Immunology
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Lecture - 47
Cytokines in Innate and Adaptive Immunity

So welcome and welcome back to our immunology lectures. So in the last lecture, we were discussing about the cytokines, in the last two lectures rather. And we will keep continuing on discussions on cytokines.

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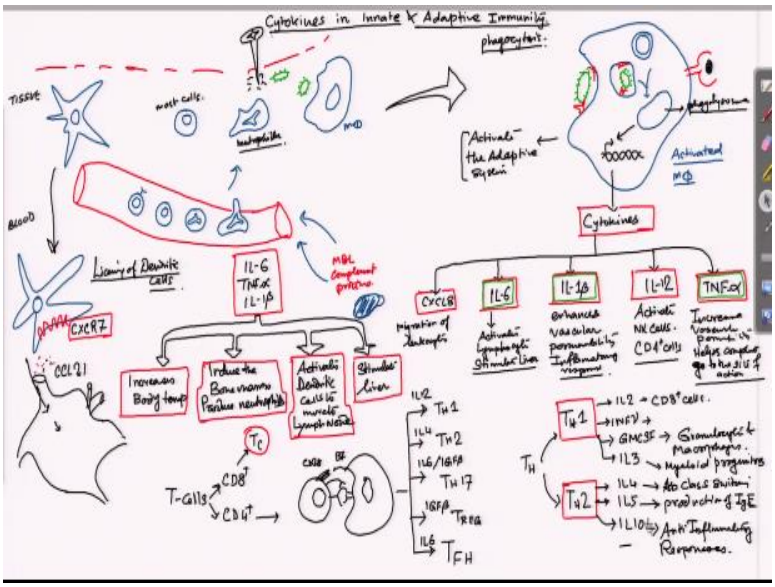

So we have learnt about what these cytokines are or what grossly they do. Grossly we have learnt what they do and what these cytokines are and how they act. So what is the function, what is the main mechanism of action of the cytokines. But we have not yet really explored the parts how or where the cytokines really work.

So as I told probably in my last lecture as well, that the cytokines are one of the major mediators and these are small proteins or glycoproteins, and they are the signaling molecules. So primarily cell to cell signaling and they are involved in both the innate as well as in the adaptive system. So cytokines are involved in both the innate system as well as in the adaptive system.

So it is not that they will only act on the innate system or only they are involved in certain adaptive pathways. So it is involved in everywhere and most of the cells of the

immune system or the immune cells, they secrete these cytokines under different conditions. Now who is the maximum cytokine secreting cells? So the answer is usually, the most of the cytokines are usually secreted from the activated macrophages.

And of course, also from the T-cells, the different types of the T-cells. So activated macrophages, where do we get them? So we get them primarily in the tissues, when there is an invasion or when there is a pathogen invasion. If you remember one of my very fast classes where I discussed about the different parts of the innate and the adaptive system and the different mediators of the innate immunity.

So in those sections, we had discussed about how a macrophage internalizes foreign pathogen or a bacteria by recognition of this PAMPs, this pathogen associated membrane patterns and other many other membrane patterns are there. And by that these cells of the immune system, they usually can engulf the pathogen. And macrophages are one of the major primary immune cells or the major cells, which can transmit this signal.

So they are transmitters of the signal. So they can also present the antigen on their surface by the MHC molecules. So they are antigen presenting cells. At the same time, they can secrete a lot of cytokines, a wide spectrum of cytokines are secreted from this activated macrophages. And these cytokines can do a lot of things. So if we come back again to the old setup where we started in the beginning like the innate system, the innate system mostly.

So if for example there is a tissue damage in this part and that leads to entry of the different pathogens in this region. So as we told that the primary cells that goes in this area or infiltrate this area are the neutrophils. So the neutrophils and the tissue macrophages and of course the mast cells or the granulocytes, so they all are present in this area. And these macrophages, they can do what is known as phagocytosis.

So this is the process of phagocytosis, you already know these things. So now once the macrophage has phagocytosed a pathogen or internalized the pathogen and has formed what is known as a phagolysosome, this is the phagolysosome. And this leads

to it sends some signal. And as we told we have different types of signaling pathways, and it sends some signal that leads to the gene transcription and secretion of the cytokines.

Now what these cytokines they do? I told in at least in two of my last two classes that these cytokines are the major mediators of or the major signaling molecules and they send a lot of signals. So it is not only in the innate system, but also in the adaptive system. So what this and at the same time, these activated macrophage can also at the same time it can activate, it can activate the adaptive system.

So this is primarily, this is done by this presentation of the antigen. So it is because it is an antigen presenting cell, so it can present the antigen. So now what are the different cytokines? So in one of my initial classes, I told up to this, that the macrophages, they can get activated by phagocytosis. After phagocytosis it is activated, it secretes cytokines, and then these cytokines can do a lot of things.

