Introduction to Complex Biological Systems
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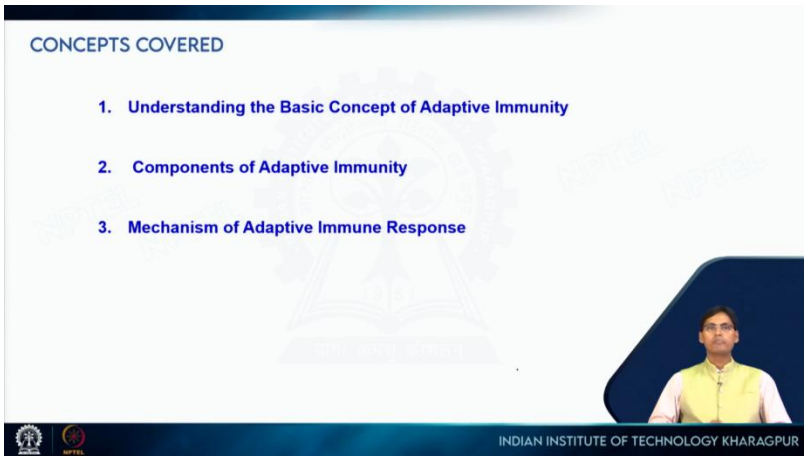
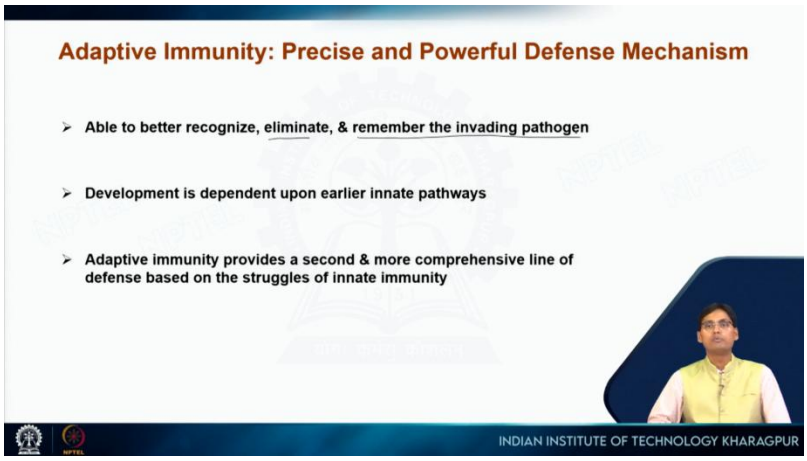
Lecture 48
Adaptive immune response

Welcome back to the NPTEL online course on Introduction to Complex Biological Systems. During our last lecture, we discussed our innate immune response. Today, I will mostly focus on our adaptive immune response. So, here I will cover the basic concept of adaptive immunity followed by different components, some cells or some molecules which are involved in adaptive immunity that I will discuss in detail, and finally, I will explain the mechanism of adaptive immune response. Now, going into adaptive immunity, this is the precise and powerful defense mechanism of the host. When I was discussing innate immune response during the last lecture, I specifically mentioned that during the innate response, at some stage, particularly dendritic cells and macrophages are engulfing pathogens and processing the information.



That means, when those pathogens are getting inside these dendritic cells. They will break down those pathogens. You can consider some bacteria, and it will make small protein fragments called peptides and those peptides will be presented on the surface of these antigen-presenting cells like dendritic cells. Now, these dendritic cells and macrophages, although they play a very important role in the innate immune response, are initiating the adaptive immune response.

So, when they are presenting antigens on their surface, they will guide other cells, for example, T cells, to develop our adaptive immune response. So, I will discuss the mechanism a little today. Although this adaptive immune response is overall a very complex thing, and within just 20-30 minutes, it is really difficult to explain all the pathways and mechanisms involved there, I will highlight the basic concept, the basic mechanism of this adaptive immune response. At the end, you will appreciate the complexity of a biological system, particularly in this context, in the context of our adaptive immune response. The adaptive arm of our immune system can better recognize the pathogen, or the enemy, you can say, and it can eliminate the enemy and finally, or more importantly, it can remember the invading pathogen. So, in the near future, if we get attacked again by the same enemy, the same pathogen, our adaptive immune response will act very promptly. Now, the second point is that the development is dependent upon earlier innate pathways, as I just mentioned that at the beginning, the innate immune system, the innate response, is going on properly, and it is actually helping to develop the adaptive immune response against that particular pathogen. Adaptive immunity provides a second and more comprehensive line of defense based on the struggle of innate immunity. As I mentioned during the last class, innate immunity is referred to as the first line of defense; that is why we say this is the second and more comprehensive line of defense mechanism for the host.



