Immunology
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Lecture - 49
Hypersensitivity

Welcome and welcome back to our immunology lectures. So we have been talking about the cytokines, their effects and in the different immune systems. So we have kind of learnt what the cytokines can do, what the cytokines how they work and all these things. We have also gotten a very clear idea about the complement system, the complement activation and everything. So we will move on to our next topic today and that is on hypersensitivity.

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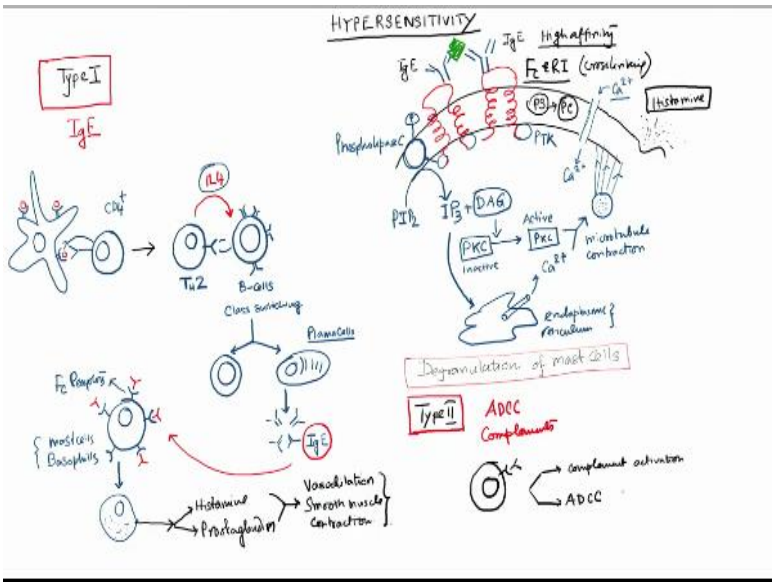

So the immune system when there is a foreign invasion, when there is a foreign pathogen attacking the immune our body or when there is a foreign invasion, we normally have a immune response. There is a immune response, the cells of the immune system, they immediately infiltrate that area, they go to that area and start to produce a response.

But sometimes, in response to certain environmental immunogens or antigens, there can also be a hyper response, that is a increased response. It is often called it is the need to I mean, it is kind of a very hyperactive response from the immune system.

And it is also kind of it probably the immune system does not need to respond in that way. And it is a pseudo response you can say also.

So there are specialized cells in the immune system, which sometimes does this kind of, elicits this kind of response. And this kind of hyper response to any kind of foreign invasion, we refer to it as hypersensitivity. That means the immune system has or shown a hypersensitive attitude towards that foreign antigen. And it is also a kind of an inappropriate, we can also sometimes it is described as an inappropriate immune response.

So it is not the appropriate immune response that should have developed. For example we face it very often like response to we can have response to dust for example. Some people have allergy for dust. Some people have allergy for the pollens and there can be many other ways of this kind of inappropriate immune responses. And this all together can be taken into consideration and sometimes they are known as hypersensitivity.

So we call it, the overall response together we call it the hypersensitivity reaction. Now these hypersensitivity reactions can occur in many ways. So there can be different types of immune responses, which there are different types of this kind of hyper responses from the immune system or inappropriate responses from the immune system when it comes in contact with immunogens or antigens, particularly allergens.

We sometimes also call them as allergens and that can lead to a hypersensitivity reaction. And the main manifestation of this kind of reaction is it will start having an inflammation to the major immune effector pathways and inflammatory pathway. So there is inflammation. And you can have histamine release, release of histamine and other inflammatory vasoactive amines, which leads to or enhances this inflammation.

And due to that you can have swelling, you can have local swelling, local redness. Even you can have systemic response and that can lead to fever and many things. So for example, a very common form of this hypersensitivity reaction is like allergic rhinitis. We all have it. We have during the change of the season when there is a

pollens in the air, and some people are very sensitive to this pollens and they can develop this kind of hypersensitive reactions.

And you can have a running nose. You can have cold, you can have fever. And all these are immune response to that particular allergen and that depends on that particular person's immune system, how he or she responds to that kind of an allergen. So this kind of immune responses can actually be again reclassified into at least four different types of hypersensitivity or four different ways the immune system can respond to these kinds of agents.

And one of the very commonest form of this response is the type I hypersensitivity. So type I hypersensitivity primarily is mediated by IgE. So it is an IgE mediated. So all these hypersensitivity reactions, let us be so there are at least hypersensitivity can actually be classified into at least four types. So we have type I. Then we have type II. We have type III and type IV.

