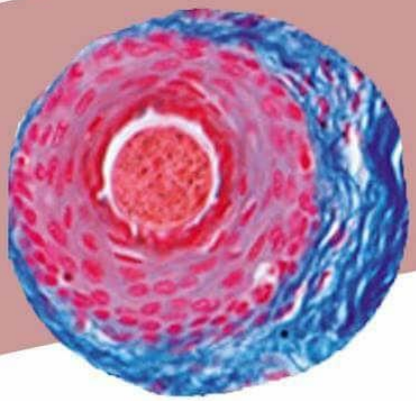
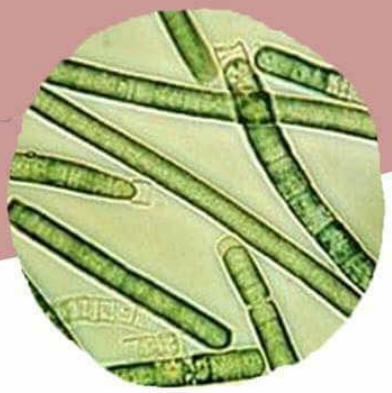
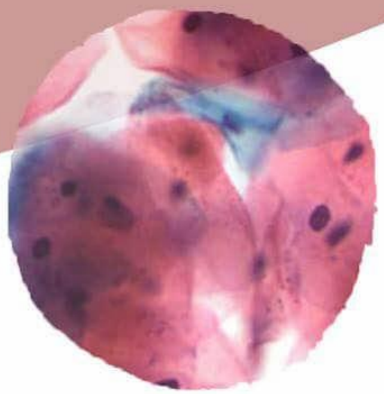
INTRODUCTION TO PATHOLOGY

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Sheet# 9

Inflammation 4: Chemical Mediators

Previously, we discussed the activation of leukocytes after reaching the site of action. We said that leukocyte activation results in enhancement of the following functions:

1-Phagocytosis.

2-Intracellular destruction of phagocytosed microbes and dead cells.

3-Production of mediators.

*The 4_{th} is liberation of substances that destroy extracellular microbes and dead cells.

*An example of this mechanism is NET.

NETs:

-Abbreviation of "Neutrophil Extracellular Traps".

-Produced only by neutrophils in response to an extracellular infection (mainly bacteria and fungi).

-The killing happens outside the cells (unlike phagocytosis where the killing happens inside the cell).

-Trap and kill infectious agents.

-NETs contain a framework of nuclear chromatin and high concentration of antimicrobial substances.

How does it happen? The neutrophil creates an opening in its cell membrane , then it releases nuclear fibrils that trap the infectious agents (bacteria) and prevent them from spreading, the trap has antimicrobial substances and toxic materials that will kill the

microbes, so when this happens, DNA will be released and the cell is beyond repair (irreversible injury).

-It could cause disease (EX: auto-immune diseases) because of the leakage of the cellular contents.

-Note: the half-life of neutrophils is only 48 hours, so it's not a big lost after all.

Now we will start talking about chemical mediators:

Inflammation involves 3 important components:

1-Blood vessels. 2-Host cells. 3-Chemical mediators.

We have already discussed the vascular changes and the cellular changes, in this lecture we will focus on chemical mediators.

*Note: Vascular and cellular changes need chemical mediators (except margination; which happens due to physical stasis NOT to chemical mediators).

These chemical mediators are proteins or lipids, but the majority are proteins.

General properties of Mediators:

1- They act by binding to receptors on target cell(s).
2- Some mediators don't require receptors (ex: ROS and lysosomal proteases).
3- One mediator can have several (different) effects.
4- One mediator can act on many cells.
5- They are either locally produced by cells at the site of inflammation **or,** they are circulating in the plasma (blood).

Two types of chemical mediators:

1- **Cell-Derived Mediators:** are either **(1)** preformed and stored inside granules/vesicles (they act quickly)**, (2) OR** need to be synthesized (need longer time to act).
2- **Plasma Protein-Derived Mediators:** they circulate in inactive form and need to be activated at the site of inflammation. Also, they are synthesized by the liver.

Regulation of mediators:

These mediators produce a very strong inflammatory response. Thus, they may cause systematic damage or damage to the tissue around them; so we need to regulate them.

Most of the Mediators are regulated by:

1- Quick decay, ex: arachidonic acid metabolites self-decay when they finish their action.
2- Enzymatic inactivation, ex: histamine by histaminase, and bradykinin by kininase.
3- Elimination, ex: oxygen free radicals by antioxidants.
4- Inhibition, ex: complement inhibitory proteins.