Let us see what the different components of the adaptive immune system are, how they are present, and how they play an important role. So, now I have divided those things into two different categories here, the cellular components, as you can see here, and the

molecular components. So, the first thing I will concentrate on is antigen-presenting cells. So, professional antigen-presenting cells; I would say the first thing that comes to our mind is dendritic cells.

From now, I will refer these cells as just DC, dendritic cells and another one is macrophage. So they are professional antigen presenting cells. The molecular components mean it is associated with this antigen-presenting cell that is called major histocompatibility complex. It's very important.

So those are some surface proteins produced by this antigen presenting cell and they present the antigen, the peptide antigen particularly on the surface of these antigen-presenting cells, and what peptide? So in this context, whatever I am discussing now, I would say the peptide coming from the pathogen. Sometimes indigenous peptides can be presented in a different context. I will touch that part also sometime later. But now consider just a peptide coming from some foreign body; it can be some bacteria or some virus, something like that.

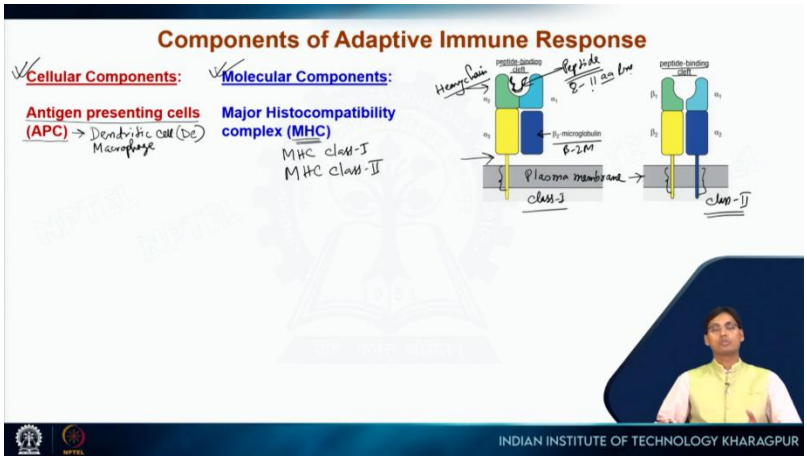
Now this MHC, you can broadly classify into two types of MHC present. One is called MHC class I and MHC class II. So this is class I and this is class II MHC. Now this class I MHC is present in our body in all nucleated cells, not just antigen presenting cells. They are present in all nucleated cells.

This is very important information. But MHC class II is present on antigen-presenting cells, particularly professional antigen-presenting cells. What is the other difference? As you can see here, their domain organization and structural features are a little bit different between class I and class II MHC. As you can see, the class I MHC crosses the membrane, so this is the plasma membrane.

The plasma membrane is the same here; this is also the plasma membrane. Now, if you see class I MHC, it crosses the membrane just once here; but the class II MHC crosses the membrane twice, and because of that, their domain organization is also different. So, in class I MHC, we say this is our heavy chain, and this is called β-2 microglobulin or β-2M. Sometimes we just say β-2M or β-2 microglobulin. So, the heavy chain is just a single

polypeptide and the β-2M is another polypeptide. So, this is some example of a quaternary structure of a protein. Two different polypeptides are associated together, and they are forming the complex. But here, the most important thing is on top of this heavy chain, this MHC you have some peptide binding group or cleft. So, the peptide will be present here.

So, this is the antigenic peptide. This is the peptide presented by some MHC molecule. Later on this peptide loaded MHC will be recognized by some T cell receptor, I will discuss soon. But in case of class II MHC, more or less, it is similar only here, as you can see alpha chain and beta chain; the organization is a little different, and also the peptide binding plate is also a little bit different. Although in this figure you cannot differentiate, I would like to say that, in case of class I MHC, the peptide length is generally from 8 to 11 amino acids long. Antigen can be presented by class I MHC, but in the case of class II MHC, the length can be even bigger. So, it is possible that this is because of some in-depth structural features of how the antigen is being presented. I am not going into that detail in this lecture. Now, as you can see here, the T cells. So, what I particularly mentioned, if I summarize here, what is happening. So, here if I say this is our antigen-presenting cell, you can say this is DC. Now when it endocytosis some bacteria. This is bacteria. In the next step, this bacterium will be broken down into small pieces and it will be presented on the surface of this dendritic cell or APC antigen-presenting cell by MHC molecule. This is MHC molecule. Now, this dendritic cell can express both class I and class II MHC because they are professional antigen-presenting cells.

