin.
c) Kinin system mediators.

-The main idea is that factor 12 can stimulate clotting, anti-clotting and inflammation (Kinin system) at the same time, and these processes are highly regulated.

2) Kinin system mediator
As we said before , these mediators circulate normally in the blood (in the form of kininogen) which is the inactive form(doing nothing but moving through the blood), if there's an inflammation then it will stimulate an enzyme called (Kallikrein),this enzyme cleaves Kininogen (inactive protein form) and converts it into Kinin(active protein form).

-Kinin system mediator is important in inflammation and has many effects including:
a) Pain
b) vasodilation and increase the permeability
c) chemotactic agent
d) stimulates the complement system mediators

TO SUM UP : what are the mediators that are chemotactic agents ?
1)IL8 2)Leukotriene B4 3)Kinin system mediator

3)Complement system mediators ,the last mediator we will talk about .They include (C1,C2,C3,…,C10) proteins .
-Just like the previous plasma mediators, C system mediators are synthesized in the liver, circulating in the blood in the inactive form, when there's inflammation they become activated by certain enzymes.

What is the mechanism of activation here?
-it's like the Domino effect, when one complement is activated, it cleaves another complement and activates it. Eventually, all complement system mediators become activated and they have an important effect during inflammation.

What triggers the stimulation of the complement system mediators?
-Other mediators do so, E.g: cytokines and Kinin system mediator.

How are the C system mediators stimulated?
-There are 3 main pathways of stimulation:
1) Classical: When there's a cell with an antigen-antibody complex on its surface (during the immunologic reaction), there will be stimulation and activation for C system mediators.

2) Alternative: In case we have bacteria moving in the blood (bearing in mind that C system mediators also circulate through the blood) , then there might be a direct contact between these bacteria and the C system mediators (particularly between the lipopolysaccharides on bacterial cell wallsand the C system mediators), if that happens (direct contact) ,the activation results.

3)Lectin-mannose pathway: certain plasma lectins (lectins mean sugars) binds to mannose (which is also a sugar) on the microbe, and both sugars complement each other after binding thus the activation occurs. (It's not a direct contact but it's a binding between the 2 sugars and they both complement each other).

-So in order to activate the C system mediators, there are these 3 pathways,at the beginning every pathway has its own way of activating for the first C mediators (for example maybe in one of these pathways the activation firstly occurs for C1 then for C2 then for C3, and maybe in another pathway the activation consequence differs) but those three pathways will all eventually reach the point where C3 is activated and they meet there.

-The activation of C3 is done by an enzyme called (C3 convertase), this enzyme cleaves C3 mediator into (C3A and C3B), when the cleavage occurs, we can say C3 is active. (C3A) is important for inflammation (anaphylatoxin) whereas (C3B) acts as an opsonin.

-**REMEMBER**: Opsonin is a host protein that coats the microbe in order to make it recognizable for phagocytes and thus it gets phagocytosed.
-**NOTICE**: the activation of these complements involves the cleavage into (A and B)

-Then C3 will also stimulate the other complements to become activated .The activation of C4 will give (C4A) and (C4B)-which is also an Opsonin-.
-The same concept is for the activation of C5 (gives (C5A)-which is important for inflammation (anaphylatoxin) and chemotaxis - and (C5B)), and so on for the rest of the complements.

- **HINT** from the Dr -makes it easier to memorize- :
-the complements with odd # and A are important for inflammation-we call them anaphylotoxins- (which are C3A and C5A)
-the complements with B are opsonins (which are C3B and C4B)

-There's also something about complements (C5-C9) ,when C5 is activated it binds to (C6,C7,C8 and C9) ,they will all act like a "drill" and start to attack the membrane of the injurious agent (bacteria or any microbe) and make pores in it resulting in losing the membrane integrity then the cell will die by lysis. We call the (C5-C9) complex : MAC (membrane attack complex).

-So as we noticed in C system mediators , killing the injurious agent (e.g:bacteria) is done by 3 mechanisms :
1)opsonization 2)inflammation 3)Lysis caused by MAC

DON'T OVERLAP : C system mediators have 3 pathways of activation (classical , alternative andLectin-mannose) ,these 3 pathways will eventually cause the death of injurious agents by 3 mechanisms (opsonization ,inflammation and lysis caused by MAC).

-And that's all about mediators. Now we will talk about another concept which is **the systemic effects of inflammation**. Although the process of inflammation is localized, we have some systemic effects through the whole body. But **WHY**?

