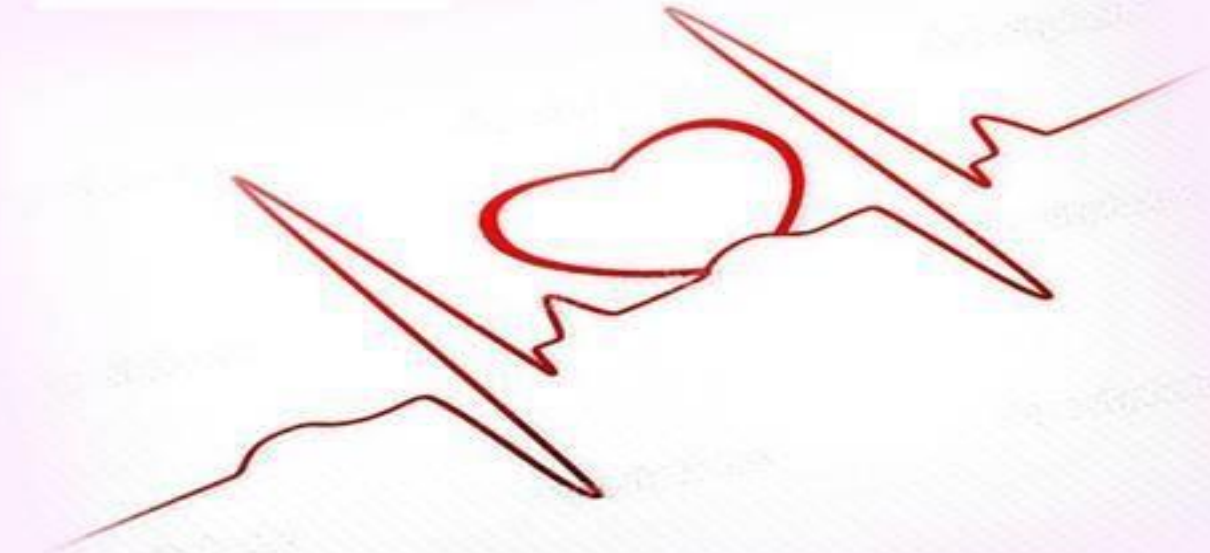
PATHOLOGY

Medical Committee
The University of Jordan

SHEET

SlIDE



Lecture Number: 7

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The Mechanisms of Inflammation

In the previous lecture, we gave a very brief picture about inflammation, today we are going to talk about **the mechanisms of inflammation**.

As we said, inflammation is a war, and when you are in a war the first thing to do is to recognize your enemy, because you don't what to kill someone who is not harmful to you, so the first thing you need is to recognize your enemy, the second thing is to bring your troops to the fight with you – recruit them, and your troops here are the white blood cells, the aim of this is to remove the agent that causes the injury and this needs to be regulated, because if it is too much this will cause harm to your body, so you need to regulate the process, because it should stop at a certain point, at last the resolution and repair.

So the R's you need to know, which are the processes that are involved in inflammation: recognition, recruitment, removal, regulation and resolution.

PS: some students asked the doctor about the studying technique for her lectures, and she recommended to read Robbins, also she said what she gives us is enough and that's what she's going to ask us about the exam, but she advises us to take a look at Robbins " and she's is saying that Robbins is not an easy book to read so warp yourself up bro and take a sneak peak at robins"

Okay back to these 5R's today we're going to talk about the first two: recognition & recruitment.

So recognition, how our cells recognize the microbial agents? The answer is, by receptors.

PS: a student answered: "chemotaxis, but the doctor said that this is another process.

SO, now we are talking about the first step in the inflammation, there is an injury, in order to make the inflammation happen we need to recognize that there is an injury, this process is called recognition, the cell recognizes that there is an injury

that there is a harmful subject, that there is a non-self thing that bind these receptors.

So we need receptors to recognize that there is an injurious agent, for example: a bacteria, sometimes we need to recognize the products of the injury, if we have hypoxia, we don't have a receptor to tell us that there is a hypoxia or there is low oxygen, we can't have a receptor for that but we have a receptor for the result of the injury we have a receptor for the necrotic tissue for example.