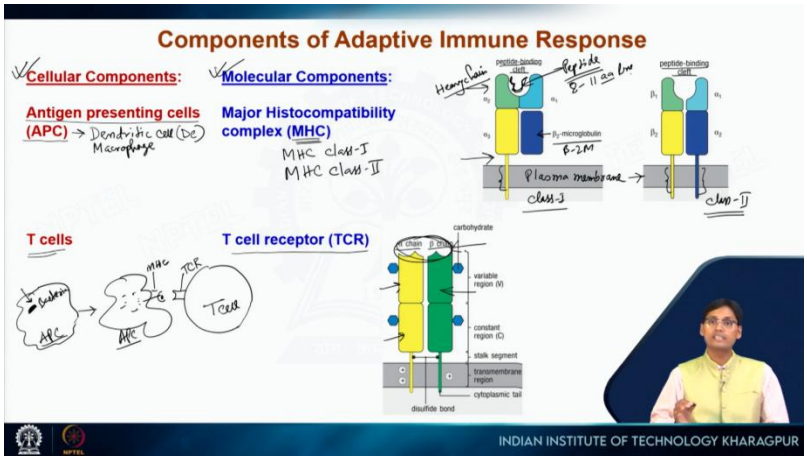


Now, what will happen to the T cell here if this is our T cell? On the T cell, you have another receptor called TCR, which stands for T cell receptor. It will recognize the peptide-loaded MHC on the surface of an antigen-presenting cell, and therefore the T cell will differentiate, and other activities will occur. Now, let us see how the TCR looks. So here, this is the T cell receptor.

So, as you can see in the TCR, you have an alpha chain and a beta chain, and in this TCR, you have the variable region and the constant region. So, this variable region, constant region, all those modules, and these domains have some protein fold, which is called the immunoglobulin fold, which I will discuss in the next lecture when I go into detail about the antibody structure. But for the time being, just try to understand that their overall structural features are the same, which is called the Ig fold. So, this is one Ig fold; this is another Ig fold, and another Ig fold. So, that is how they are organized.

But that is not important here. The important thing here is that this TCR, this is the binding portion. So, through this portion, they can recognize the peptide-loaded MHC on the surface of the APC, but here we have to be careful about our understanding. The TCR on the T cell surface can rearrange itself, and its sequence can vary. Based on this, the TCR, an antibody with many variations in sequence and the specific structure of the antigen-binding site, can vary significantly, with a huge amount of diversity available. Similarly, in the TCR region, this diversity also exists. So, as a result of that, they can recognize peptide-loaded MHC and this MHC has some kind of restriction. MHCs are restricted so this cannot interact with any type of TCR. There is some matching required. So we say that peptide-loaded MHC will be recognized by a cognate receptor, a specific type of T-cell receptor. So, that is all.

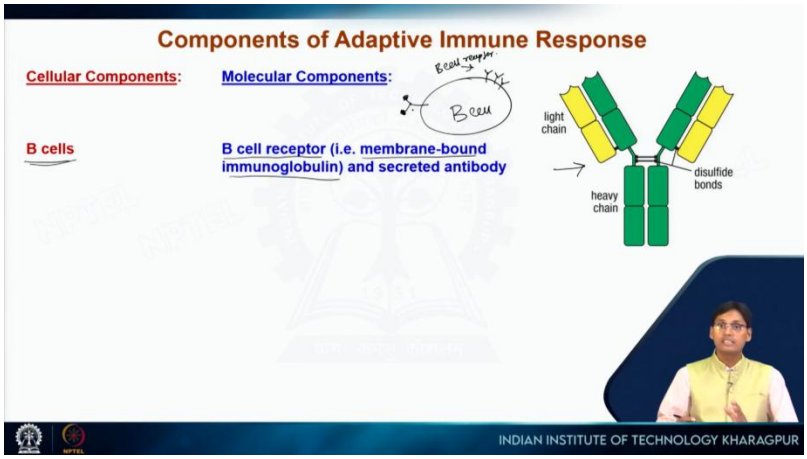
Now, what did we discuss here? We discussed antigen-presenting cells and how they present antigens through MHC molecules, and we also discussed T cells. T cells have T-cell receptors on their surface, and this TCR-MHC recognition is one of the most important steps in the adaptive immune response. Now, the next topic is B cells. B cells are also very important, like T cells, and they play a major role in our adaptive immune response.



