Immunology
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Lecture - 20
Antigen Recognition by T cells: Major Histocompatibility Complex (Contd.,)

Welcome, to today's lecture, this is lecture number 20. We are going to continue about the MHC major histocompatibility complex, because we in last lecture we are studying the last slide was about the size of peptide which MHC s 1 and 2 can accommodate, I am just reminding you again the MHC 1 can accommodate 8 to 10 or in some books you will find 9 to 11 and MHC 2 can accommodate bigger and more wide variety of peptides and that is a 13 to 20 so, we already know why these peptides is important.

Because these peptides which is actually processed and presented by MHC are going to recognize by T cell receptor, we are talking about the B cell epitopes you know by now, what is a epitope, a epitope means a segment of the antigen which is recognized by B cell receptor is known as B cell epitopes and the segment of the antigen which is recognized by T cell receptor is called T cell epitopes. So, for a particular antigen that T cell epitopes and B cell epitopes may be same.

So, the same antigen may be recognized by B cell and recognized by T cell, but in many times or several times what happened? The B cell epitope is not exactly the same which is T cell epitopes because B cell epitopes always should be at the surface of the antigen or the protein which is recognized, so, it should be on the surface, so that an antibody can recognize it, but in case of T cell what happened this whole peptide will be open and chopped into pieces, suppose this whole hand is antigen, it will be chopped into different pieces.

So, that all the fingers will be separated one of these finger after processing will be represented by MHC, either 1 or 2. So, that may be buried inside the cell inside the antigen. So, it is not necessarily it should be higher on the surface of the antigen, so, there is a difference, but definitely the surface and surface epitope also may be presented by T cell. So, the size is

different. MHC 1 is smaller, I mean, in presentation the peptide that MHC one is presenting is small with respect to MHC 2.

So, today before going to tell discuss about they let see what we will see discuss like, we have multiple copies of MHC. So, every individual has different copies of MHC 1 and MHC 2 and MHC genes are one of the most polymorphic gene, so far discovered maybe the most polymorphic gene, so far discovered. So why this polymorphism and more number of copies required not only that because these presentation or the antigen binding cleft is not as specific as T cell receptor or B cell receptor.

But still we need so, many number for several reasons, one of the most important reason is that multiple MHC can present multiple different type of peptides after processing. This is number 1, number 2 is if there is only 1 or 2 say suppose there is only 1 MHC 1 on 1 MHC 2 which can represent all possible peptides, then what will be the problem just in case if there is a mutation in that MHC or problem in that MHC the whole immune system will be collapsed,

Because whole T cell activation will be collapsed. So, that is one reason that one copy is always bad for this kind of protective system. Second is there are many viruses, which can manipulate the MHC, they can somehow block the MHC function. So, if that is the case, then if there is only 1 MHC by any chance it is blocked, not mutated or not deleted. So, that means we are not inherited but viral infection if it can stop, what is going to happen is the whole immune system will be blocked again.

So, if we have multiple copies, 1 virus can block 1 2 but still we will have enough in number so that our immune system is not completely blocked or lockdown. So, we still we will have immunity. And polymorphism is definitely very important because until unless we have a multiple I mean this polymorphic situation we cannot have many variety of MHC and different MHC can present different variety of antigen which will made the immune system more diverse. So, more T cell can be accommodated in to involve in the immune system, so, let us go to the slide is to see, again, we are going to discuss about our immune system.

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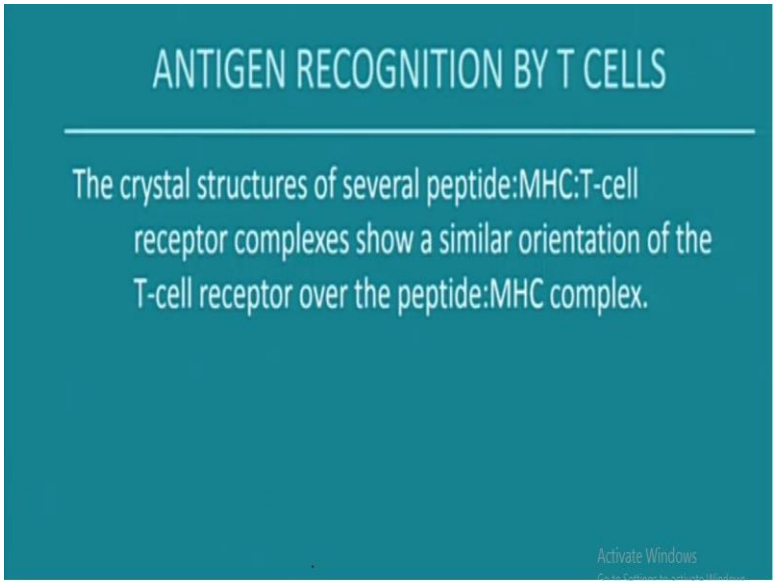

