Immunology
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Lecture-7
Inflammatory Response

So welcome to the lecture 7 of our immunology lectures. So, in the last class we discussed about the innate immune system.

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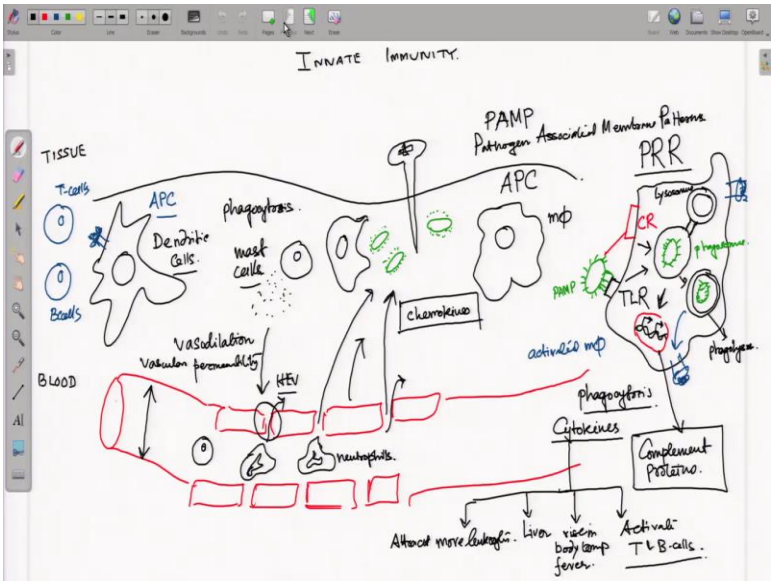

And if you remember the last time the picture, so we have discussed about how the immediate response to a foreign invasion starts or is initiated by the innate immune system. And the major cells that are involved in this response are the neutrophils which are the fastest acting cell of the immune system. So, the neutrophils they move to the site of action and then there are many other cells of the immune system like the mast cells, the tissue macrophages, the dendritic cells the antigen presenting cells which then phagocytose; the pathogen or the bacteria and transfers the signal to the adaptive system.

I told in the last lecture that the innate system is the first line of defense and it tries to restrict the bacteria or the pathogen that has infected our body or invested our body and it tries to kill that on the first site. While in doing so it can lead to a complex response which we sometimes described

as inflammatory responses. And this inflammatory responses can be local responses or they can be global responses or acute systemic responses.

So the local responses or the local inflammatory responses are primarily mediated by the neutrophils, the mast cells and to some extent by the activated macrophages as well. And then when there is phagocytosis, internalization of the pathogen and secretion of the cytokines. Then there can that can also lead to a systemic response. So, one of the major phenomenon that is very central to this inflammatory response is the migration of the leukocytes to the site of action or to the tissue where actually the damage has occurred.

So because these leukocytes there in the bloodstream primarily so now they have to move to the site of action and one of the major cells that mediate this inflammatory response is the neutrophils and the mast cells. So, the neutrophils has to go there and how do they go there immediately? So, what it has been seen that immediately after an infection or and tissue damage the number of the neutrophils they increase almost 10 folds.

Already the neutrophils are the number of the neutrophils are very high in the blood and that even increases even by 10 folds and that neutrophils those neutrophils they start to migrate they start to migrate to the site of action or the damaged tissue where the pathogen has infected. Now how does this happen? Let us for the time being leave this picture here and whatever we have seen in the last class so we will leave this picture here.

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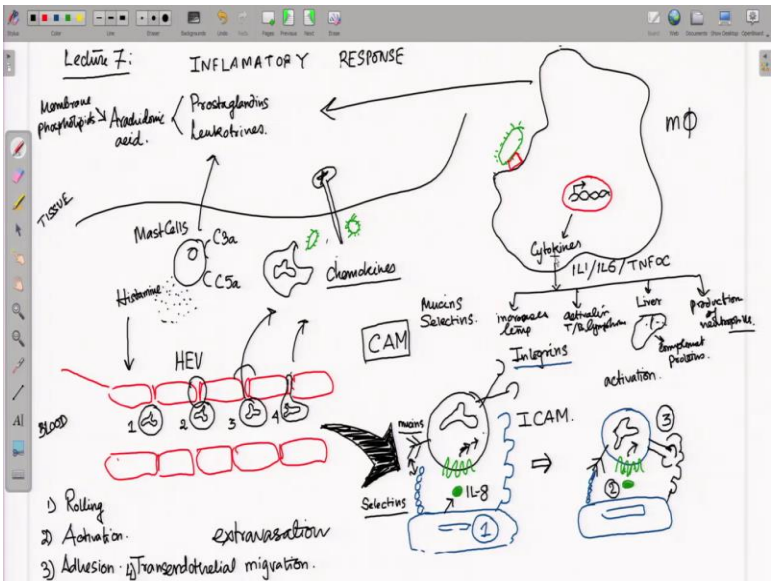