B cells have another receptor on their surface called the B-cell receptor. This structure looks almost like an antibody. This is an antibody. But what is the difference between the BCR and an antibody? The BCR, or B cell receptor, is a membrane-bound immunoglobulin. So, if this is a B cell, they have this here. But they are still bound to the plasma membrane.

So, during that time, we are saying that this is our B cell receptor, but this B cell, when it differentiates into a plasma cell, will secrete a specific type of antibody. Those proteins are now being secreted, and we will say those are antibodies. Now, then, what is the role of BCR? So, BCR present on the B cell surface also recognizes antigen, but that antigen does not need to be presented by an MHC molecule. That is the very important thing. I would say, if this is a B cell and you have a BCR, it can recognize antigen, and this antigen might not be a small peptide; it can be a bigger protein also. So, as a result of that, what will happen? The B cell can directly recognize antigen. It can be some secretory protein coming from some pathogen, from bacteria, and it will be recognized by this B cell receptor. So, this is the difference between the recognition of antigen by B cells and T cells. TCR needs the help of MHC present on antigen-presenting cells, and the antigen-presenting cell processes that foreign protein into small pieces, and that peptide is presented. Now, this peptide-loaded MHC can be recognized by the T cell receptor, but in this case, the B cell can directly bind to the antigen. That is all. Now, I would like to mention here this immune system, particularly related to adaptive immune response. It's a huge advancement in our biomedical field, if you see. Here, particularly, I'm mentioning a few of those Nobel Prizes related to our immune response, particularly related to

adaptive immune response also. I'm just mentioning; I'm not bringing a scientist's name here.

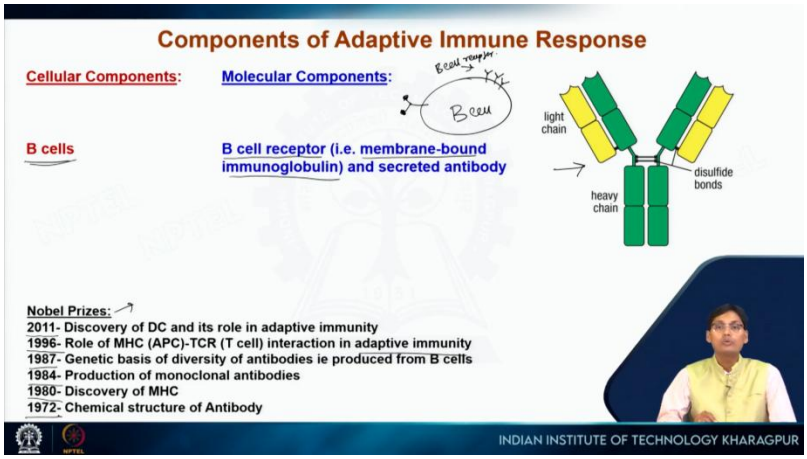


It will be a very big list. So, here as you can see in 2011, all are in the category of physiology and medicine so in 2011, I would say the discovery of dendritic cells and their role in adaptive immunity. So, with this award, maybe some other findings by other scientists are also involved there. That means the prize, when awarded, is clubbed together with some other findings, but I am only focusing on those related to our adaptive immune response.

Now, if I just go back, I started with 2011. Now, in 1996, the role of MHC-TCR interaction in adaptive immunity has been awarded the Nobel Prize. In 1987, the genetic basis of the diversity of antibodies produced from B cells. I just mentioned that B cells can produce countless different types of antibodies and based on the pathogen, the diversity of antibodies, that particular genetic basis, has been discovered. In 1984, the production of monoclonal antibodies had huge therapeutic importance also then in 1980, the discovery of MHC molecules, the major histocompatibility complex, and in 1972, the chemical structure of antibodies.