So, we discussed about MHC presented antigen and the TCR interacting, but how they are interacting the crystal structure actually tell all about this the crystal structure of several peptide MHC complex T cell receptor. So, the MHC peptide and T cell receptor complex or crystallized and the structure is saying that similar orientation.

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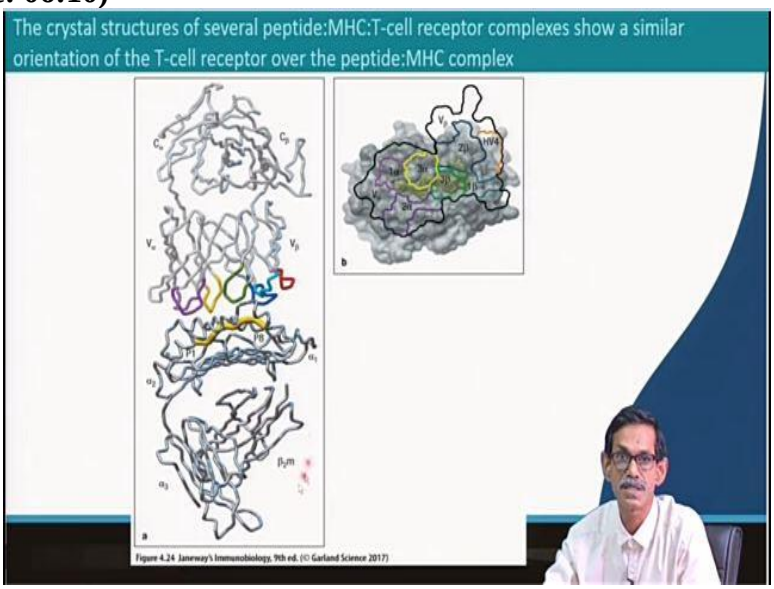

What I mean by similar orientation that means, so, this is MHC 1 this is a crystal structure this is a MHC 1 let us go to next slide this is a MHC 1 if you see this is alpha 1 domain alpha 2 which is the peptide binding region the yellow 1 is a peptide and alpha 3 domain and this is beta 2 m that means beta microglobulin. So, these alpha 1 and alpha 2, if you see this is the peptide and

this is the T cell receptor, you see b beta because T cell receptor MHC the T cell receptor has 1 alpha chain another beta chain.

So, the alpha 1 of MHC is interacting with beta chain variable region and alpha 2 is interacting with variable region of alpha chain of T cell receptor. So, beta alpha 1 and so, this is not only one. So, several MHC peptide TCR complex crystal structure has been solved, and most of the cases, it was found that the crystal structure shows that the interaction is between alpha 1 of MHC 1 with beta variable region and alpha 2 of MHC 1 with beta alpha variable region.