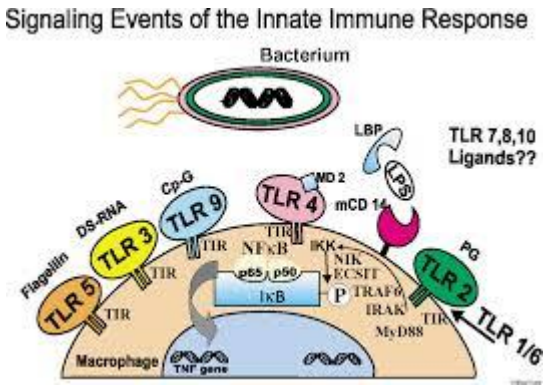
SO, the first thing is to recognize the enemy as an enemy, recognize the non-self, recognize the offending agent, and this is done by receptors.

Now, where do you think that these receptors should be in the cell? In the cell membrane, because many injurious agents are outside the cell, and we need to recognize them from outside, so the receptors must be outside.

Is there any place that the receptor can be? It can be found intracellular sometimes in the cytoplasm especially if we we're talking about the necrotic byproducts or intracellular organisms if they escaped from the first mechanism "membrane receptors", they can be recognized from the inside.

Also we can have receptors in the lysosomes, the phagosomes or the endosomes, we can have receptors there to recognize the engulfed bacteria or the engulfed causative agent, and these are the three sites where we need receptors to be. Outside in the cellular membrane & inside in the lysosome and the cytoplasm.

Now let's talk about these receptors, there are receptors for microbes that are specific for microorganisms and they are present in a group their family name is **toll-like receptors**, toll " this name came from German scientists that discovered genes in the drosophila (it has genes that are similar to ours " from here we had the word like) and this is great!, THIS IS TOLL ☺ , toll means great"

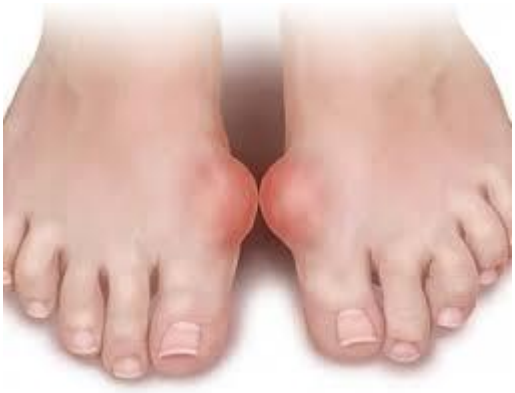


So, toll like receptor are receptor to recognize microbes.

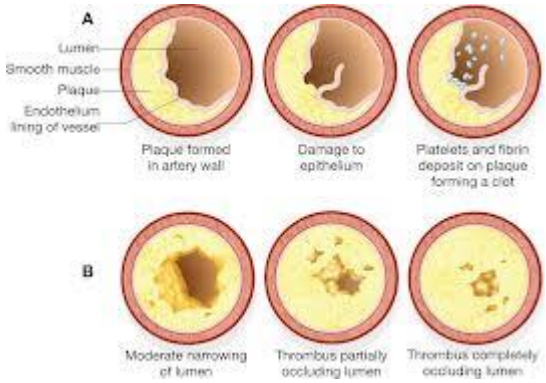
We find them in the cells that encounter microbes like white blood cells, epithelial cells so they don't enter from the skin and dendritic cells (is very important antigen-presenting cells and we're talking about them later) and microphages because we need them to be engulfed. So most types of cells have these receptors because we have many cells that encounter bacteria.

PS : toll like receptors are not specific they recognize general things in the products of bacteria, because it doesn't recognize the hole protein it just recognize a group of the protein, so it can recognize several proteins if they have the same group.

So, another type of receptors is needed to recognize the byproducts of cell damage, these are called **sensors of cell damage**, this the second type of receptor that's needed to recognition, so these receptors doesn't recognize that this cell is damaged it recognize the products of cell damage, for example gout disease, and its caused by uric acid accumulation which is a product of protein, so we're talking about something damaged a protein damage, or even DNA damage can cause production of uric acid, now this uric acid is recognized by the sensor of cell damage and it causes an inflammatory response in gout.



Another example about sensors of cell damage are cholesterol crystals which are products of cell damage which are recognized by sensors of cell damage, they accumulate in the blood vessels and when they are recognized an inflammation happens and a disease occurs which is arthrosclerosis .



In other cases when the DNA come out from the nucleus into the cytoplasm it will be recognized as non self or if it is damaged it will be recognized as non self or when the damaged cell is engulfed by phagocytes the DNA are recognized by sensor of cell damage and they can also cause an inflammatory response.