And we move on to the next page and see what actually happens during an inflammatory response. So, from the last class we have seen that the tissue macrophage so this is the tissue macrophage or the antigen presenting cell the macrophage or the antigen presenting cell has already engulfed or phagocytosed a bacteria or a pathogen and have started secreting the cytokines. So, these are the cytokines that are secreted as an immediate response after internalization of the bacteria.

So now this is an activated macrophage on the right side. And this is the blood so this is the blood part and let us say this is the tissue. So, and here we have a damage on the tissue may be due to a nail piercing or something like that. So, then we have the bacterias here or the pathogens that has entered the body in this part and we have the neutrophils moving to this part. So, this to some extent looks still very familiar from the hour from our last class.

And now also you have the mast cells. So, now the question is in response to this how these cells or these neutrophils and the other cells of the immune system of course and primarily the neutrophils we are talking about the neutrophils primarily how they migrate to this site of action and mediate the inflammatory response? So, this migration of the neutrophils to the site of action is also a part of the inflammatory response.

And this migration of the neutrophils is also the process is also sometimes known as extravasation. Because they cross the blood vessels and where do they cross from so they cross from this regions on the blood vessels which are known as the high endothelial venules or the HEV the high endothelial venules from there they cross it. Now this process of migration of the neutrophils which as I described is a part of the inflammatory response this occurs in steps and this is also mediated by certain mediators which are known as the CAM's or the cell adhesion molecules.

The CAM the cell adhesion molecules, if you look into this picture here this part so this is just a magnified diagram of what we are seeing here and single neutrophil and an endothelial cell which is magnified in this region. So, there we can see there are at least 4 different classes of this CAM's or the cell addition molecules. And these are the mucins which are usually expressed on the surface of the neutrophils.

So these are the mutants, the selectins, so the selectins which are usually expressed on the surface of the endothelial cell. Then you have the integrins and a fourth class of the cam which are known as the ICAM which are also known as the immunoglobulin superfamily cell addition molecules or the IG superfamily CAM's or the cell addition molecules and that is why they are known as the ICAM's. So, now what happens in this part so this migration of the neutrophils this occurs by 4 different steps.

If you see here the step 1 the step 2 the step 3 and the step 4, so the step the 4 different steps are step 1 is known as rolling, then it is activation, then addition, and then finally trans endothelial migration. Now if you try to correlate this 4 steps 1, 2, 3 and 4 in this region here so step 1 is rolling step 2 is activation step 3 is addition and the 4th is the trans endothelial migration that means it migrates through this high endothelial venule and crosses the blood vessel and enters into the tissue and goes to the site of action.

So now we try to understand the four different steps and how this four different steps actually occur. The first step so the first step is initiated by the binding of the mucins to the selectins. So, the musings are a class of the CAM's or the cell addition molecules that can specifically bind to

the selectins which have been expressed on the surface of the endothelial cells. So, the mucin binds to the selecting and as this binding occurs so the cells which were kind of flowing in the bloodstream they are now attached to the endothelial cell the first step of attachment.

And they start to roll on the on the surface they start to roll. The second step is very important that is the activation. Now activation involves the effector molecules or the chemokines. So, we will describe or we will discuss about the cytokines and chemokines in our later classes in details for the time being we just try to understand how these chemokines as the name suggests they are actually chemo attractants. So, they attract something.

So the chemokines usually work by binding to specific receptors expressed by specific cell types for example neutrophils they express a class of chemokine receptor. The T-lymphocytes express a class of chemokine receptors. The b-lymphocytes they also express a class of chemokine receptors. So, most of the cells of the immune system they on their surface have the chemokine receptors being expressed so, if you look into the picture here this here is a chemokine receptor for example which is expressed on the surface of a neutrophil.