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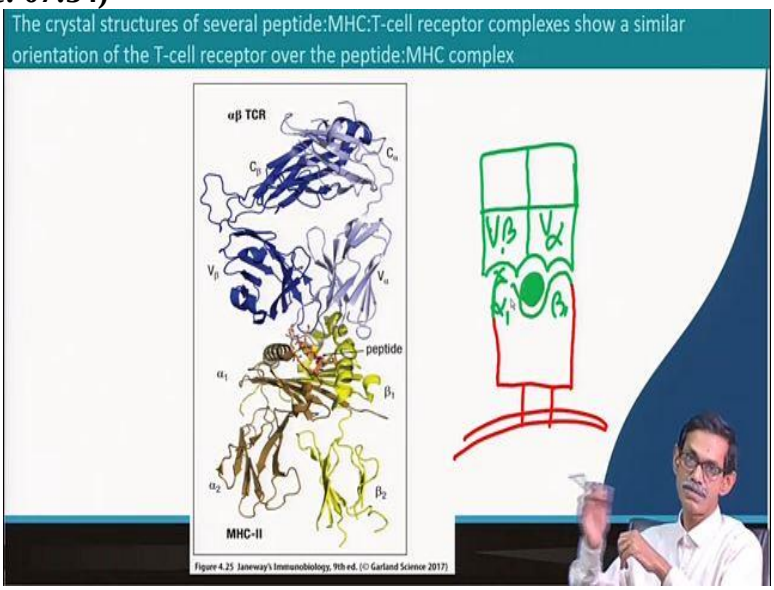

Same way, when you see the MHC 2 TCR complex, similar, like this is the beta 1 beta 2 of MHC 2 and this is alpha 1 alpha 2 of MHC 2, you can always remember alpha beta, so, why I am saying alpha beta because you see, the MHC 2 alpha 1 is interacting with variable beta. So, alpha beta and alpha beta. So, this alpha variable region is interacting with beta 1 domain of MHC 2 and beta variable region is interacting with alpha 1.

So, it is very easy to remember that this is MHC molecule. This is peptide definitely the internal part I told you in a finger with a finger, that internal part and if you just if you correlate with the antigen. So, the if this is so, let me draw if this is MHC, like the way we used to see if this is a MHC this is a membrane and this is the peptide. This is peptide now, if I use the TCR is green, this is TCR. You see this part is interacting. So, TCR this part, if it is let me put in like this is V beta and this is V alpha.

And it will be alpha 1 and this will be beta 1. So, this I am comparing with this. So, since this domain is interacting with alpha and beta and the center part of the T cell receptor is actually interacting with the antigen. So, that way the alpha i mean in TCR that we will see in T cell receptor also the part interacting with the MHC is not that much variable and the central part of the TCR is contributed by what I told you before also this is the CDR 3.

So CDR 3 that is why most variable in T cell receptor in antibody also, because they are interacting with a variety of antigens, though they are our variety of MHC, but it is not as much as different variety of antigen. So, it is not going to be as much as do as many variety of antigen because MHC has a limited number antigen is unlimited.

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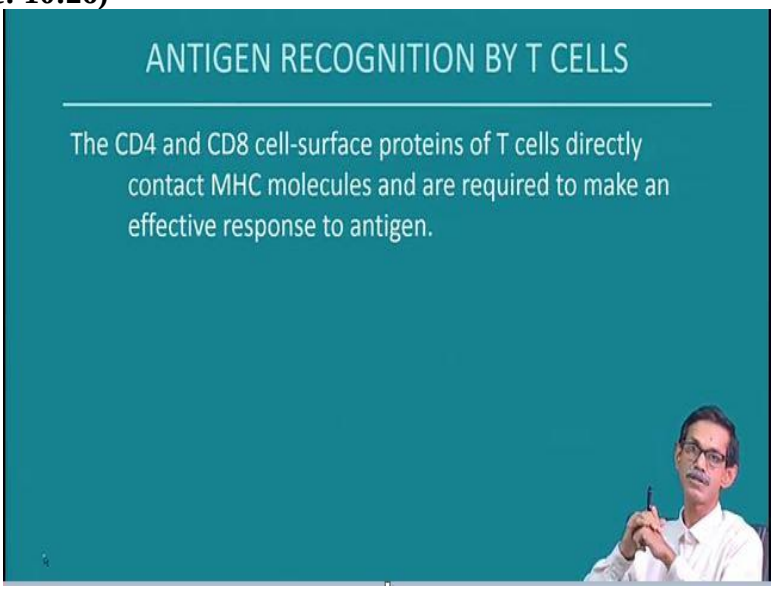

So, these MHC definitely interacting with the TCR MHC with antigen is definitely interacting with their TCR but along with that, it is also interacting with the CD4 and CD8 cell-surface protein. We already discuss about CD4 and CD8 as a co receptor of T cell. While we are discussing the TC varieties of T cell receptor, so it is also interacting with CD4 and CD8. If you remember I told that CD for presenting in the helper cell and see the 8 present in the cytotoxic T cell.

