Immunology
Prof. Agneyo Ganguly
Department of Biotechnology
Indian Institute of Technology-Kharagpur

Lecture - 50
Hypersensitivity (Contd.)

So welcome back to the immunology lectures and we were discussing in our last lecture, we were discussing about the hypersensitivity. We discussed about type I and a little bit about the type II hypersensitivity. And while discussing about type II hypersensitivity I was giving an example of this very serious issue of erythroblastosis fetalis. And what this erythroblastosis fetalis actually is?

So erythroblastosis fetalis as I told is a very severe hemolytic condition that can initiate if a mother's blood has does not have the Rh antigen. So if the mother is basically Rh negative, and if the fetus has Rh positive antigens, so it is Rh positive. Now during the first pregnancy, there is no blood mixing usually. Very little blood actually comes from the fetus to the mother, which is not sufficient to elicit any immune response maybe.

But during the delivery, there is mixing of the fetal blood with the mother circulation with the mother's blood and that can actually lead to the activation of the Rh specification B cells. Now these B cells when they are activated, they will differentiate into the plasma cells and the memory B cells. The dangerous part is the memory because they will remember what they have encountered.

So they have encountered the Rh antigen. So now they will develop a memory against this Rh antigen of this fetus and of course the plasma cells they will secrete the immunoglobulins, which will actually clear the Rh positive cells. But the memory will be there. Now in the second pregnancy, when the mother will again have, if the mother conceives again second time, then there is a threat for the fetus.

Now then the fetal blood if it enters into the mother's system little bit, then that this Rh antigens will now elicit a second immune response and now it can activate the memory cells because it has the memory cells. So now the mother has the memory.

So now the mother will start to produce the immunoglobulin and it will start producing this IgG and this IgG can actually cross the placental barrier, and it can go into the fetus.

And if it goes into the fetus, then it can elicit a immune response and that can lead to very deleterious effect on the fetus. So now it can try to lyse the cells, so lyse the RBC, the fetal RBC. So that can be very dangerous. So usually, but thank God we now we have remedy to this. But thank God that we have this an antibody against this Rh antigens.

So if the mother is detected with a Rh negative nowadays, if a mother is detected with the Rh negative and the fetus is detected with Rh positive during the first delivery, so immediately after the delivery within 24 to 48 hours of the delivery, the mother is injected with the antibody called the RhoGAM. So it is called the RhoGAM.

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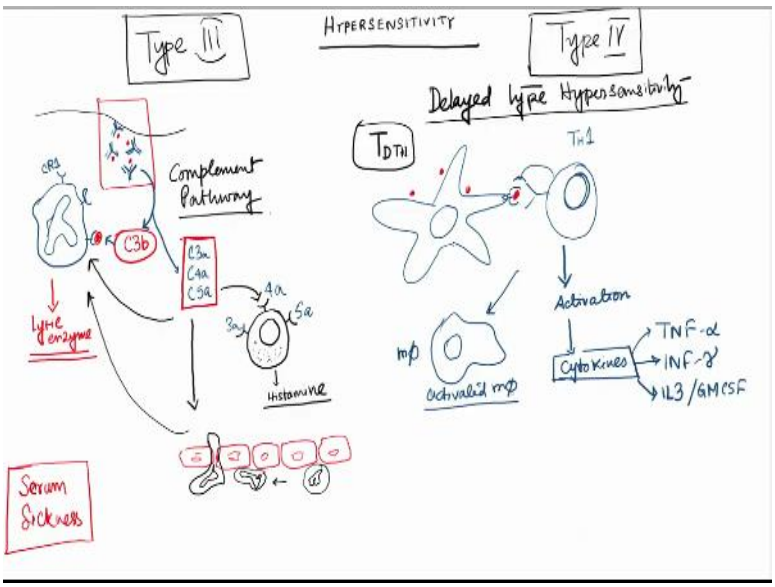

So this is basically the antibody against the Rh antigens, which the mother is immediately injected with. Why? Now because this antibody will now go into the mother's system and will immediately clear up all the Rh positive antigens or the cells that has entered into the mother's system from the fetus so that it can stop the memory, so that there is no memory B cell formation. So there is no memory B cell.

So no B cell activation, no memory B cell formation. And if the mother does not does not have the memory of this Rh antigen, then there is no problem. Then she can safely

have a second pregnancy, it is not a problem. So this RhoGAM is a very good advancement in terms of this dealing with this type II hypersensitivity, which is described as the erythroblastosis fetalis.