What are the things and what are the different cytokines that are being produced? So let us see, what are the different cytokines that are produced from an activated macrophage and what do they do actually. So one of the very important cytokines or rather it is a chemokines is the CXCL8. And this CXCL8 is actually required for migration of the different leukocytes.

So it attracts more leukocytes or helps in migration of more leukocytes to the site of action. We have learned about how this migration of leukocytes, migration of the neutrophils, they help in enhancement of inflammation, inflammatory responses. So this is one of the way that an activated macrophage can secrete the CXCL8, which is a chemokine.

And this chemokine in turn can lead to or can enhance the migration of more leukocytes to the site of action or it brings or attracts more leukocytes to the site of the action. Then we have interleukin-6. This is one of the very important cytokines, the interleukin-6. So it does is interleukin-6 primarily activates lymphocytes. So it activates the lymphocytes. We will see what interleukin-6 can do.

Interleukin-6 has a very important role in differentiation of the lymphocytes, particularly the T-cells, the T helper cells, and so it activates the lymphocytes, activates lymphocytes. And also it can stimulate the liver. Now why the liver? Liver is one of the main source of various proteins and various proteins which are the immune proteins involved in the immune system.

So like the complement proteins, for example. So they are secreted from the liver. So this IL-6 is one of the major cytokines which induces or which stimulates the liver to secrete more of these proteins. Then we have one of the very important cytokines like interleukin-1 beta or IL-1 beta. Its primary function is to enhance vascular permeability. And as well at the same time, it can also enhance the vascular permeability and enhance inflammatory responses, okay.

So then we have interleukin-12 or IL-12. So interleukin-12 which activates the NK cells or the natural killer cells. It can activate the NK cells, the natural killer cells, as well as it helps in the differentiation of the CD4+ cells. We will discuss about this how it helps in differentiation in the CD4+ cells or where it is required. So it helps in differentiation of CD4+ cells, this interleukin-12.

And then another important cytokine that is being secreted by the activated macrophage is the tumor necrosis factor alpha, the TNF alpha, the tumor necrosis factor or the TNF alpha. The TNF alpha also has a very important role in increasing vascular permeability. So it also increases vascular permeability and helps the complement proteins, the complement protein.

So the complement proteins as I told, the complement proteins are mostly secret from the liver, but they need to come to the tissue to the site of action. So TNF alpha is one of those which helps in the that brings the complement proteins and helps the complement proteins to go to the site of action, okay. So these are the five major cytokines or the five major class of cytokines that are being secreted by an activated macrophage.

And these are the different actions that these cytokines usually mediate. Apart from this, so now among these as I told the most vital of these cytokines are this

interleukin-1 beta, the interleukin-6 and the TNF alpha. They mediate a lot of inflammatory responses. Now these are mostly they mediate inflammatory response and how and what are the inflammatory responses these cytokines they mediate.

So if we look into the TNF alpha, the IL-6 and interleukin-1 beta. So let us see what exactly these four cytokines or these different four different cytokines they actually are doing. So firstly, they can increase the body temperature. So one of the major functions of these cytokines is lead to fat hypothalamus and increases the body temperature.

So now you can understand why we get fever when we have an infection or when we have some external pathogens infecting us, so we can have a fever. That is primarily mediated by this one of the cytokines. So and then that leads to a fat hypothalamus leading to enhancement or increase in the body temperature. So you get fever. Then they also induces the bone marrow to produce more neutrophils.

Induce the bone marrow and produce neutrophils, more neutrophils. So because I told the neutrophils are the fastest acting cells of the immune system, and they migrate to the site of action immediately. So the requirement of neutrophil is also high. So you need more neutrophils. So now this cytokines, they can enhance the neutrophils. So by inducing the bone marrow they produces more neutrophils.

And then they can also activate the dendritic cells. So this is one of the very important functions remember, because we also discussed previously, the dendritic cells are one of the major connectors between the adaptive, the innate and the adaptive system. So they connect between the innate and the adaptive system. Other APCs also do. But the dendritic cells are one of the major cells of this type.

And they need to go to the adaptive system. So they have to present the or help the adaptive system to develop the immunity. So how do they do? How do they go to the adaptive system? So that means, they have to migrate to the lymph node somehow. So they has to go to the migrate to the lymph node and meet the naive T and the B cells there.

So the naive T-cells and the naïve B cells they are waiting there and this dendrite cells are one of those major cells that connects between these two. And this process of movement from the innate to the adaptive system is usually known as licensing of the dendritic cells. So they become licensed to go to the adaptive system. So that means, they need a license or a pass to go there.