How it is determined that and if I ask you a question like which kind of antigen is presented by MHC 1? MHC 1 is presenting the intracellular antigen that means, a protein synthesized inside

the cell is presented by MHC 1 and that is recognized by cytotoxic T cell. So, that cytotoxic T cell is going to what is going to do they are going to kill the cell. So, cytotoxic T cell is recognizing either virus infected cell or tumor cells in both the cases the protein is synthesized inside the cell and that is presented by MHC 1.

In that case it should be recognized by cytotoxic T cell and cell should be but in case of MHC 2, it is mostly helping or mostly presenting the T helper cells, because that T helper cells are going to get the signal from MHC TCR complex antigen complex and that signal will ultimately help the B cell to proliferate. So, anything coming from outside is going to present by MHC 2 and MHC 2 is interacting with CD4 cells that means helper cells, so, how it is determined, actually.

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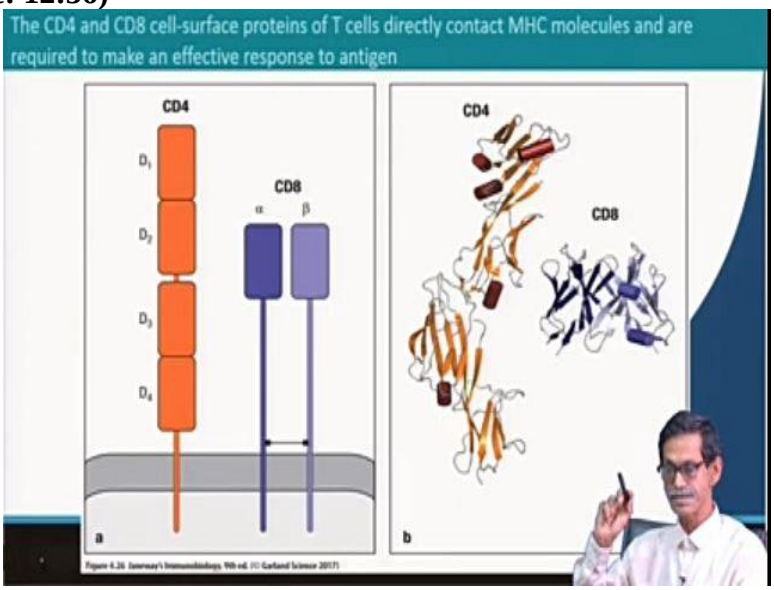

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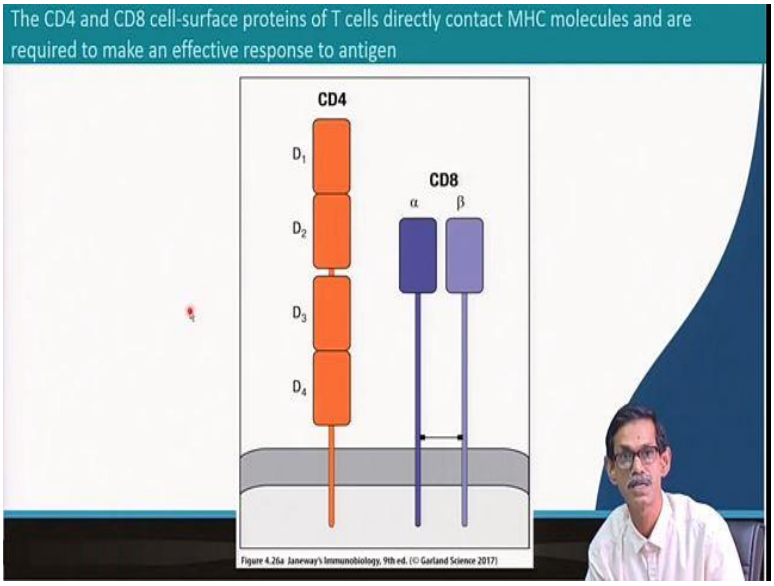

