PATHOLOGY

◉ Sheets ○ Slides

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Subject: Inflammation

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Inflammation

-What's the meaning of inflammation?

"Flame" is the origin of the name inflammation.

-what is the definition of inflammation?

Inflammation in our bodies is a protective response, it protects us from injuries (Cell injury is anything that disturb The Homeostasis) and any exogenous invaders, so it is not a disease.

In inflammation**: 1)** the host cells "the cells of our bodies "are involved such as inflammatory cells e.g. ; macrophages ,lymphocytes, plasma cells neutrophils, also **2)**blood vessels are involved **,3)**chemical mediators .So our lecture will be about the inflammatory changes ,changing in the host cells , inflammatory cells ,in blood vessels ,and The mediators involved in inflammation.

-what is the aim of inflammatory response

To **protect the cells** and this involves the **elimination of injurious agents** for example a bacteria or a virus, to **eliminate dead tissue (necrotic tissues)** and **repairing the site of injury**.

-we said that inflammation is not a disease it's a protective response so why we give the patient anti-inflammatory treatment?

The same inflammatory cell and the same mediator will affect our cells, This is called **collateral damage** Since you have potent mediators affecting injurious agent As well As your normal tissue that's why we need to limit the process of inflammation By giving the patient anti-inflammatory treatment, To decrease the unintended outcomes (signs and symptoms of the inflammation).

-So what are the symptoms of the inflammation?

There are five symptoms:

1- **calor**→ " hotness"

2- **rubor** →"redness,

3- **tumor**→ " swilling"

4-**dolor** →"pain"

5-**Functio laesa**→"loss of function"

(Refer to the slide to see the symptoms).

-so what are the causes of inflammation?

- Cell Injury (Might be caused by impairing the homeostasis)
- Infections (By some microorganism could lead to necrosis thus will activate inflammation

-now we have very important distinction to make, we need to understand the difference between infection and inflammation:

Inflammation is the protective response we talked about previously but infection you need an infectious agent like bacteria or virus or any microorganism to cause a disease so infection is caused by microorganism, inflammation result due to infection or to other causes.

Inflammation can be short lived "**acute inflammation** "or it can be long lived "**chronic inflammation"** so we need also to distinguish between them so acute inflammation is a rapid onset inflammation ,short-living ,exudation of fluids ,and the main cell of this response is the neutrophils .whereas chronic inflammation is : long-lasting and the predominant cell is the macrophage(include lymphocytes but mainly macrophages) also the acute inflammation is fast "Minutes to certain hours the symptoms start appearing whereas chronic slow process it need days to symptoms to start appearing but last longer.

-tissue injury and fibrosis is minimal in acute inflammation but is marked in a chronic inflammation ,systemic signs and symptoms will be prominent in the acute inflammation that's why Many people think that acute inflammation is more painful than chronic inflammation.

How does the inflammation happen?

When there is an injury "any injurious agent or any cell injury "these cells and these mediators (found in blood) need to go out of the blood to the site of injury to cause a protective response. This is the basic mechanism.

-the chemical mediators involved can be: **Pre-synthesized** (stored in granules of neutrophils or mast cells) thus they will act fast acting.

The cytoplasm contains the granules and the granules contain mediators so just release them.

Histamine for example is stored in mast cells. most of the mediators are in the cells but some mediators circulating in the blood which are mainly **the complement system mediators.**

how inflammation is controlled?

Inflammation is **self controlled**.(it must be controlled Since it might cause collateral damage) but how ? By controlling the cells involved and the mediators (can be short-lived or detoxified) also the same mechanism that starts the inflammation will start the repair and start the anti-inflammatory process.

How does inflammation start?

To start the inflammation we need to **recognize the injurious agent or injury**

By certain receptors, those receptor can recognize the foreign antigen and start the process of inflammation and these receptors are called **pattern recognition receptors,** they recognize the pattern (of wide range of antigens)they are two types :

1- toll-like receptors:

We have something called toll receptors they discover it in the drosophila and when they discover it in human they called it "toll like receptors " toll in German means great this receptor recognizes microbes how ? it can **recognize DNA/RNA** of the infectious agent, the **endotoxins produced by it** and **the proteins of this agent**. They are present on the **plasma membrane** so any infectious agent outside the cells can be seen but they are also found **inside the lysosomes** (recognize ingested microbes). Now when they recognize the foreign body it sends signals to the nucleus (transduction signals) in order to the nucleus to start synthesizing certain mediators such as cytokines(interleukin→ very potent mediator).

2- Inflammasomes**:**

Inflammasome recognizes microbes and necrotic tissues , they are complex and found in the cytoplasm of mainly inflammatory cells(can be found in fibroblasts)

1-they recognize crystals such as Uric acid crystals. People who have gout disease have high Uric acid forming crystals of the Uric acid, they will continue to aggregate so these mediators recognize these Crystals as foreign bodies (starts inflammation)

2- Inflammasome can recognize cholesterol crystals that present in the blood vessels the inflamasomme recognizes this as foreign and start the inflammatory response which ends in atherosclerosis inside the vessels

3- They can also recognize ATP why? Since they can recognize the products of necrosis and fragmented DNA and fragmented protein.