*Mediators that exist in the blood (also called plasma protein-derived mediators) are synthesized in the liver, and circulate in the blood in inactive form; they need enzymatic cleavage to be activated. The most important ones are kinin system and complement system. (Next lecture)

*For the time being, let us discuss mediators one by one…

-First family is called Vasoactive Amines:

*Vasoactive means they affect blood vessels.

-They are cell derived preformed mediators.

This type includes: 1-Histamine 2-Serotonine.

1-Histamine:

-Vasodilator

-Increases permeability (in general any mediator that causes vasodilation will increase the permeability, (not always)).

-Preformed *mainly* by mast cells… also, by basophils and platelets.

-Quickly acting mediator.

-Inactivated by Histaminase.

-Since it causes vasodilation and increased permeability; it causes some cardinal signs of inflammation (hotness, swelling (edema), and redness).

2-Serotonin:

-Opposite to histamine.

-Vasoconstrictor.

-Preformed and stored in platelet granules.

-It's important in clot formation; so it's more important during repair than in inflammatory response.

-It's also a neurotransmitter (called hormone of the happiness)

Platelet-Activating Factor:

-Generated from the membrane phospholipids of inflammatory cells, by the action of the enzyme "phospholipase A2".

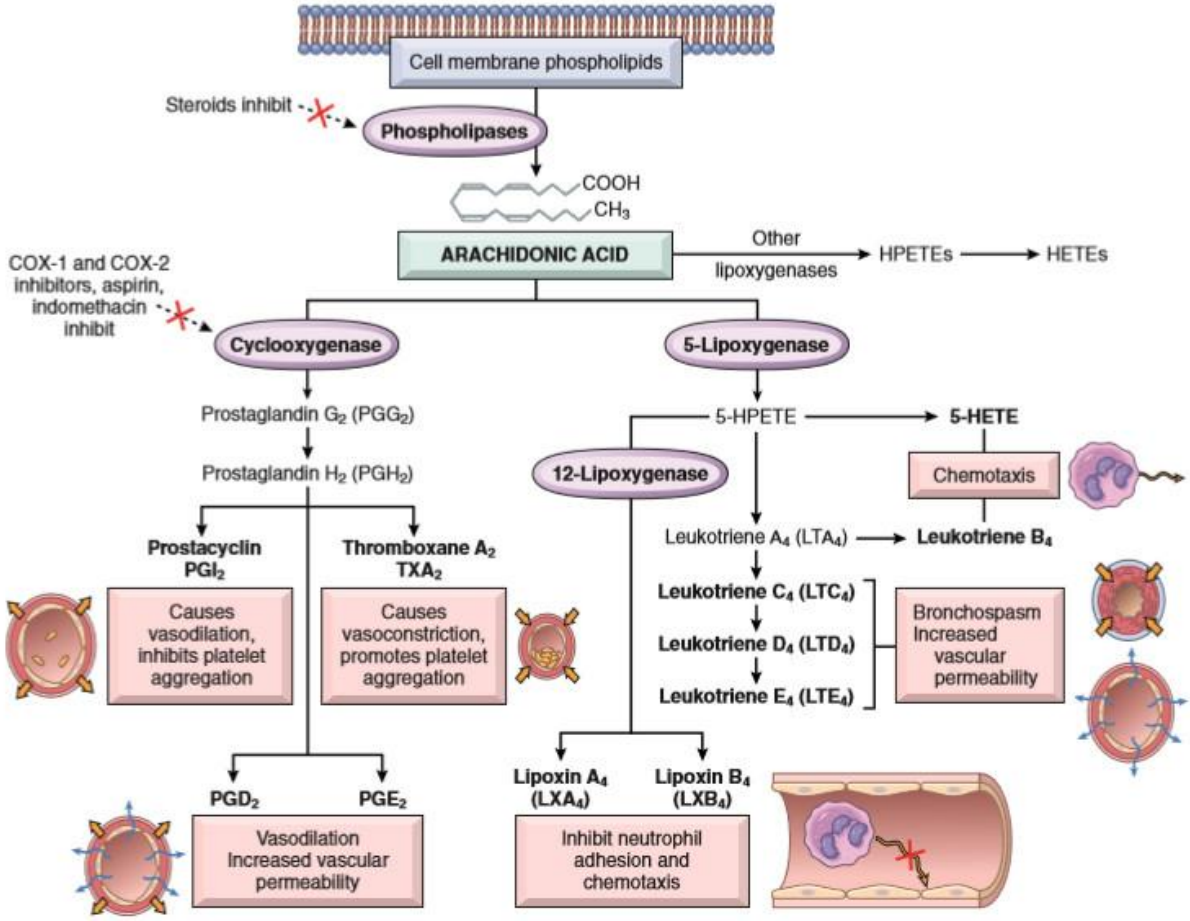
-It's important for platelet aggregation.

