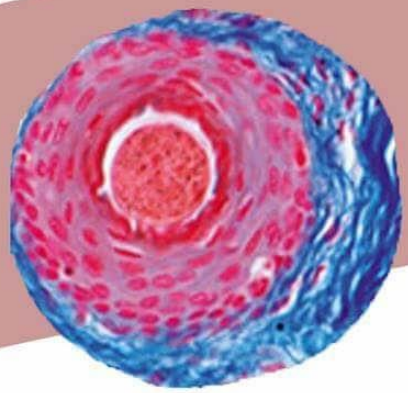
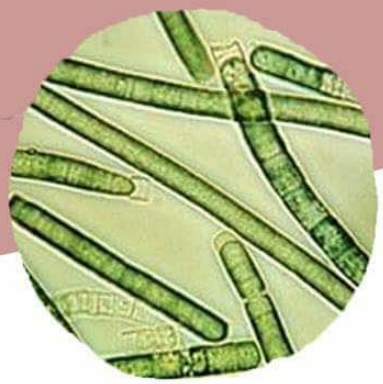
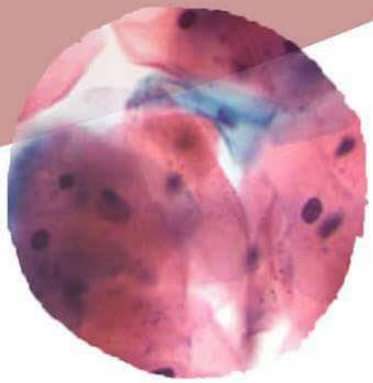
INTRODUCTION TO PATHOLOGY

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Sheet# 7 Salah Abualshaikh

In the last lecture we discussed about inflammation, its definition, causes, signs and symptoms. In this lecture and next lectures, we will discuss **Steps of inflammation** in details.

First step of inflammation: <u>RECOGNITION of injurious agent</u>

Recognizing that there is an injury (offending agent)

The cells that can recognize an injury/offending agent are: **

All inflammatory cells (cells that have a receptor)

- Monocyte: the most important >>> in blood it is called monocyte. However when it moves toward the cell or tissue it is called microphage
- Dendritic cells
- Endothelial cells
- Lymphocytes
- Neutrophils

How do they recognize the injurious agent? Through RECEPTORS

We have to know that the receptors recognize **<u>only</u>** ***<u>molecules</u>*** (protein, sugar, DNA, RNA …); *they don't recognize pain or pressure.*

*** There are two types of receptors in our body:

1. ***Specific receptors***
2. ***Non-specific receptors***

Nonspecific receptors are called pattern recognition receptors, because they recognize structures common to many microbes or dead cells.

BUT WHY these receptors are not specific? Because inflammation is the first mechanism that protects our bodies (first line of defense); so we need it to be non-specific, also there are a limitless number of foreign antigens that they may detect.

To understand the meaning of a pattern; here are some examples :

- Lipopolysaccharides are found on bacterial cell walls; so we need to recognize them as a whole family without knowing the sequences of any of it (any family of lipopolysaccharides).
- They recognize DNA without looking at the sequence of DNA; if the cell is injured and DNA moved outside of the nucleus, an abnormal condition, the receptor can recognize that there are nucleotides in the cytoplasm and act.

So pattern recognition receptors are a group of molecules that recognize certain molecules but not specific ones.

On the other hand, specific cell receptors can only detect one specific antigen. For example, they recognize certain proteins with specific amino acid sequence and certain conformational structure, not anything else." They are used in immunologic reactions "(immunologic reactions are considered as a late response).

PATTERN RECOGNITION RECEPTORS (Two Families)

- ✓ **Toll-like receptors**
- ✓ **Inflammasomes**

*** We have two types of inflammation:

1. Inflammation caused by **infection** >>> uses **toll-like receptors**
2. Inflammation caused by other factors; such as hypoxia, heat and pressure (**non-infectious**) >>> uses **inflammasomes** (triggered by the products of cell injury).

✓ Toll-like receptors

"Microbial pattern recognition receptors"

Scientists discovered a receptor which can recognize infectious agents in the *drosophila* at first and they called it toll. Then when they discovered it in humans they called it toll-like receptor (toll in German means good or great).

Toll-like receptors can **only** recognize ***infectious agents,*** such as***;***

- bacterial products: endotoxins, lipopolysaccharides or DNA,
- viral products: RNA,
- and patterns: e.g.: liposaccharides in general, not a specific type, DNA chains, not a specific sequences.