And this green circle here this describes the chemokine. So, now a chemokine is being secreted by the endothelial cell and by virtue of that so the chemo crime to chemokine receptor is something like a iron to magnet attraction. So, it is just iron magnetic attraction. So, now when there is a chemical present in the surrounding and a cell which has on its surface which is expressing a chemokine receptor then it will be quickly attracted towards that chemo that towards that chemokine.

So that is the principle of chemo attraction. So, this cell will now get attracted towards the endothelial cells and there are some downstream signaling here inside. There are some downstream signaling we are not describing those signals for the time being. So, what happens is now if we look into the next step that is the activation step. So, this step here describes the first step or the rolling step so it is only binding of the selecting to the mucin thus the cell has just anchored.

So it is just anchoring of the cell on the endothelial surface on the endothelial cells and by the Select by the selective mucin interaction and then there is release of the chemokines and this leads to the chemokine binding to the chemokine receptors and to cell, so immediately it is more attracted towards a endothelial cell the chemokine binds to the chemokine receptor and here the mucin which is already bound to the selectin molecule like this.

And then you have another class of the; there is another class of this cellavision molecules which are the integrins. Now there is integrins they are present in a given conformation if you see in a conformation something like this in a crossed conformation that is something like this in a crossed conformation. Now when there is a chemokine binding to the chemokine receptor there are downstream signaling leading to reorganization of the integrins that means there is a change in the conformation of the integrins.

So the integrins which were initially looking like this they become like this so they arranged in a different way. Now these integral molecules or these integrins cell addition molecules they become competent to bind due to this conformational change they become competent to bind to another class of cell addition molecule which are known as the ICAM's. So, now these integrins and this process is known as the activation. So, when there is the chemokine binding to the chemokine receptor that leads to reorganization of the integrins.

And this reorganization allows the third step to occur. So, this is the second step and then there is activation and then there is addition. So, this allows it the third step to occur where this ICAM to integral interaction is completed. So, this ICAM to integrins interaction is completed. And now the cells they adhere more firmly to these endothelial cells. So, this is the step three and then due to the opening of this high endothelial venules.

The high endothelial venules are opened up and then there is trans endothelial migration that means now these cells can quickly move on and move out of the bloodstream and go to the tissue. Now as soon as it goes to the tissue now the question is it goes it goes out of the bloodstream that is fine now how does it reach the site of action? It has to reach the site of action

also. So, it has to go to the site of action, so now there are further further chemo attractants there are more other chemo attractants.

In this tissue in this region there are other chemo attractants and there are also presence of chemokines of course chemokines and other than chemokines there are other chemo attractants as well that also attracts this neutrophils or the other cells of the immune system to go to this site of action. Among this among them are the chemokines the some cleaved complement products we will discuss compliments in details and then we will at that time we will discuss more in details about the complement mediated, the complement cleaved products and complement mediated inflammatory responses.

So there are complement cleaved products like C3A and C5A which can also act as attractants which can also lead to which can go and bind to the mask cells. So, this complement clip products like C3A, C5A they can go and bind to the surface of the mass cells and they can also lead to the degranulation of the mast cells leading to release of histamine. And this histamine is actually what is it doing it is increasing the vascular permeability and by that it is allowing more of this trans endothelial migrations through this trans endothelial migration is more facilitated.

So, the more cells it leads to vasodilation this increases of vascular permeability allows more neutrophils and more cells to go to the tissue and there are other chemo attractant in this area which actually helps these cells to migrate to the site of action. Apart from the histamines apart from the histamines this granulocytes like the mast cells for example the mast cells as well as activated macrophages they produces other types of small molecules or effector molecules other than histamine like the prostaglandins the leukotrienes which are also mediators of inflammation.

So there are several mediators of inflammation so the process of inflammation primarily starts with migration of the leukocytes the primarily the neutrophils the neutrophils have major role in inflammation because they are the fastest acting cells which of the immune system which goes to the site of action and the movement of the neutrophils from the blood to the site of action is primarily assisted by this kind of cell adhesion molecules the specialized cell addition molecules and certain chemo attractant like the chemokines for example.