And these cytokines are one of those major mediators which helps in licensing of the dendritic cells. So they also activates the dendritic cells, activates the dendritic cells to move to lymph node. So the dendritic cell moves to the lymph node, okay. And as well as I told earlier, they also stimulate the liver.

So the liver which is a major producer of different proteins, like MBL, fibrinogen, complement other complement proteins, complement proteins, this mannose-binding lectin all these things, they are produced from the liver. And they go to the blood. Now, coming to this part. So this is mostly the innate part. So these are the cytokines, there are many other cytokines which are working in the innate adaptive system.

Sorry in the innate immune system. There are many cytokines, but these are the major cytokines or the major players that are secreted from immediately secreted after phagocytosis by an activated macrophage. And they mediate all these kind of different functions. Now what happens? Now this, let us come to this dendritic cell, the tissue dendritic cell.

The tissue dendritic cell as I told it has to migrate to the lymph node. It has to go to the lymph node and where they can activate and help in the process of differentiation of the T-cells, primarily the T-cells and the B cells as well. So now where what happens in these dendritic cells is that, this dendritic cells this dendritic cells on their surface, they start expressing the chemokine receptor.

For example, one such receptor is CXCR7. And as we describe the lymph node, so from the lymph node you have, it produces CCL21. So as you can understand from the nomenclature, the CXCR7 containing this R indicates it is a receptor. And CCL21 it is the ligand. So this CCL21 can bind to the CXCR7 and it can attract it towards the lymph node. So basically these dendritic cells, they can now enter the lymph node.

Now this process is called the licensing of dendritic cells. So you can see that the cytokines, rather the chemokines, which is also which also falls in the class of the cytokines, they have a very significant role in licensing of the dendritic cells, that is migration of the dendritic cells from the innate to the adaptive system. Now what happens in the adaptive system, we have learned when we have learnt about the T-cells and the T-cell activation and the maturation.

So we have learnt that the T-cells are activated by these antigen presenting cells by the class I or class II MHC molecules, depending on the CD4+ or the CDA8+ cells, which cell is being activated. So the T-cells, which are either CD8 or CD4, CD sorry, which are either CD8+ or CD4+ cells. So these cells, they usually develop into T cytotoxic cells and these cells, what is the fate of these cells?

So this CD4+ cells, they develop into the T helper cells. Now this T helper cells there again, when it comes to the T helper cells, the T helper cells or the TH cells, they are one of the major sources of cytokines. All these T helper cells, they produce different types of cytokines and the differentiation of this T helper cells that is different classes, that also depends on the presence of the cytokine.

What kind of cytokine is being secreted and what kind of cytokine is being present, depending on that it develops into a TH1 or a TH2 or a TH17 or Treg or T follicular helper cell. So this T-cells, they contain on their surface the T-cell receptor. And it can interacts, it interacts with one of these MHC molecules, the class II MHC molecules with the T-cell receptor and of course, the core receptor.

And then there is the CD28 interaction with B7, the CD28 to B7 interactions, all these things we have already discussed in our earlier classes. Now once this interaction occur, then depending on the types of cytokine that are present, they can differentiate into different types of T-cells. So if it is interleukin-12, IL-12 it usually produces a TH1 cell. If it is only interleukin-4, IL-4 it develops to a TH2 cell.

If there is interleukin6, IL-6 as well as IGF beta present it develops into a T helper 17 or TH17. If it is only IGF, if it is only IGF beta, then it develops into a T regulatory

cell. So Treg. And if it is only interleukin-6 present, then it develops into a T follicular helper cell. So we have seen these follicular helper cells, they are required in the B cell development stages in the lymph node.

So these are the different subtypes and they primarily are developed depending on the different types of interleukins or different types of cytokines that are present in the surrounding or in the environment. So now this TH cells or the T helper cells, the T helper cells are also major source of different cytokines that can mediate different functions. So in the adaptive system, so as we discussed this part mostly is the innate part.

So this entire part mostly is the innate part and this is the adaptive part and in the adaptive part, this T helper cells has a major role in mediating different in secreting different cytokines and mediating different actions. So when it comes to the T helper cells, the major two effector T-cells, the major two subtypes are the TH1 and the TH2, the T helper one and the TH2.

And these cells, they can produce different classes of cytokines that are involved in different important functions. So for example, TH1 can secrete interleukin-2. So TH1 can secrete interleukin-2. Interleukin-2 of course, helps in CD8+ cell differentiation. So a differentiation of the CD8+ cells.

Then it produces interferon INF gamma, interferon gamma, which helps in, interferon gamma is mainly involved in different, generating inflammatory responses in different non-viral infections. So type II interferon and then it can also produce the GMCSF, the granulocyte macrophage colony stimulating factor. So which mainly helps in production of the granulocytes and the macrophages.