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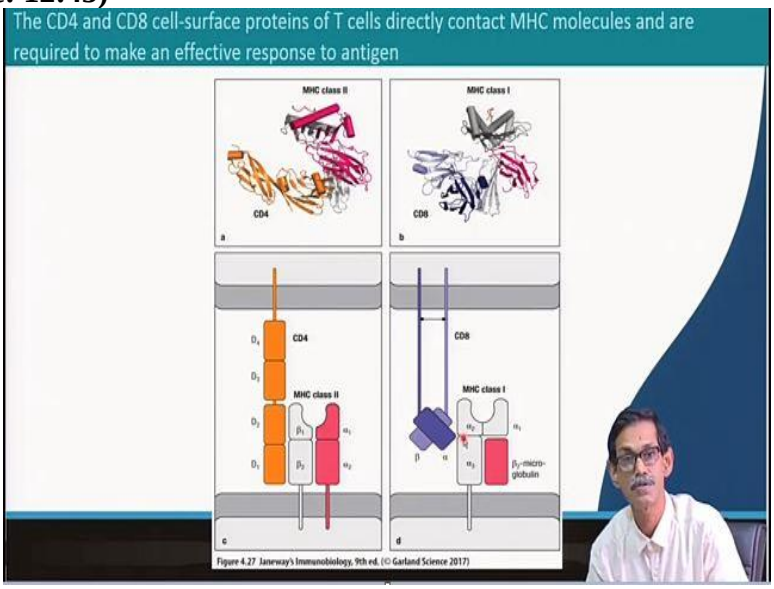

I f you see, this is this picture, this slide you already have seen this slide, the CD4 and CD8, you know, I am not going to go detail, but if you see this picture, if you see this picture, you see the MHC class 2 molecule alpha beta is interacting with cytotoxic I mean with T cell receptor along with the peptide, but it is also interacting with the CD4. So, this interaction is this the interaction that means the beta chain of MHC class 2 are very specifically interacting with CD4. Similarly, the alpha 2 and alpha 3 domain of MHC class 1 is interacting with CD8.

So, just this MHC 1 and CD8 cell that means, a cytotoxic T cell interaction was also not only made sure, because if these cross react that will be a serious problem in the immune system

suppose, suddenly the CD8 started interacting with MHC 2, CD8 started interacting with MHC 2 that will be a serious problem you can imagine.

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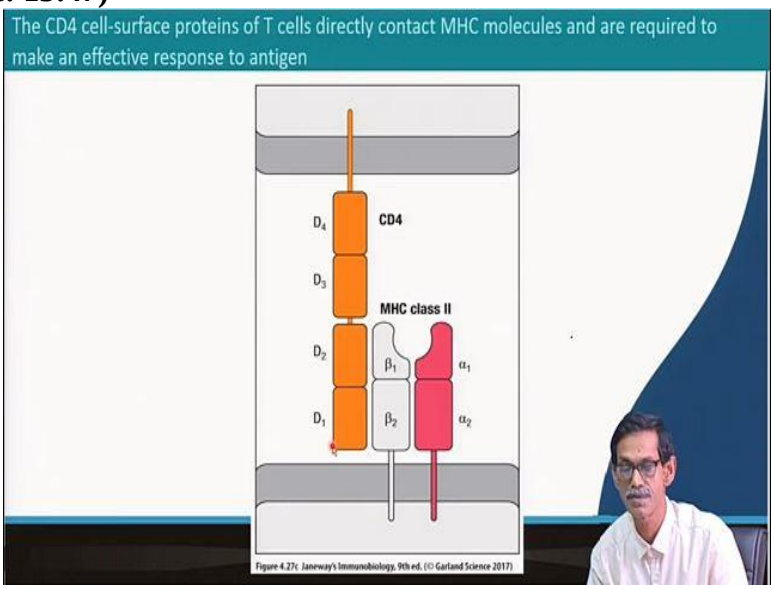

I will tell, but this is also this is a weaker person that MHC interact with TCR as well MHC 2 interact with TCR as well as interacting with CD4 co receptor of the T cell. Similarly, CD8 interact with MHC class 1.