-most of the inflammatory mediators work locally by autocrine effect (the cell secretes the mediators and affects itself), others mediators have a paracrine effect (the cell secretes the mediators and affects the neighboring cell) and finally we have mediators with endocrine effect (the mediators reach the blood stream and other sites in the body SO THEY CAUSE SYSTEMIC EFFECTS).

What are the systemic effects of inflammation (also called acute phase reaction)?

1) Fever
2) elevated acute phase proteins
3) leukocytosis (high rates of WBC's inside the blood)
4) increase in heart rate and blood pressure

-All of these effects are caused by **Cytokines (TNF, IL1, IL6),** they are produced locally but they have endocrine effects so they will move through the blood and cause systemic manifestations.

-Now starting with **fever**, **why** does it occur?Because of prostaglandins, but how? We firstly have to know what regulates our body temperature as all.It's the Hypothalamus, it works in order to keep our body temperature within the normal ranges (almost 37 Celsius).
-In the case of inflammation, prostaglandins are there. They go to the hypothalamus and make it increase the temperature (for e.g up to 38 Celsius).

-But what makes the prostaglandins do that?
Because we have certain proteins called **Pyrogens**-remember Pyrexia means fever-. Those Pyrogens stimulate the synthesis of prostaglandins in the hypothalamus which stimulates the production of neurotransmitters to increase the temperature, resulting in fever.

-what are these Pyrogens?
We have 2 types of Pyrogens and each type consists of certain materials
1) External Pyrogens and it's a bacterial product, the bacteria secrets certain proteins (peptides/saccharides) and these proteins act as Pyrogens.
2) Internal Pyrogens and this type includes (**IL1 and TNF which are Cytokines**), so cytokines can act as internal Pyrogens and that's how they cause fever.

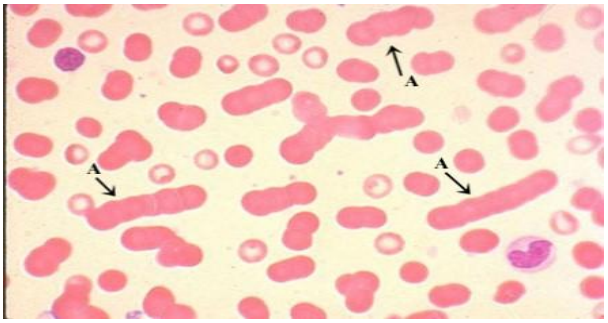
SO TO SUM UP
-For the fever to happen it needs:
1) pyrogens (mainly cytokines)
2)prostaglandins

The second systemic effect is the **elevated acute phase proteins** :they are certain proteins in our body that increase dramatically during some types of inflammations.

Examples of Acute phase proteins:
1) CRP (C reactive protein)
2) Fibrinogen
3) Serum amyloid A (SAA)

-The function of CRP and SAA is that they act as opsonins, we also use them as indicators for inflammation (we mostly use CRP in clinical practice) **For e.g** : if I have a patient suffering from knee pain , he either has inflammation or a degenerative disease .How can I know ? By monitoring the value of CRP protein, if it's high then it's inflammation.

-What about fibrinogen?
We don't directly use fibrinogen levels as an indicator for inflammation but we monitor the effects of it on the RBCs.**HOW**?
-Normally RBCs are moving in the vessels, if fibrinogen increases then the RBC's will slightly aggregate (not as much as clotting but they become closer to each other). Check the following picture to see how these aggregations look like:



Now remember what we took in Biochemistry 1 about centrifugation we do on the blood samples in order for the liquid part to separate from the solid part, if the taken blood sample has high levels of fibrinogen(RBC's are closer to each other) , then sedimentation rate for the solid part (Erythrocyte(RBC's) sedimentation rate **ESR**) will be relatively high>20

And that's how we indirectly use fibrinogen as an indicator for inflammations (inflammation causes increase in fibrinogen levels → higher ESR) -common question in the exam.

Finally we will talk about the third systemic effect which is **Leukocytosis** (increase in the levels of WBCs in the blood much more than normal ranges).

Why does leukocytosis happen?
- During some inflammations, our body needs more WBCs so there will be more signals for the bone marrow to synthesize more WBCs which will move through the blood, therefore we will find high amounts of WBCs in the blood during inflammation.

-Sometimes the amounts can be dramatically high (40-100 thousands) which seems like leukemia and we call this case leukemoidreaction.

Please refer to doctor Manar's slides for more details that weren't mentioned in the record.

"You were born with the ability to change someone's life, don't waste it"