We have learnt about the type I, type II hypersensitivities. And I shortly very quickly mentioned about the other two types of hypersensitivity reactions that are also we deal with. One is the type III hypersensitivity, another is type IV hypersensitivity. Now type III hypersensitivity is mostly mediated by the immune complexes. So it is the immune complex mediated hypersensitivity.

Now what is the immune complex mediated hypersensitivity and why can such a hypersensitivity occur in our system? So as in the beginning I told hypersensitivity reactions are kind of inappropriate response of the immune system. So it is not a very correct way of responding. So it is usually an inappropriate response. And type III hypersensitivity occurs from if there is a huge amount of immune complexes being formed within the system.

And that can also occur from antigens, which are so the antigens that are not very the weak antigens, let us say for example. So they can also elicit these kind of hypersensitivity reactions like the type three reactions. And type III hypersensitivity primarily occurs when this antigen antibody complexes are formed on certain locations where they should not have formed for example, where they should not have found.

Now what this how does an antibody work normally? So an antibody goes and binds to the target antigen, preferably on the surface of the target cell. And then there are processes like neutralization, opsonization, complement activation, all these processes will immediately start when there is an antibody antigen binding. So that is basically it initiates the clearing of the pathogen by phagocytosis.

So again, if you look back to your complement classes, then ultimately activation of complements would lead to opsonization or would lead to membrane attack complex formation and killing of the target cell. Now if there is nothing to phagocytose, there

is no cell to phagocytose, so what will the immune system do? What will this complex do?

So then the cell or the phagocytic cell that will try to phagocytose the complex the antigen antibody complex. And this there is if there is this kind of huge antigen antibody complex formation in huge amounts, particularly on the and there is deposition of these antigen antibody complexes, particularly on the blood vessels or any other tissues, that can start or initiate or elicit a response which we describe as a type III response.

And type III response or type III hypersensitivity responses are primarily mediated by complement activation. So the cleavage products of the complement, the complement proteins like the C3a. So when we were studying about the complements if you remember, I told that the complement proteins when they are cleaved, they form the two types of products the a and the b. So there is C3 breaks down into C3a and C3b.

4 breaks down into 4a and 4b. So the smaller products which are the soluble products, which actually are not the membrane bound products. The membrane bound products are the bigger ones or the b for example, it is a normal convention is like that. So C3b for example, which is a membrane bound form.

So these smaller cleavage products the soluble smaller cleavage products which are also sometimes called the anaphylatoxins like the C3a, the C4a, the C5a, they are kind of responsible for eliciting inflammatory responses. So they can enhance inflammation. They have a role in enhancement of inflammation. And that is what these type III hypersensitivity reactions actually occur through.

So and they are mostly initiated by the neutrophils, basically. Because neutrophils as we described several times I have told that the neutrophils are the fastest acting cell of the immune system. So they move to the site of action, the first they are the first cells that will go to the site of action, immediately migrate to the, and they will infiltrate the whole side of action, try to engulf the pathogen do a lot of things immediately.

And they will send signals to all other cells and bring more cells there. All these things starts happening immediately. So the neutrophils are the major mediators of this hypersensitivity reaction, this type this antigen antibody, complex mediated hypersensitivity reaction. So what actually happens is, so whenever there is a response against an antigen like this and you see.

So whenever there is an antigen antibody complex that is being formed, a complex like this is formed. Now this complex, now this antigen antibody complex that is being formed or deposited somewhere, that can actually lead to activation of the complements. So there can be complement activation. And of course, whenever there is complement activation, one of the major products of complement activation or the complement cleavage is C3b.

So the main the central protein in the complement activation is the C3b. And of course, there are other complement cleavage products like the C3a, the C4c, the C5a, all these are present as well. Now this C3b the C3b they can actually bind to the surface of the cells and they can also bind to the cell surface receptors as well.

So this for example, the neutrophils, the neutrophils on the surface, they expresses this kind of complement receptors, for example CR1. And these complement proteins they can, this complement cleavage proteins, they can bind on the surface of the neutrophils. And as well these cleavage products, what does this cleavage products do? These cleavage products, they can also have dual functions.

So these cleavage products can also bind to the cell surface receptors as well as these cleavage products if you remember from our classes of inflammation, on our lectures on inflammation, these cleavage products can also help in migration of more neutrophils. So neutrophils can migrate from the blood into the site of action by the action of the complement cleavage products.

So they act as chemoattractants. So these kind of smaller compliment cleavage for as a soluble compliment cleavage products the C3a, 4a, 5a they can act as chemoattractants as well. And they can attract more of these neutrophils c3a, 4a, 5a for example. They can attract more neutrophils to the site of action.