As you can see, all those major keywords I already mentioned like MHC, TCR, antibodies, dendritic cells, adaptive immunity, and innate immunity. So, let us see. Now, I will discuss the mechanism of adaptive immune response together. As I already mentioned, it is a complex process, but I will try to explain it as simply as possible. Let us see what happened. I will go step by step now. Whatever I mentioned when discussing cells and

components of the adaptive immune response, I will add some additional complexity here.



So, from here, if I start, this is a dendritic cell, and it is presenting the antigen. So, this is the antigen. I would say here; I am writing peptide-loaded MHC. Now, the T cell is here. The T cell now has a TCR.

This is called a TCR or T cell receptor. So, a specific interaction between TCR and MHC will lead to this adaptive immune response. Now we have mainly many complex things there, but mainly we have two different types of T cells involved here. One is called a CD8 T cell, which means, in this T cell, besides the TCR, you have another co-receptor. This is called a co-receptor.

What kind of co-receptor? CD8 co-receptor, the major receptor here is the TCR, and this is the co-receptor. Now, when this interaction is going on between MHC and TCR of a CD8 T cell, then this T cell will differentiate into a cytotoxic CD8 T cell. So, we will say cytotoxic CD8 T cell.

Now, they have the similar TCR, the TCR they saw this antigen which was loaded on MHC. So, as a result of that you have TCR present here in this cytotoxic CD8 T cell, and next, what will happen from the name suggests that it is cytotoxic; so, this cytotoxic T cell can directly kill virus-infected cells like our host cell in fact. So what happens if I say this is our virus infected host cell? Now, the viral proteins are also present inside this cell, and finally, class I MHC will present antigen here, which is coming from this virus. They

will be presented by class I MHC and now this CD8 T cell will recognize this antigen because they have already seen this antigen when it was presented on a DC or dendritic cell. So, therefore, the cytotoxic cell or this cytotoxic CD8 T cell exerts its effect.

So, from the name it suggests that it will kill the cell. So, this CD8 T cell will kill the virus infected host cell. So, that way it will try to clear the infection. This is just what I mentioned about the CD8 T cell. But another group of T cells are available. So, when dendritic cells are presenting antigen through class II MHC. So, the previous one, whatever I discussed about the CD8 T cell and MHC interaction, this one I would say is class I.

So, class I MHC interacts with the TCR of CD8 T cells. Now, the class II MHC will interact with CD4 T cells. So, here you have TCR and the co-receptor, which is called the CD4 co-receptor. So now, when these CD4 T cells interact with antigen-presenting cells via this MHC-TCR interaction, these CD4 T cells will differentiate and exist as helper T cells. These are also called helper T cells, but they have TCRs present on their surface; those are the TCR or T cell receptors.

They know what kind of antigen needs to interact. Now, these helper T cells, as their name suggests, will not directly kill infected cells. Rather, they will help some other cells, and that will be a very big part of adaptive immunity. So, these helper T cells will help B cells to produce antibodies, it will help the B cells to be differentiated as plasma cells, and therefore that plasma cell will produce antibodies, but what is the mechanism? Now what is going on here, as I already mentioned before, is that B cells can also directly see antigen that can directly bind to antigen through their receptor called BCR or B cell receptor, and as a result of that, what will happen is some of those antigen will be endocytosed. So, the antigen will come inside maybe a big protein and it will be broken down into small pieces, and then B cells can express class II MHC on their surface. So, this is class II MHC and they will be presenting this peptide on their surface. Now, see what I told; that CD4 T cell already recognizes the antigen loaded on class II MHC present on the dendritic cell. Now these B cells are also presenting this class II MHC and they are presenting this peptide antigen. Now this MHC class II presented on the B cell

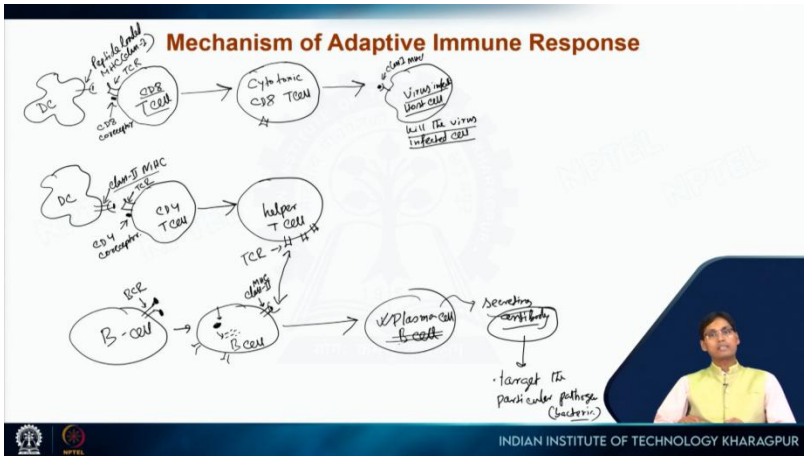
surface will interact with the helper T cell and as a result of that, this interaction will give the signal to the B cell to be differentiated, as this B cell will now be converted into a plasma cell.