So all these hypersensitivity reactions type I, II, III or IV whatever it is, all of these hypersensitivity reactions, they originate from, they can either be originating from the humeral branch of the immunity or from the cell mediated branch of the immunity. So they are usually either antibody driven or T-cell driven. So they are cell mediated. So for example, type I, type II and type III, these are mostly antibody driven.

Type I is IgE driven. It is mostly driven by IgE. Type two IgG mediated and type III is antigen antibody complex mediated. So it is formation of the antigen antibody complex. And type IV is mostly cell mediated. So it is T-cell mediated. So these are the four different types of hypersensitivity reactions that can occur. Either it can be IgE mediated, IgG mediated, or it can be an antigen antibody complex mediated or it can also be a T-cell mediated hypersensitivity.

So let us look into what exactly occurs in each of these hypersensitive reactions and what kind of manifestations they actually produce. So let us first concentrate on the type I, what is the type I hypersensitivity reaction and how it occurs? So moving on to the type I hypersensitivity reaction.

So as I told that most of these allergies that we see, allergy to pollen, allergy to dust, most of these allergy caused by the allergens that is the allergy causing agents, they are mediated by the type I hypersensitivity and they are mediated by IgE in immunoglobulin E. Now of course that means it involves the B cells. So then the initial part of this hypersensitivity reaction is initiated by this dendritic cells.

And these dendritic cells, as we described that these dendritic cells are one of the major connectors between the innate and the adaptive system. So whenever there is an allergen coming in into our system, these dendritic cells, they can actually process and present that allergen. So they can present the allergen and that, as an antigen, so that antigen is presented to the CD4+ cells.

That means the cells that develops into the T helper cells. So they are presented by the MHC class II and are presented to this kind of CD4+ cells. Now this CD4+ cells, this specific CD4+ cells, they become the T helper cells primarily the, it is a TH2 type response. So they develop into those cells, which developed into the TH2 cells. Why TH2? Now there is a question why TH2, why not TH1, why not the other cells?

So because the TH2, if you remember from our cytokine classes, that all these subsets of the T-cells or the T helper cells, effector cells, they produce different types of cytokines. And the T helper cells are the major producer of the cytokines that can help in class switching of the B cells. Because you need to class switch the antibodies on the B cells.

So they will start, now this B cell, so this T helper cells, they prime with the B cells, which are expressing antibody on their surface. Now these B cells they prime with this. So the TH2 type cells, they prime with this B cells and they start to produce this interleukin 4. If you remember from our cytokine classes, interleukin 4 is one of those major cytokines that is required for class switching. And this leads to class switching.

And that in turn actually helps these B cells to develop into either the plasma cells or the memory cells. Now this plasma cells, these are the plasma cells. Now these plasma cells, they will now start producing the antibodies. And these plasma cells,

they now start to produce the IgE, the immunoglobulin E. And this IgE, why IgE? Now this IgE is the major mediator of the type I hypersensitivity.

Now how it mediates the type I hypersensitivity? Now this IgE can now go and bind to, so the effector pathways are very much similar. That we have learnt earlier as well. The effector pathways and the effector molecules they are very much similar. So they are either the vasoactive amines like the histamines or there are lytic enzymes or complement activation. So these are the effector pathways.

So in this case, this IgE molecules they can go and bind to the surface receptors that are present on the mast cells or the basophils. So now they can bind to a specific class of receptors that are known as the Fc receptors. And this Fc receptors they are present on the surface of the mast cells or the basophils. So these are the mast cells or the basophils. So now and that leads to degranulation of the mast cells.

Now these mast cells which contains the granules and these granules are nothing but these granules are carrying the histamines. So the vasoactive amines and they will start to release the different vasoactive amines like histamine, leukotrienes and many other things. So they will start to release histamine, prostaglandin. And what do they do, these things? They collectively what they do is they increases the vascular permeability or they lead to vasodilation.

They can also lead to smooth muscle contraction and then you will have enhancement of inflammation. So there will be an enhanced inflammatory response and then you will start to have itching, you will start to have fever, you will start to have cold, you can have cough, you can have cold, you can have redness and swelling, a local swelling, redness, all these things starts to occur.

So these things are primarily mediated by histamine. And that is why if you now can connect these things, then that is why this when people have this kind of type I hypersensitivity, that can actually be treated, and how? It can be treated by taking antihistaminic. So a very simple way of doing it is by having or by intake of antihistaminic. So if you take antihistaminic drugs, then you can actually deal with this kind of hypersensitivity.

So there is a histamine receptors are then blocked and then they do not these histamine is cannot function and this kind of response cannot be elicited. Let us look into what exactly the mechanism of this hypersensitivity reaction is, how this reaction is mediated. So as we have learned that these B cells, they are primed and they are that there is a class switching.