*inflammasome when recognize this it stimulates a enzymes called caspase1 which will activate the production of interleukin-1. Ilk-1 will result in inflammation sign and symptoms so sometimes they are very sever in that case we can use anti-Ilk-1 to stop them (it's just a theory).

-please refer to the slides to see the examples-

4- it can be deported in type 2 diabetes because it can recognize free fatty acids crystals in obese people ,free fatty acids are recognized by inflamasomme as foreign bodies so it will activate caspase one which will increase interleukin one which will result in inflammatory response which will destroy islets cells of the pancreas which causes diabetes . if we use anit-Ilk-1 we might be able to stop that damage thus curing diabetes 2.

The acute inflammation and chronic inflammation involve vascular changes and cellular changes. Why vascular changes??

because all the cells and mediators need to go out of the blood vessels to the site of injury in order to be able to work but how ? **dilatation in blood vessels and increase the permeability ,**this will allow more mediators and cells to come out to the injury .

But First they is **vasoconstriction** it lasts only for seconds. It is a protective response a very brief one, then it is followed by **vasodilatation caused by histamine**. Histamine is pre-synthesized so it will act fast but short-lived, thus at the same time cytokines will be produced, they will act as vasodilators once histamine stop. Also the blood pressure will slow down this allow the cells to move out not to get carried away e.g. WBC's

so very brief vasoconstriction ⟹ then vasodilation ⟹ then increase permeability ⟹ increase permeability will cause the cells to and fluid go out.

This will result in edema. We have two types of edema:

1) Transudate

2) Exudate

- if fluid diffusing out is mainly water(No cells/proteins low specific gravity) so this is a **transudate** .
- if it is a accompanied by cells and cellular debris and proteins (high s.g) so this is an **exudate** .

when the fluid that get out is mainly water ?

when there is a problem in the hydrostatic pressure and oncotic pressure. The imbalance between the hydrostatic and oncotic pressure such as a patient with renal failure or cardiac problems this will cause transudate. In inflammation, we need exudate because we need fluid and some cells to go out.

Clinically, how I can know if this sample contains exudate or transudate fluid???

if it's fluid only it is transudate , if it is fluid with very low amount of cells it is also transudate , but fluid with increase cell debris , protein ,cell content ,so it is exudate

why it is important to know ?

Simply to know the cause of this edema. let's say that you take a fluid from a patient with ascites so you take it and you notice that it is full of protein and white blood cells and cell debris Then the patient has inflammation. But if you take a fluid sample from the plural cavity and you find that it is mainly consists of water you will know that there is problem with balance of the pressure (not inflammation)

What are the causes of increase blood permeability?

In acute inflammation the blood permeability increases due to histamine.

How it cause that?

- **1**-The blood vessel has endothelial cells lining it these cells prevent the free movement but we have small gaps between each cell and another. If I

increase size of the gap I can get fluid as much as I can because the cell get smaller due to histamine(**cell contraction**) .

- **2-**Another mechanism in increasing the permeability, is **endothelial cells destruction**. the barrier between the blood and tissue will be lost so the fluids can go out also cells will easily move

- **3-**Another mechanism increasing the **transcytosis.** Transcytosis means a transcellular transport of certain extracellular components or proteins or structures across the interior of the cell.. These components will be captured in vesicles on one side of the cell drawn across the cell and ejected on the other side. Causes changes in osmotic pressure thus also fluid moves out

-In general Water moves with solutes, wherever there is an increase in solute concentration, water will diffuse in that direction thus restoring the solute balance again. So if we have more solutes outside the cell this will cause water to go outside causing edema .Also

- **4- Leakage from newly formed blood vessels (neovascularization)** we said that when inflammation starts we have regeneration at the same time and part of the regeneration or tissue repair is the process of increasing blood vessels. These newly formed blood vessels are not well formed thus they are leaky since the junction between the epithelial cell are still not well formed enhancing leakage that causes edema. Increased permeability in acute inflammation is the result from four processes:

1) endothelial cell retraction or contraction..

2) damage to the endothelial cells..

3) neovascularization –newly formed blood vessels-..

4) increased transcytosis

All these can cause edema and increase vascular permeability in acute inflammation. Endothelial vascular contraction is the most common cause that increase permeability. It is a very rapid response because histamine is formed inside the granules just it needs to be secreted thus acting rapidly. Endothelial contraction not only caused by histamine but also by bradykinin and leukotrienes . also by cytokines that needs time to be produced(not pre-synthesized but it will last longer .

Endothelial cell contraction has two type and both of them are acute inflammation:

- The common type is caused by histamine ,bradykinin and leukotriene. It is quick and short lived..
- The other type is caused by cytokines..this one is long lived but takes longer time to start it’s effect but still it is acute inflammation..

Lastly example of endothelial injury is burns. Any change or injury to the endothelial cell can cause edema.

Note:

The use of the drug depends on what you are going to treat. For example, the effect of histamine is short lived so it is used acutely. Histamine is mainly used in allergic condition. So we give anti-histamine for allergic condition.. Histamine also is potent so at the beginning of the disease this effect must be finished and taken care of.

Other drugs are used also, as anti- cytokines and anti-leukotriene depending on the treatment. Each one of the granules is secreted from a different cell. The stimulation of these cells and the release of the mediator depends on the stimulating agent. The effect is caused by a balance between the mediators.

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