Toll-like receptors are found in two places in the cell:

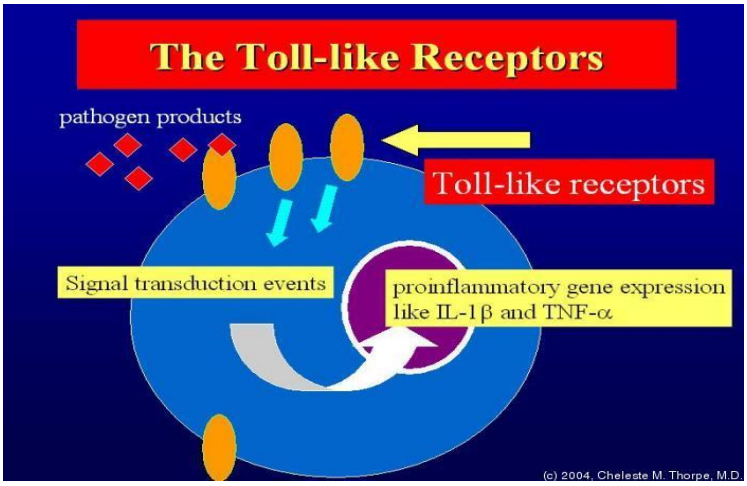
1. In the plasma membrane (cell surface).
2. Inside the cytoplasm.

So, they can recognize extracellular and ingested microbes.

Toll-like receptors deal with inflammation caused by infection.

At first, after recognizing the foreign body, they send signals (transduction factors/second messengers) to the nucleus; afterwards the nucleus starts to synthesize certain inflammatory mediators (chemical agent).

** We will discuss this mechanism in details in the mechanism of repair.



✓ Inflammasomes

"They are multi-protein cytoplasmic complexes"

In case of sunstroke, hypoxia, pressure… >>> There are receptors to recognize the products of the dead cells, such as uric acid, extracellular ATP, crystals (accumulation of molecules), some microbes…

***E.g.: An abnormal case when the DNA gets out of the cell and inflammasomes recognize this DNA.

This mechanism is important in many diseases such as Gout Disease >>>

-This disease happens by taking a lot of purines from excess consumption of meat.

-Purines break down into uric acid >> if the kidney can't get rid of this uric acid it accumulates and forms uric acid crystals >> these crystals get recognized by the inflammasomes and an inflammatory reaction starts.

How does the inflammasomes work? (Mechanism of inflammasomes)

When the receptor recognizes the products of cell injury, an enzyme called caspase1 is activated. Caspase1 cleaves interleukin 1 (IL-1) and makes it active. Then, signs and symptoms of inflammation appear due to the activation of IL-1.

**IL-1 protein is found in the cytoplasm and it is a potent (strong) mediator.

**Recognition >> activation of caspase1 >> cleavage and activation of IL-1 >> mediation of inflammation.

So, we have to ask ourselves, why do we study this mechanism??

Simply, to treat inflammation by knowing its mechanism.

For example:

1. **With a Gout** patient, if we know that there are uric acid crystals, we will block the IL-1 by a drug, so we can decrease the symptoms of this disease and help this patient (we didn't treat the disease, we decreased the pain).
2. **Diabetes** type 2, an abnormal condition, caused by free fatty acids. The receptor recognizes these free fatty acids and activates caspase1 which increases IL-1. That will cause destruction of islets of Langerhans cells in the pancreas, causing diabetes. So if we block IL-1 we will stop the damage.
3. **Atherosclerosis** is caused by accumulation of cholesterol, which forms cholesterol crystals. They get recognized by inflammasomes, thus activating

caspase1 then increasing IL-1, which leads to inflammation and closure of blood vessels.

*so, again, blocking IL-1 will help these patients.

Note: both families of pattern recognition receptors are found on the cell surface and inside the cytoplasm.

★ You may wonder why when we blocked IL-1, we didn't treat the disease! ……. Well, sometimes we look to treat the symptoms rather than the disease itself; mainly because the treatment is not working.

How can we stop the inflammatory response? By blocking *IL-1*

Why do we stop inflammation, although it's a protective mechanism?