And by so opening up the so there as I told this immune complexes that are deposited, this immune complexes can elicit the complement activation pathway. And so it elicits the complement pathway. And in this complement pathway, you can actually have this cleavage product. So either you can have the soluble cleavage products like the C3a, C4a, C5a or this kind of C3b.

So we have learnt in our complement class that the C3b is one of the central cleavage products in the complement activation pathway, which mediates a lot of functions. So the C3b can actually go and bind to the target cells. They can bind to the target cells. They can also produce more C3 convertases, C5 convertases and helps in cleavage of C3, more C3 and more C5.

So C3b is one of the central components of the compliment cleavage pathway. And also we have this soluble cleavage products like this C3a, C4a or 5a, which we describe together or collectively as the anaphylatoxins and they can also perform a lot of functions. Primarily their function is to enhance the inflammatory responses. So they enhance inflammation. How do they enhance inflammation?

So what they do is they can perform a lot of functions, they can also bind to the complement receptors on the surface of the neutrophils and other leukocytes, those cells which express this kind of complement receptors of course. So most of the APCs like the macrophages or the neutrophils, they express on their surface the complement receptors like the CR1 for example and they can also help in the migration of the neutrophils.

As well as they can bind to the cell surface receptors on the mast cells or the basophils. What are the mast cells and the basophils? They have the granules containing the histamine. So they are the granulocytes. So they can produce histamine. So now if this C3a, 4a, or the 5a they can bind also on the cell surface receptors of this kind of mast cells and that can actually lead to the release of vasoactive amines like histamine.

And this in turn can lead to opening of this high endothelial venules in the blood vessels and also helps in the migration of the neutrophils. So the neutrophil migration we have learned as well. So there is rolling activation and then there is migration of the neutrophils. They migrate and they migrate to the site of action.

So this is a kind of combined effect from the complement pathway activation from the formation of the, these kind of immune complexes here. And this immune complexes they elicit the response via activation of the complement pathway formation of this complement cleavage products, which can have many roles many functions. They can help in release of histamines.

They can help in bind to the surface of the neutrophils. The cell surface complement receptors of the neutrophils, they can help also in migration of the neutrophils because these complement cleavage products also acts as chemoattractants, just similar to the chemokines we have described previously. So they can also help in migration of these neutrophils to the localized to the site of action and that can lead to release of many lytic enzymes.

As I told, this neutrophils, so they cannot really they try to phagocytose this antigen antibody complex that is being formed. And in this process, they start releasing this lytic enzymes. And from there what we see is the local, this is a local hypersensitive reaction. So a type III hypersensitivity reaction can usually be a local reaction. Also it can be a systemic reaction. It can be a global response as well.

How this kind of global responses do they occur? So for example we have a snake bite. When you have a snake bite, you will administer with an anti-venom. But this anti-venom usually is raised in a different animal. Let us say for example in horse. So you are basically and then you get the antibodies from there. And these antibodies against the snake venom is being administered to the patient.

But along with the antibodies of the against the snake venom, you are also sometimes injecting a little bit of antigens from the horse serum. And that can elicit a systemic response in that patient as well. And that is also a type III hypersensitivity and it can be a systemic sometimes also it is referred to as serum sickness.

It is also sometimes called as the serum sickness that can also lead to a type III hypersensitivity reaction because of the formation of the antigen antibody complexes and deposition of this antigen antibody complexes on the blood vessels or on the basement of the membrane. And that can actually lead to phagocytosis of these antigen antibody complexes by the neutrophils and elicit this kind of responses.

Sometimes, some people who are very sensitive to certain kind of allergens, like for example you have an insect bite, you can immediately develop a type I hypersensitivity reaction. But you can also develop a type III hypersensitivity reaction after a few hours maybe. So not immediately, after there is an antigen antibody complex formation and deposition of the antigen antibody complexes, you can also start to develop a type III response in those cases as well.

So this hypersensitivity reaction, so these are kind of as I told or in the beginning, these are kind of inappropriate responses. The immune system really does not know what to do and it starts responding in this way, and some people can develop this kind of reactions. So going back to the different types of the hypersensitivity reaction. So this is type III and as I told there is another there is a type IV.

So all the hypersensitivity reactions that we have described so far we have seen there is somewhere involvement of the humoral branch of the immunity. That means, you have the role of the antibodies be it the IgE or it is the IgG or there is the antigen antibody complex, we have seen it is mostly being elicited from the humoral branch of the immunity. So you have the role of the antibodies.