So it produces more granulocytes, granulocytes and macrophages. It can also produce interleukin-3, IL-3. And interleukin-3 is mostly required for growth of the myeloid progenitor cells. Just like the TH1, the TH2 can also produce different types of important interleukins or different types of important cytokines like interleukin-4, interleukin-5, and interleukin-10. Interleukin-4 is primarily required for antibody class switching on the B cells.

So antibody class switching on B cells. Interleukin-5 is also required for class switching of antibodies and production of IGE, production of IGE. We will discuss about the IGE when we will come to the hypersensitivity reactions, immunoglobulin type E. And then it also produces interleukin-10 which is primarily an anti-inflammatory response, which is required for anti-inflammatory responses.

So looking into the overall picture back again, so if we start from here, so this cytokines as the, as today's lecture topic is, cytokines in the innate and the adaptive system. What are the different cytokines and what are the different roles they play in the innate and the adaptive system. So cytokines are mainly produced in the innate system. The cytokine is mainly produced from the activated macrophages.

And the major cytokines or the primary cytokines that have been produced from these activated macrophages are the CXCL8, interleukin-6, interleukin-1 beta, interleukin-12 and TNF alpha. And the CXCL8 as the name suggests it is a chemokine, it is a chemokine. It can help in the migration of the leukocytes. Interleukin-6 is primarily it helps in activation of the lymphocytes and it can also stimulate the liver.

Interleukin-1 beta, it enhances the vascular permeability and it can also enhance the inflammatory responses. Interleukin-12 activates the NK cells, the natural killer cells and the CD4+ cell. It can also help in the CD4+ cell differentiation as we have seen in case of the adaptive system. And then TNF alpha, the tumor necrosis factor alpha, which increases the vascular permeability and helps the complement proteins to move to the sites of action.

And then so these the combined effect of this the three major cytokines or this IL-6, the IL beta and the TNF alpha, the combined effect of these three cytokines primarily in the innate system, it increases the body temperature. So makes the hypothalamus fat, increases the body temperature, induces the bone marrow and it produces more neutrophils and sends more neutrophils to the site of action.

Activates the dendritic cell, so helps in activation of the dendritic cells and allows them to move to the lymph node. And it also stimulates liver to produce different

kinds of proteins like the complement proteins, mannose- binding lectins and all these things, which then circulates in the blood which goes into the blood and helps in opsonization of the pathogen.

And then at the same time, then you have this dendritic cells, the dendritic cells, they starts to express on their surface the CXCR, which is a chemokine receptor, so the CXCR7. And this CXCR7 is very quickly attracted towards the chemokine, CCL, CCL21, which is a chemokine. It is a ligand to this receptor. So that is why it is CCL and this is the CXCR. So once this is attracted, it enters into the lymph node.

And it goes to and it presents to the naive B and the T-cells. Inside the lymph node, the T-cells, they get activated and develops and then it differentiates into the different subtypes of the T-cells. You have the TH1, TH2, the TH17. So these are the effector T-cells. You have the T cytotoxic cells as well from the CD8+.

The CD4+ they after interaction with the antigen presenting cell, they can then differentiate into the different subtypes the TH1, 2, 17 or the Treg or the T follicular helper cells. And this basically depends on the presence of the cytokines which kind of cytokines is available, availability of the different cytokines. If interleukin-12 is available, it becomes a TH1 cell. If interleukin-4 is available, it becomes a TH2 cell.

When it is interleukin-6 and IGF beta it becomes a TH17. If it is only IGF beta it develops to a T regulatory cell or Treg and if it is only IL-6 it develops into T follicular helper cell. Now the two major types of this T helper cells which are the TH1 and the TH2 are the major producers of the cytokine. So they produce a lot of cytokines, different types of cytokines.

And they produce interleukin-2, interferon gamma, the GM-CSF, interleukin-3. And these are mainly produced from the TH1 and the TH2 produces IL-4, IL-5 and IL-10. So we will stop here for this lecture today. And so this is an overview of the cytokines action mostly what are the different cytokines. So I will not go into very details of all the cytokines, all of their actions that will be very complicated.

So it is better not to, so I tried to focus mostly on the major cytokines that are required in the innate as well as in the adaptive system that are produced by the innate system and what are the downstream functions they perform. So this was the major topic of, this was the topic of today's discussion. So we will not be I will not be telling you about all the different cytokines that are being produced by the different types of T-cells and what are the different functions they do.

So that is a very complex thing, very complex subject. You can read by yourself if you have an interest in it. So we will move on to a very interesting topic on another specific class of cytokines, the interferons. So we will be talking about the interferons in our next class. So for today, it is that much is enough. Okay. Thank you.