And then they start producing the immunoglobulin E the IgE and this IgE actually leads to binds to the Fc receptors on the mast cells and the basophils and that actually leads to the degranulation of these mast cells and the basophils leading to formation of or release of histamine prostaglandin, which actually leads to the vasodilation and the smooth muscle contraction.

Now what exactly happens on the surface of the cell are in these mast cells, that leads to this degranulation process. So that process is also sometimes referred to as mast cell degranulation. So let us consider this as a double layered bilayer, lipid bilayer membrane. And on this membrane, we have this kind of receptor. So this is a receptor, let us say an Fc receptor. And this Fc receptor can bind to the antibodies.

So they can bind to the antibodies, the Fc region of the antibodies. And when there is the allergen is present, that allergen when the allergen is present here, let us say this is the allergen and if this allergen is present, this allergen binds to the antibody. So these are the IgE. These are the IgE immunoglobulin E. And this IgE can bind to the Fc receptor. This is a specialized is receptor Fc epsilon RI.

And these are also known as high affinity receptor. So they have very high affinity for this antibodies the IgE.. So these are the high affinity receptors. And when they bind to this Fc epsilon RI, they bind to this IgE that leads to cross linking of the receptor. So now the two receptors, they are cross-linked, they are together. So this is a receptor cross linking. So there is cross linking of the receptors.

And these receptors or all of these receptors, they are associated with protein tyrosine kinase. And then this protein tyrosine kinase is activated. And activation of the protein tyrosine kinase actually leads to phosphorylation of a component called the

phospholipase C. This phospholipase C is then phosphorylated. Now this phosphorylated phospholipase C has many functions.

What it does is this phospholipase C can now convert the phosphoinositol bisphosphate to inositol triphosphate that is IP 3 and diacylglycerol. I hope you know all these terms. If you have read Biochemistry and Molecular Biology, you have seen in cell biology signal transduction, you have already learned these terms or you have encountered these signaling pathways.

There is conversion of the PIP 2 two that is the phosphoinositol bisphosphate which is then converted to IP 3 or inositol triphosphate and diacylglycerol or DAG. Now this DAG, both of these components this IP 3 and the DAG, they perform separate functions. The IP 3 is primarily required for the release of calcium from the endoplasmic reticulum. So from the endoplasmic reticulum there is release of calcium.

And what this DAG does is it activates the protein kinase C. So the protein kinase C which is normally inactive is now active. PKC, now this is the active PKC. Now the active PKC along with the calcium these together they are required for contraction of the microtubules. So they are required for microtubule contraction process. And this, so now these granules these granules are nothing but sacs containing histamine and the vasoactive amines.

Now this granules, they can now due to the contraction of the microtubules they can now travel to and go and fuse with the membrane. And once they fuse with the membrane, there is exocytosis. So now there is exocytosis and release of this granules into the extracellular space leading to release of histamine or other vasoactive amines. And this process this entire process is known as the degranulation.

There is one more thing happening. So on the on this plasma membrane, this plasma membrane usually it is a lipid bilayer and it has the phosphatidylserine. So which is a lipid, so lipid molecule present in the lipid bilayer. And there is conversion of this phosphatidylserine to phosphatidylcholine.

So due to this receptor cross-linking, cross-linking of this Fc receptor, the Fc high affinity receptor another event occurs is conversion of the phosphatidylserine into phosphatidylcholine. And that leads to an increased fluidity of the membrane. So now the membrane fluidity starts to increase and now it opens up channels or pores for more calcium entry. So there is more entry of calcium.

So the calcium channels and the calcium pores they open up more and there is more calcium entry into the cell and that also assists this process of microtubule contraction and that pools the these granules or these sacs containing the histamine and allows it to go and fuse with the plasma membrane. Now once they fuse with the plasma membrane that leads to exocytosis of this and that.

So it basically delivers this histamines the materials it carries, it just delivers it outside the cell extracellularly and that leads to the degranulation of the mast cell. So this entire process, this entire process is known as mast cell degranulation of the mast cells. This also occurs with the mast cells and the basophils both.

So and this is how these vasoactive amines they come out of this mast cells leading to the all these manifestations or the inflammations, increasing the inflammations leading to vasodilation and smooth muscle contraction. And once there is vasodilation there is more immune cells, more of this leukocytes migrating into the site of the action and enhancing this whole process.

So this is the very summary of the type I the mechanism of the type I hypersensitivity reaction, how it occurs. And the main thing we need to understand is that the type I hypersensitivity is an IgE mediated process, that is an immunoglobulin E mediated process. And it starts with the TH2 cells, which are able to prime with the B cells and leading to the class switching of the antibodies.