But there can be another type of hypersensitivity reaction, which is cell mediated. So basically from the T-cell mediated. It is basically mediated by the T-cell. So initially it was people thought I mean, the exact T-cells were not really assigned for this kind of hypersensitive reactions and they were known as the T DTH. So this type IV hypersensitivity reactions, were also sometimes described as the delayed type hypersensitivity, because it does not occur immediately.

So it is a delayed type hypersensitivity reaction and it does not really occur immediately after exposure to the antigen. So it can take some time, like one, two, or three days. So that is why it is also called the delayed type hypersensitivity. And initially this subset of T-cells, which actually mediate this kind of hypersensitivity reactions, they were named as T DTH.

Later on, it was basically found it was a small subset of the T-cells, which are mostly the TH1 cells basically and to some extent CD8+ cytotoxic T-cells are also involved, but it is mostly the TH1 cells. So the TH1 effector cells, which are responsible for this delayed type hypersensitivity reaction. Now what these delayed type hypersensitivity reaction actually that elicits from?

So it elicits from mainly the antigen presenting cells and primarily the dendritic cells, which are present in the epidermal region. So in the epidermis, the Langerhans cells, let us say. So this Langerhans cells they can basically, so they can basically they interacts with the antigen and they can present this antigen which can then prime with a CD4+ T helper cell, a TH1 cell.

And this priming, so there is a priming with the T helper cells. So they can activate this T helper I class of cells, when there is binding of this antigen and presentation of this antigen to the TH1 type cells, they can actually lead to activation of the T-cells and they can start secreting different types of cytokines. If you remember the classes that my lectures from the cytokines, then you will see what are the different types of cytokines that have been released by this kind of TH1 cells.

And these are mostly mediated by for example, the tumor necrosis factor, the TNF alpha, the INF interferon gamma. These are all or interleukin 3, IL-3 or GMCSF and that leads to that brings more and more of this macrophages. And this macrophages this interaction in turn they can activate a macrophage and activation of, so if there is an activation of macrophage, so an activated macrophage can in turn produce a lot of cytokines.

And this cytokines in turn they can lead to there are many pro inflammatory cytokines that are being released that can lead to inflammatory responses. So they can lead to

local swelling, redness, itching and all these things can occur and you can see a delayed response to such kind of an antigen. So very good example of delayed response hypersensitivity is the Mantoux test.

If you have heard about the Mantoux test is a very common type of test against MTB for example, mycobacterium tuberculosis. So if you go to any pathological center, previously people used to do a Mantoux test and they used to inject a mixture of peptides and carbohydrates isolated from the MTB which also known as a tuberculin. So this antigen it is being injected intradermally so under the skin.

And then you wait for two days and if you see after 1, 2, 3 days, if there is a small redness and swelling in that area, then basically you will conclude that you can have a that person has an exposure to MTB. So had been exposed to the TB or MTB. And this kind of responses are usually delayed responses.

So because they need activation of this involvement of this T helper cells and activation of the T helper cells that can lead to release of this kind of cytokines and this is mostly this inflammatory cytokines which leads to this kind of inflammations. And also activated they can also activate the macrophages locally and the tissue macrophages, and then you can have this kind of inflammatory responses.

So overall, we have kind of learnt four different types of hypersensitivity reactions that the immune system actually shows against different types of allergens, different types of antigens, and the type I, type II, type III, type IV, it is very easy to remember the different types of hypersensitivity reaction. So all type 1 to 3, the first three types of this hypersensitivity reaction is mediated by antigen antibody.

So it is mostly antibody mediated, and of which type I is mediated by IgE, type II is mediated by IgG and type III is mediated by an immune complex that is a complex antigen antibody complex formation. And the type I hypersensitivity is primarily mediated by degranulation of the mast cells, the basophils and all this. Type II hypersensitivity can occur by complement activation, formation of the membrane at a complex, lysis of the target cell and also by ADCC.

And type III hypersensitivity as I described, it is mostly by the formation of the antigen antibody complexes and thereby mostly mediated by the neutrophils, and also to some extent by the mast cells by release of histamines. And the type IV hypersensitivity is mostly T-cell mediated hypersensitivity. So it is by a small subset of the T-cells, which actually mediates these kind of hypersensitivity reactions.

And it is mostly due to the release of the different cytokines that elicits or enhances the inflammation, inflammatory responses. So that elicits more inflammatory responses. So this is all about the hypersensitivity. I have tried to keep it very in the basic part and lucidly. So you will if you want to read more about this hypersensitivity reactions you can refer to any of the books that we have already referred like Kuby or Janeway.

All these books, they describes all these hypersensitivity reactions very clearly. You can go through those books to get a much clearer idea about it. And hope you have enjoyed the lectures so far. And thank you very much.