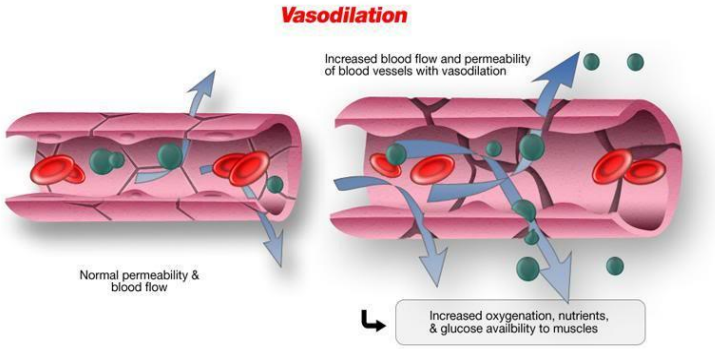
Because it may cause collateral damage and we need to cure it.

Second step: VASCULAR CHANGES in acute inflammation

Changes in blood vessels happen before the change in injurious cells or tissues.

At first the vessel undergoes transient **vasoconstriction** that lasts only for seconds. It is a protective response, due to neural reflex, then the **vasodilatation** begins followed by an i**ncrease in permeability.**

** The main purpose of vasodilation is to bring a lot of WBCs to the area, also to increase the permeability; to allow these WBCs to reach the injured tissue.



We have 4 mechanisms for increased vascular permeability:

1. **Contraction of endothelial cells** (most common mechanism)

Signals reach endothelial cells, then they contract >>> gap junctions between them widen >> permeability increases >> lymphocytes move out of blood vessels.

It is immediate but short lived.

**** Histamine is the common signal (mediator). Although, it is not the strongest one; but it's the first mediator to act.

**** The mediators that cause vasodilatation are the same mediators that cause increase in permeability.

**** Other mediators are cytokines, prostaglandins and nitric oxide.

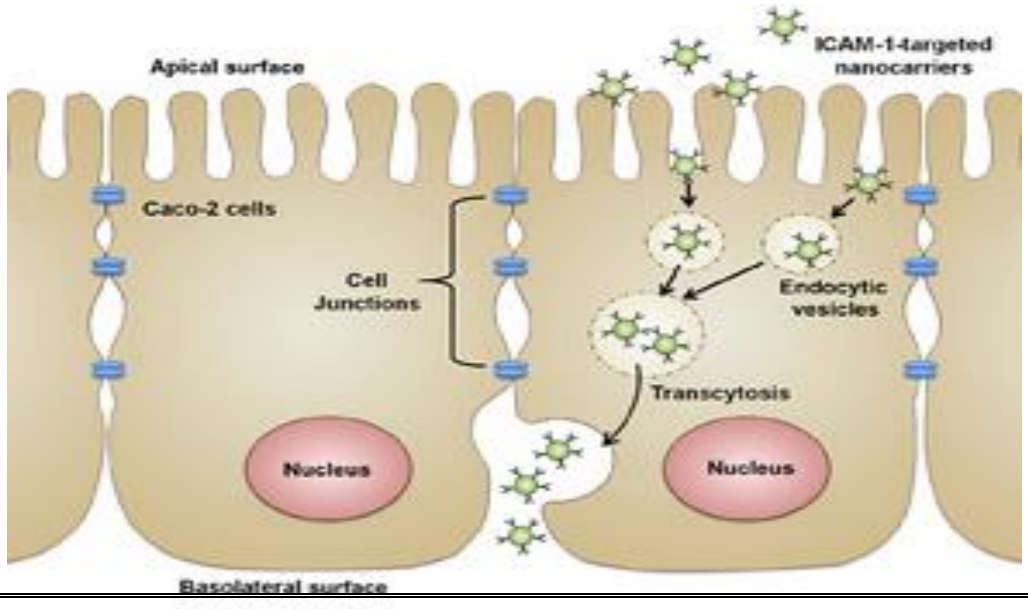
2. Endothelial cell damage

By severe damage, due to injurious agents (X-Ray, sunstroke), we lose the barrier that prevents fluid from going out of the vessels. That will cause the destruction of endothelial cells and increase in permeability.

It can start immediately but lasts for several hours or days.

3. Transcytosis

It means transcellular transport of certain extracellular components, 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; causing changes in osmotic pressure, so fluids move out.



4. **Neovascularization (** New blood vessels formed during repair)

   These newly formed blood vessels are not well-formed, thus they are leaky; since the junctions between the epithelial cells still are not well-formed, they will have a high permeability.

All these mechanisms are responsible for the movement of water with cells from blood vessels towards the tissue (extracellular) >>> Edema.