And that leads to the formation of this IgE. Now this IgE, which are the allergens specific, they can bind to the corresponding allergens. And now this allergen which binds to this IgE can cross link the Fc receptors, the high affinity receptors present on the surface of the mast cells, the basophils leading to degranulation.

And this degranulation process leads to release of excess amount of histamine, leukotrienes prostaglandins, and all this vasoactive amines and that leads to the subsequent process of inflammation or enhancement of inflammation. So this is kind of the type I hypersensitivity and the type I hypersensitivity can usually be elicited by a wide variety of allergens like the pollens, like dust.

It is actually not, dust is actually not dust, it basically contains some proteases like DARP for example. So these proteases are actually the responsible for eliciting the hypersensitivity reaction. This protease is the allergen actually, it is not the dust. Dust does not mean anything. Dust is not just dust. So those people we very often say that I have dust allergy. We often say I have allergy to pollens.

So people who has allergy to pollens, they has to be very careful during the month of the spring when there are a lot of pollens in the air and that can cause this kind of type I hypersensitivity and leading to allergic rhinitis and many other manifestations in those people. So this is the type I hypersensitivity which we tried to understand. And then there we can, then there is a second type of hypersensitivity we call it the type II hypersensitivity.

As I told it is mostly mediated by the type II hypersensitivity. So the type II hypersensitivity as I told is mostly an IgG mediated, immunoglobulin G mediated hypersensitivity. So antibodies, which are produced against the cell surface antigens, they mediate the cell destruction. So this cell destruction can be many types. So one of the very commonest type is the antibody dependent cell mediated cytotoxicity.

We also call it ADCC that is antibody dependent cell mediated cytotoxicity. So it is a cell. There is a specialized cell which can kill the target cell. So but it is directed or governed by the antibodies. And there can also be complement activation, of course. So there can also be activation of the complements. So basically, when there is a target cell for example, when there is a target cell and there are receptors on the surface that binds to this IgG.

If this is the target cell, then that can either lead to recognition of these receptors. So they binds to so this so if these cells they have on their surface, for example, they

have on their surface the antibody receptors, like the Fc receptors for example, they can bind to these antibodies. And these antibodies actually can bind to the target and that can lead to ADCC, so antibody dependent cell mediated cytotoxicity or can also lead to activation of complements.

So complement activation or ADCC. So these are the two major ways it can mediated the type, it can mediate the type II hypersensitivity. Now type II hypersensitivity is a very common hypersensitivity in particularly in case of blood transfusion. For example, when there is this, we have this A, B, O, AB blood groups and of course, we have also this Rh antigens.

So the Rh negative or it can be blood groups can be Rh negative or Rh positive. So if somebody who is Rh negative receives an Rh positive blood, for example, then he or she will start to develop antibodies against the Rh antigen. And that can lead to a type II hypersensitivity. So this IgG can lead to a type II hypersensitivity reaction. And this is a very common case, particularly in case of woman during delivery of fetus.

So if a woman, if the mother for example, she has Rh negative blood group. So she is Rh minus. And the fitters somehow has Rh positive. So that means, now if by any chance that fetal blood enters into the mother's blood, that will elicit an immune response, very clear. So that will clearly start to elicit an immune response and immediately that will activate the B cells.

And the B cells will, this Rh specific B cells they will now start to produce either the plasma cells, the plasma cells which will produce the immunoglobulin against the Rh antigen and will clear up the cells or the most dangerous part is that they can start develop the memory against it. So if it keeps in the memory, so it will remember, so it will remind it, so it will remember and it can be deleterious, it can have deleterious effects if the mother conceives for a second time.

That means, if the mother has a second pregnancy, in the first pregnancy it is not a problem, because the mother's blood and the fetal blood is very well separated. There is very little mixing between the two blood. So the fetal blood hardly mixes with the mother's blood. So there is hardly any mixing of the fetal blood with the mother's

blood. So there would not be any response during that delivery, during that pregnancy.

But during the delivery, you have to there is a mixing of the blood. So now there is mixing of the fetal blood with the mother's blood and a lot of fetal blood can enter into the mother circulation, and that can lead to a global response and that can lead to a humoral response in the mother. So now if this Rh positive antigens enters into the mother's circulation that will start developing the, so the mother will start developing the antibodies.

So the antibodies will immediately come and neutralize and will clear those cells, the fetal cells for RBCs. But it will generate memory and this memory is dangerous. Because now if the mother wants to conceive for a second time or she has a second delivery, then the memory will still be there. And that can be that can have very dangerous deleterious effect on the next pregnancy or on the fetus.

Anyway, we will keep discussing on this topic on the type II and also we will learn about type III and type IV hypersensitivity a little bit in our next lecture. So this is all for today's lecture. Thank you.