So, that is why I am crossing this B cell so no more B cells. I would say this is now a plasma cell. So, in this B cell we had BCR on the surface. So, this is BCR, and here in this cell, they are secreting antibodies.

Antibody means some complex protein molecules that will bind to antigen. What kind of antigen? The antigen is the same antigen which was recognized by the BCR. The same antigen which is recognized by this class II TCR is presented by the class II MHC on the surface of DC.

But those antigens are coming from that particular pathogen, particular bacteria. As a result of that, this antibody will target the particular pathogen, say bacteria. So this way, it will make a robust immune system, the adaptive immune system. In one way, CD8 T cells are directly killing some virus infected cells. On the other hand, CD4 T cells, after recognizing the antigen on the surface of antigen presenting cells, are helping B cells to produce specific weapons against the pathogen.

Weapon means antibody here and this antibody will mark those particular pathogens that will increase the efficiency of phagocytosis by some other cells and also help in the killing process. It will be much better. So this is how the adaptive immune system works. Now I have a few things to discuss here; because whatever I told, this is the basic thing. But, still I am trying to bring all this complexity also. Now here are a few points: what is the requirement of B cells by CD4 T cells, and then they are only getting converted into plasma cells and secreting antibodies. They already saw antigen, so they can directly differentiate into plasma cells and they can secrete antibodies, but there is a catch. So a very important thing is that at some point, maybe in the first class of this immunology or this module, I mentioned that T cells, although they are generated in bone marrow, are getting matured in the thymus.



When they are getting matured in the thymus, those T-cells are actually learning which is self and which is foreign. That means they are taught that these are the whole ensemble of our self-antigens, and you shouldn't act against this antigen in the future. What I'm trying to say is that T-cells learn what is self so they shouldn't act against the self peptide. Self peptide means our host cell peptide. Otherwise, a lot of different types of autoimmune diseases will develop. But B-cells on the other hand are not taught this system. So they mature in bone marrow in a confined environment, and they are not that way; learn this thing. So this interaction between CD4 and this B cell through this antigen class II MHC loaded antigen and TCR, whatever I am showing here. This interaction is required because the CD4 T cell or CD8 T cells are aware of the cell peptide so that they will not act against the cell peptide. So whenever this interaction is happening, that means the CD4 T cell is giving a signal to the B cell that it can differentiate into a plasma cell and make an antibody against that particular antigen, and therefore it will produce one. Clear? So, this is what I just mentioned about this B cell and T cell and their differences. Another important thing here I must mention is class I MHC and class II MHC.

See class I MHC present antigen when those antigens are processed or they are synthesized by our own machinery. As you already know in the previous module, I discussed that when viruses infect host cells, they don't have protein synthesizing machinery, so they utilize the host cell machinery. So, it's an endogenous protein; although ultimately, the virus particle will be generated, but these peptides, since they are produced through the endogenous pathway, our own cellular pathway, will be presented by class I MHC. Similarly, some cancer antigens, for example, those are again, some

mutant proteins, some bad proteins, which are produced inside our cells through an endogenous manner.

Those peptides will also be presented by class I MHC and will be recognized by CD8 T cells. On the other hand, the class II MHC is actually present on antigen presenting cells, not in all cells, and these antigen presenting cells have a very good capability to phagocytose things. So they will phagocytose the pathogen, for example, some bacteria. It will be present inside the phagosome, endosome, and they will break those small pieces and it will be presented by class II MHC.