Clinical application

Inflammation >>> vasodilation >>> increase in permeability >>> cells and fluids move out >>> these fluids cause ***EDEMA***

So we have two types of edema:

1. ***Exudate***: caused by inflammation
2. ***Transudate***: caused by imbalance in the hydrostatic and oncotic pressure.

How can we know the types of edema from a sample of fluid??

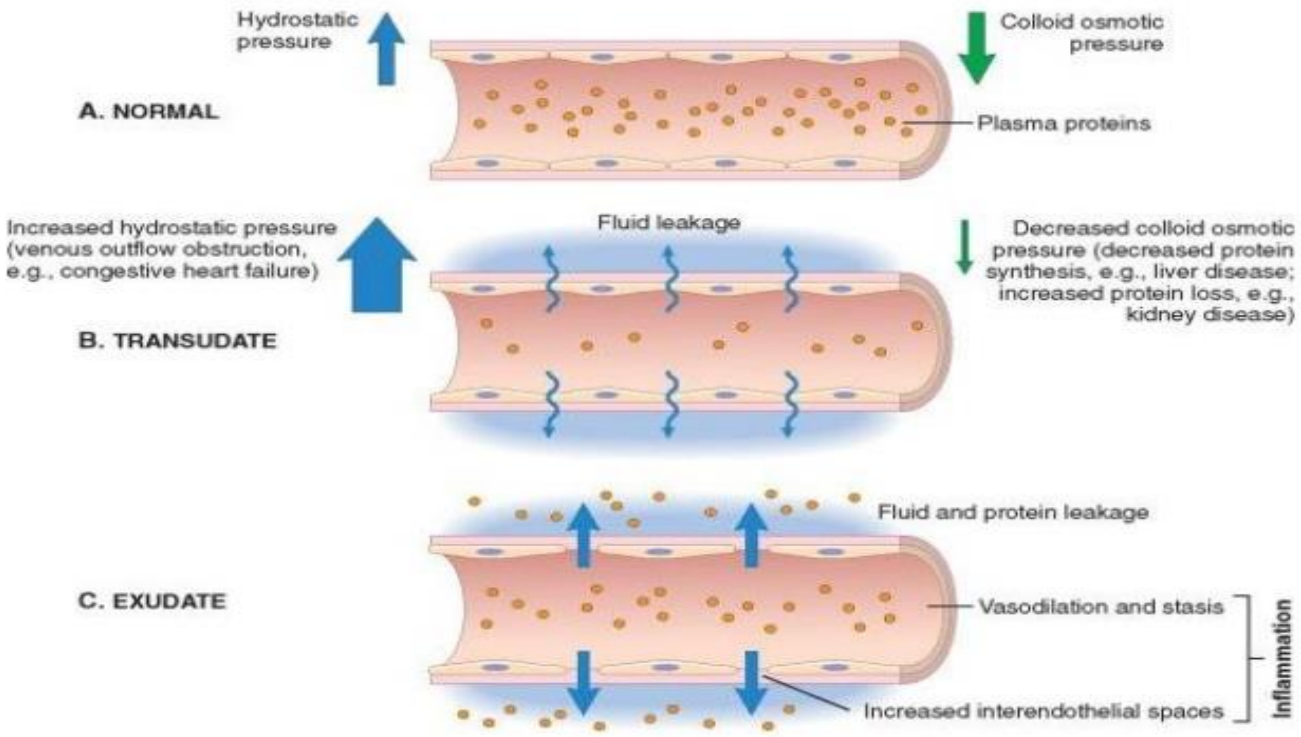
By contents:

Exudate: it is accompanied with cells, cellular debris and proteins >> high specific gravity.

Transudate: mainly water, low proteins, low cells debris, no cells >> low specific gravity (close to the specific gravity of water).

**Specific gravity = density of fluid / density of water

**Density = mass / volume



What is the difference between transudates and exudates?

Transudate

is a fluid with low protein content and a specific gravity of less than 1.012

It is essentially an ultrafiltrate of blood plasma that results from osmotic or hydrostatic imbalance across the vessel wall

without an increase in vascular permeability

Exudate

An inflammatory extravascular fluid that has a high protein concentration, cellular debris, and a specific gravity above 1.020

It implies significant alteration in the normal permeability of small blood vessels in the area of injury

Don't forget the homework on Dr. Heyam's website

GOOD LUCK "CURE"