So these receptors recognize the byproducts of cell damage and begin the cascade of the inflammation

PS: ATP is recognized as a byproduct of mitochondrial damage and it has its own sensors of cell damage.

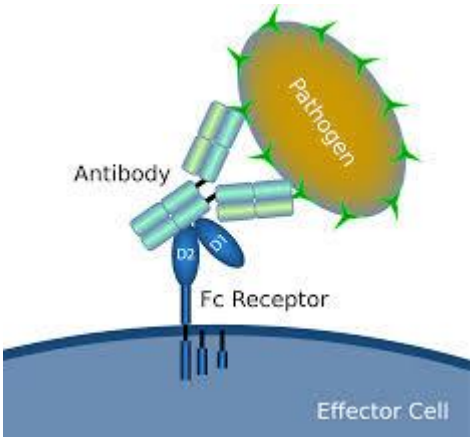
The mechanism of these receptors:

When these receptors are activated they activate a protein complex which is called inflammasome " inflama means cause inflammation ", this inflammasome acts by producing interleukin 1, and one of this interleukin's functions is to recruit cells " step 2 ", so this is the cascade that happens, it starts with the recognition the activation of the inflammasome then the inflammasome activates interleukin 1 after that we will end up with the recruitment of white blood cells.

So all cells have these receptors, because all of them need to recognize cell damage.

And the location of these receptors is in the cytoplasm, because the damage happens inside the cell not outside, so it doesn't make sense for having them outside the cell, so they're located mostly in the cytoplasm.

Also white blood cells can express certain receptors for the Fc part of the antibodies and the complement components as we took in the biochemistry, they indirectly recognize the microbe by recognizing the antigen.



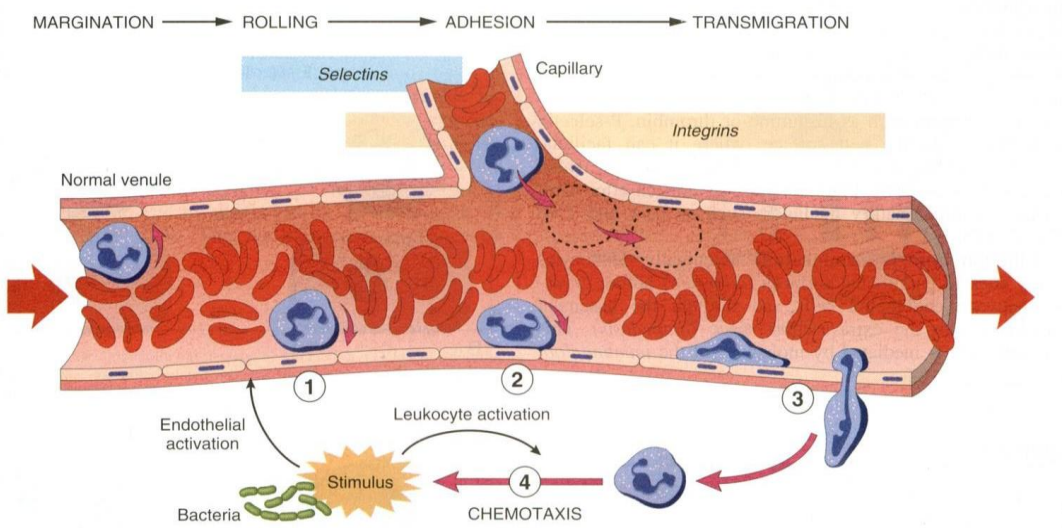
But receptors isn't the only way to recognize things, we can also recognize things by touching them, there are other mechanisms for recognition, such as circulating proteins, that can mainly recognize microbes such as complement proteins, "mannose binding Lipton _ we won't be asked about it _ just for more info ", and mannose means sugar, so it recognize the sugar in the bacteria. And collectins. " all what you need to know is the complement ".

Complements are proteins that recognize injurious agents.

So to sum up the first R, recognition is done by two means: receptors these receptors are divided into 3 types "toll like, sensor of cell damage, WBC receptors" and the other mean is proteins "complement protein mainly"

After we recognize we recruit white blood cells, the second step in inflammation progress is recruitment.

How we recruit white blood cells it starts with margination, rolling, adhesion, transmigration and then chemotaxis.