And of course chemokines are a class of cytokines we will discuss them later on and then you have this activated macrophages and the my tissue mast cells which produces certain small molecules like histamine, the prostaglandins and the leukotrienes which also are mediators of a inflammatory response. So, these are all responsible for local inflammatory responses and that can lead to; so whenever you have for example an insect bite let us say an insect biting or a nile going in or a small pin sharp object going in damaging your tissue then you can have a redness or swelling in that area.

So these are local responses and this can occur from this kind of mediators of inflammation like histamine, prostaglandin leukotrienes because they are all most of them increases vascular permeability and they also assist in movement of the neutrophils to the site of action. So, these prostaglandins and leukotrienes they are also secreted from the both from this activated macrophages they can come from activated macrophages as well as the mast cells.

And how do they come from so they are basically products the precursor of this prostaglandins and leukotrienes are the arachidonic acid which originates from the membrane phospholipids. So, this we will discuss more in details when we will be discussing about hypersensitivity reactions. For the time being we just know that these prostaglandins and leukotrienes they come from the arachidonic acid and they are produced by the mast cells as well as from activated macrophages and as well as there is histamine from the mast cells. So, they all of them their main function is to activate to increase the vascular permeability and to bring more and more of the neutrophils to the site of action.

And now if you look into this activated macrophage on this side this activated macrophages as we described in our last class secrets cytokines and what does this cytokines do? So, these cytokines can lead to some global responses like increase the body temperature increases temperature leading to fever. So, you can have high body temperature activates the T and the B lymphocytes, activates lever to produce more of the proteins like the complement proteins.

And they can also lead to production of increases the production of the neutrophils. So, there are certain leading to some systemic inflammatory responses as well this from the response of the cytokines that have been produced from this activated macrophages. so, if we look into this overall picture what is happening in case of an inflammatory response we will see it is the innate immune system which is acting in response to a tissue damage or a pathogenic invasion.

And there is very quickly I try to summarize so there is this movement of the neutrophils, the neutrophils which are present in the blood they try to move immediately to the site of action because the neutrophils are the fastest acting cells. So, there are four steps in the neutrophil movement one is the rolling the second is the activation the third is the addition so adhering to the serve to the endothelial cells.

And the fourth is the trans endothelial migration. So, now these four steps proceeds by the action of certain cell addition molecules like the mucins the selectins the ICAM's and the integrins. So, the initially there is a mucin to selecting binding which we described as the rolling. Then there is activation. Activation is primarily because of this secretion of the chemokine the major chemokine that is involved here is interleukin 8, IL8 which is responsible for second step or the activation step.

So, when there is the chemoline were binding to the chemokine receptor here that lead activates and leads to rearrangement or conformational change of the integrins leading to or facilitating its binding to the immunoglobulin superfamily of the receptors of the cell addition molecules which are present on the endothelial cell leading to the third step or the addition. And then there is the fourth step or the trans endothelial migration.

And by that they migrate to the tissue there is neutrophils they migrate to the tissue and then inside the tissue there are other chemo attractant there are many other chemokines other small molecules that are present in the tissue which attracts these neutrophils more towards the site of action or the damaged tissue and brings them closer to the pathogen. And then they will start engulfing the pathogen.

And then there are the tissue macrophages which also initiates another parallel response there is a parallel response being initiated by the tissue macrophages where what we see on this right side in this part. So, now the tissue macrophages they can bind to the pathogen by recognizing the PAMPs as we had described in the last class. And then this whole set of action that starts on and then there is the cytokines which have been produced and the cytokines they mediate a lot of systemic responses.

At the same time the mast cells they are activated by the complement cleavage products mainly and leading to release of histamine leading to the release of the histamine. And also other molecules like prostaglandins, leukotrienes which all tries to increase the vascular permeability and allow more neutrophils to be produced more neutrophils to migrate from the blood to the tissue and coming to the site of action and enhance the inflammatory response.

So we have tried to summarize in from the last class. And this class what we can summarize is how the innate system tries to respond immediately when there is a invasion a foreign bacteria or a foreign pathogen invading our body. And what is the immediate response coming from the inert system and the local inflammatory responses that are initiated immediately. So, that is all for this class and we will continue describing all these more in details slowly in our next lectures, thank you for today.