-It's (100-1000) times more potent than histamine in vasodilation and increasing the permeability.

-Also it's a potent broncho-constrictor.

-Stimulates the synthesis of other mediators.

*Arachidonic acid Metabolites:



-They are cell derived mediators that need to be synthesized.

-Arachidonic acid metabolites are also called “eicosanoids”.

-Arachidonic acid is a 20-carbon polyunsaturated fatty acid with 4 double bonds.

-We get arachidonic acid from foods like eggs and sea food.

-It’s an important part of the cell membrane.

-It needs to be released from the membrane to the cytoplasm by an enzyme called <u>phospholipase A2.</u>

-So activating phospholipase A2 will increase arachidonic acid metabolites production, and also will increase the production of platelet activating factor.

*Now we have the arachidonic acid in the cytoplasm, there are two families of enzymes that can act on it:

1-Cyclooxygenases 2-Lipoxygenases

1- Cyclooxygenase Pathway:

-Produces prostaglandins “PG”.

-These prostaglandins are: PGE2, PGD2, PGI2, Thromboxane A2 (TX-A2).

PG-E2 and PG-D2: -Vasodilators, increase permeability.

-They cause pain, fever and edema. (fever because they interact with cytokines).

PG-I2: -It’s called “prostacyclin”

-Secreted from endothelial cells.

-Vasodilator.

-Inhibits platelet aggregation (which causes bleeding).

TXA2: -Secreted by platelets.

-Vasoconstrictor.

-Increases platelet aggregation (blood clotting).

*The balance between PGI2 AND TXA2 is very important .

*If PGI2 increased, it will cause bleeding. And if TXA2 increased, it will cause over clotting.

2- Lipoxygenase Pathway:

-Produces: 1-Leukotrienes 2-Lipoxins.

A) Leukotrienes:

-They are: LT-A4 / LT-B4 / LT-C4 / LT-D4 / LT-E4 (4 indicates to the number of double bonds)

*LT-B4: - Is a chemotactic agent.

- Produced mainly by neutrophils.

*LT-(C4,D4,E4): - Broncho-constrictors.

- They increase vascular permeability.

- Produced mainly by mast cells.

Summary

Action	Eicosanoid
Vasodilation	PGI_2 (prostacyclin), PGE_1, PGE_2, PGD_2
Vasoconstriction	Thromboxane A_2,
Increased vascular permeability	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotriene B_4

***Note:** Leukotrienes C-4, D-4, E-4 also cause bronchoconstriction and vasoconstriction.*

B) Lipoxins:

- are: LX-A4 , LXB4.

- are anti-inflammatory agents. (reduce inflammation).

-inhibit the activation of WBCs (adhesion and chemotaxis).

*As inflammation starts; production of anti-inflammatory agents occurs as well.

*So lipoxins are one of the regulators of inflammation.

Anti-inflammatory drugs:

The main targets are arachidonic acid metabolites in case of anti-inflammatory drugs.

1) Steroids:

Block the action of phospholipase A2, now arachidonic acid can't exit the membrane. Thus, steroids inhibit (deactivate) both cyclooxygenase and lipooxygenase pathways.

They also inhibit "Platelet Activating Factor" formation.

EX: Glucocorticoids.

2) Non-Steroidal anti-inflammatory drugs:

-Inhibit COX enzymes family (both PG and TX). But we still produce leukotrienes and lipoxins through lipoxygenase pathway.

*Examples: aspirin, and ibuprofen.

Problems related to non-steroidal anti-inflammatory drugs:

There are two types of COX:

1) COX-1:

-Normally acts inside our cells all the time. It's important in maintaining homeostasis; by producing certain prostaglandins that are important to protect our tissues.

Some prostaglandins protect the stomach by increasing mucous secretion, and others protect it by balancing water and electrolytes in the kidney.

2) COX-2: produces prostaglandins involved in inflammation.

** By blocking COX-1 and COX-2, we will not have protective prostaglandins. Resulting in diseases like gastric ulcer.

** Blocking COX-2 only; inhibits harmful inflammation (inflammatory prostaglandins) but not the protective prostaglandins.

** Another problem is that TXA2 is produced by COX-1. So if we inhibit COX-2, the balance between PG-I2 (which is produced by COX-2) and TX-A2 is disrupted.

-High TX-A2; increases thrombosis, causing cardiovascular diseases (ex: MI) and cerebrovascular diseases.

** We inhibit lipoxygenase in case of asthmatic patients.

#Refer to the book page (44-47)

#Also, refer to Dr.Manar slides in case we missed anything!

Everyone wants happiness……. No one wants pain

But you can't have a rainbow……. Without a little rain ;)