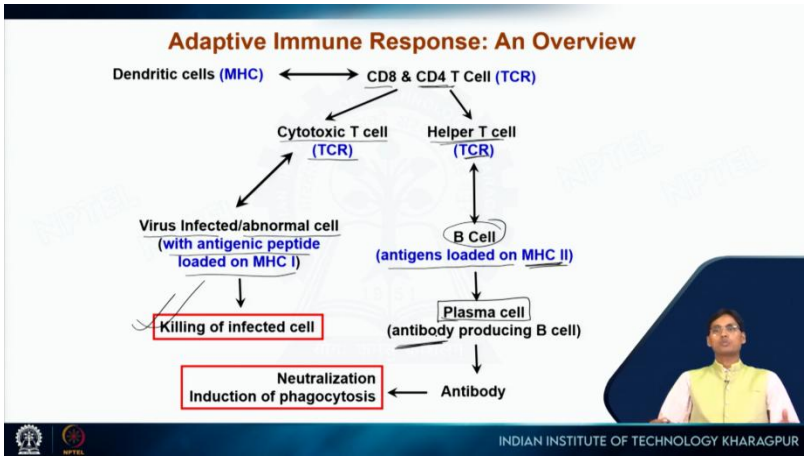
Now, if you notice here these proteins are not being synthesized by the host cell itself. It is directly coming from the pathogen and this is presented by a class II MHC molecule. This is the difference, but at the starting point when the dendritic cell presents antigen to CD8 or CD4 T cells because dendritic cells are professional antigen-presenting cells; they have both class I and class II MHC molecules. They have the ability to cross present peptides. There are a lot of interesting features available with dendritic cells. I'm not going into those details, but all these things help our adaptive immune system to either develop antibodies against a particular pathogen or help CD8 T cells to become cytotoxic T cells and directly kill virus-infected cells or some other abnormal cells.

After all of those things, some cells will remain in circulation and remain in our body; those are the memory cells, for example, some memory B cells. So in future infection with the same pathogen, they can quickly assess all those things and then accordingly they will behave. Here another important thing is where all those things are happening. I would say when T cells didn't see antigen yet, just here for example, you can see they are seeing antigen loaded on the antigen presenting cell. So before that, those T cells we say are naive T cells. Those naive T cells are present in different lymph nodes, for example, particularly in the spleen. So, now the dendritic cell catches some information, I would say, when it engulfs some pathogen. This dendritic cell has a very good ability to move around. So, it will migrate. It will go to some lymph nodes, some draining lymph nodes, where T cells are waiting.

So, as a result, they will teach T cells what should be done in the next step. On the other hand, macrophage is generally present in tissue like tissue resident macrophages. So, their major role is there itself, but dendritic cells are very good at it. So, it will travel through the lymphatic system and they will reach some lymph nodes and teach our naive T cells what to do next.

Now, whatever I discuss this is the summary. Now, I will go very quickly, but it is already written here step by step, I will show, but whatever I just mentioned will be a little bit less detailed here. So, see the dendritic cell on the surface of MHC. They present MHC on the surface and then it can interact either with CD8 T cell or CD4 T cell through TCR, as I already mentioned. If the interaction is with a CD8 T cell with the class I MHC loaded antigen, then that CD8 T cell will now be a cytotoxic T cell, and this cytotoxic T cell will recognize the virus-infected cell or abnormal cell, as I just mentioned, for example, some cancerous cells also with antigenic peptide loaded on class I MHC present on their surface and the outcome is the killing of the infected cell. It is very important. On the other hand, if you see the recognition between class II MHC and CD4 T cell, then that is actually a helper T cell; that CD4 T cell will be a helper T cell, and they have that TCR on their surface. Now, I have already mentioned how B cells see antigens, and that antigens will be loaded on the surface of the B cell by class II MHC. Do not forget: this is not class I MHC; this is class II MHC because this part we are talking about the interaction between the helper T cell and the B cell. On the surface of the helper T cell, whatever TCR you have will bind to class II MHC when it is presenting a peptide.

Not the class I, so that's why. Whenever this helper T cell gives a signal to the B cell, this B cell will differentiate into a plasma cell. This is a very important step, and now this plasma cell will make antibodies. The final outcome is that these antibodies will bind to the target, and neutralization and the induction of phagocytosis will happen. So, as a result of that, the infection will be cleared soon after all these steps. As I already mentioned, some memory will also be there, and those memory cells will help in the end, the end meaning even after a few months or a few years if we get infected with the same pathogen, and that is all about the adaptive immune response.



Thank you very much. You can follow Janeway's Immunology for additional details. That's all.