So the first thing is margination, normally we find white blood cells at the periphery of the blood stream, the first thing to happen in the margination process is some stasis "slowing"

This stasis gives more chance for the white blood cells to gather at the periphery, so this is how margination happens it is a physical thing it doesn't involve any chemical agents. So the doctor repeated this statement again this process is only a physical process that happens by stasis "and it could be an exam question"

The second thing is rolling, rolling means that there is some adhesion, but it's not tight enough so they associate themselves again, move again, adhere again , this will slow them down so the target of rolling is to slow the white blood cells down, when they slow down they have more chance to adhere tightly, so rolling and adhesion have the same target, rolling is as sort of adhesion which sort of transient " remember that the aim of rolling is to slow them down, and this will give them chance to adhere tightly to the endothelial cells that lines the vessel ", rolling is followed by adhesion, rolling is transient, but adhesion is tight so both are caused by the same mechanism, and here we need a complementary adhesive molecules which are found in the endothelial cells and the white blood cells in a complementary fashion "like sticking a paper by putting glue at both side you need to stick", so what causes rolling and adhesion? The answer is the adhesive molecules, and why the rolling is transient and the adhesion is tight? because we

have different adhesive molecules , we have two types the selectins and integrins , selectins are the adhesive molecules that adhere them in a transient way , so they are weak adhesive molecules, and the firm adhesion is caused by integrins _ v cam & I cam { vascular & intracellular adhesive molecules }and these molecules hold the cell tightly " if you look at the book you will find lots of names for the adhesive molecules , but you don't need to go through all this details just know the basic idea".

So. Rolling and adhesion is a chemical process, all what you need to know is the adhesive molecules must be complementary, they are divided into selectins for weak adhesion and integrins for tight adhesion.

PS: complementary means that these molecules interdigitate between each other {lock and key}

Ps: lock and key model is not specific, and it's an old theory for understanding the complementary binding and its substitute is the induced fit model.

Keep in mind that the selectins are used in rolling, cause it a weak adhesion, but in the adhesion process we need integrins to have a firm adhesion "like using either glue or superglue"

Now the migration process , which is the goal of the hole process in order to get the WBCs to the inflammatory site, so these WBCs leaves the vessel from the pores between the endothelium, but these pores are not wide enough, so we need the white blood cell to change its shape for this also we need another type of adhesive molecules so that it can leave, these adhesive molecules between the endothelial cells grabs the white blood cell and let it slide through the endothelium pores, these adhesive molecules are called p _cams means platelets endothelial cell adhesion molecules " don't care too much about the name ", so these p – cams are transmembrane proteins, this differs than carrier proteins because carrier proteins allow chemical agents to go in & out but transmembrane proteins are proteins that spread along the whole thickness of the membrane.

After leaving the endothelium, the cell will encounter the basement membrane, and as we know the basement membrane is made mainly of collagen, so we need to digest the collagen so that it can leave, but we don't have gaps in collagen, it's a

fibrous tissue, so it need to digest it first in order to leave, by an enzyme called collagenase so it secret collagenase and this will allow the WBC to leave the basement membrane

Now the cell will move to the site of injury in a process called chemotaxis, which is a process in which the cell moves towards a chemical gradient, so there is no movements of any chemical, and these white blood cells move by making extensions or pseudopods that pull it toward the gradient.

But what is the composition of that chemical gradient?

Its composed of both exogenous and endogenous products, the exogenous products are the bacterial products " like it telling the cell to come and eat it " these products includes proteins and lipids that cause the chemotaxis for the white blood cells, but these products must have a complementary receptor in order to move the cell, so it's a specific process in a lock and key fashion, and each type of bacteria make chemotaxis for specific type of white blood cells: neutrophils, mast cells, etc. Endogenous substances like cytokines and from these chemical we have a small family called chemokines, interleukin 8 is one of these chemokines "this name is important " and it's a strong chemotactic agent. Complement are important to the cause a lot of things "such as recognition", C5A cause chemotaxis and also the arachidonic acid metabolites especially lekutrinB4.

How do they work?

The white blood cells recognize these substances also by receptors when these receptors bind the white blood cell they will cause formation of the pseudopod toward the chemical gradient.

A student asked about the state of these complement, they are preserved in an inactive state for preventing a spontaneous cascade of inflammation.

Finally, these 5 R's happen mainly in the acute inflammation, because in the chronic inflammation we don't have resolution and repair – but we have the same first steps.

Written by Mohammed Al Adawai