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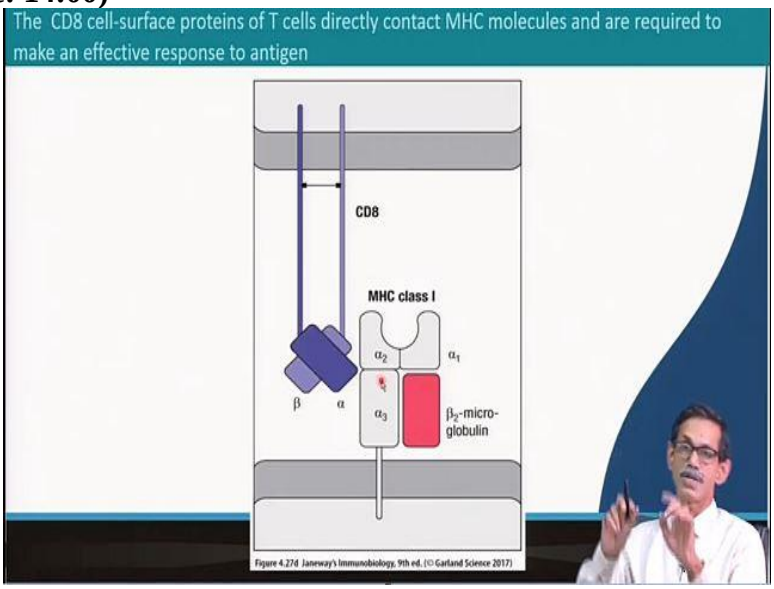

Because this interaction is necessary because cytotoxic T cell recognition is not a good thing. So, if by mistake EP to recognize any of our own cell that will kill our own cell. So, that mistakes should not happen. So, only virus infected cell and tumor cells should be recognized by the

cytotoxic T cell, otherwise it will be here big problem if there is any cross matching, like if MHC 2 is recognized by the CD8 cells.

This is kind a weird. I am repeating the same thing. This way or that way. It may be a little confusing, but it is very simple, I already wants told is very simple and straightforward will come when antigen presentation will come. That time it will be pretty much clear why these things happen though it is discussed in very early classes.

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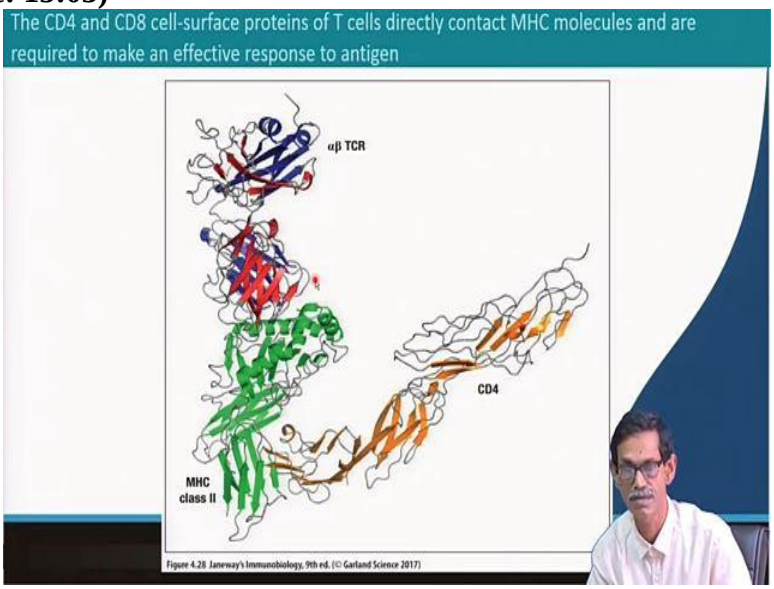

So, this is the crystal structure where it is showing that alpha beta T cell receptor, MHC class 2 CD4, all interacting. It is not just, I mean why I am showing this picture, you do not have to remember all this thing, but it is not just the cartoon I draw that is, so, when it is crystallized, it is also found that the CD4 is interacting with this MHC class 2 and definitely the TCR molecule of alpha beta type. So, this is to prove on the confirmation that whatever in the previous slide was shown, it is not just people thought that this thing is happening, it is happening and it is proved by crystallization of the whole complex.

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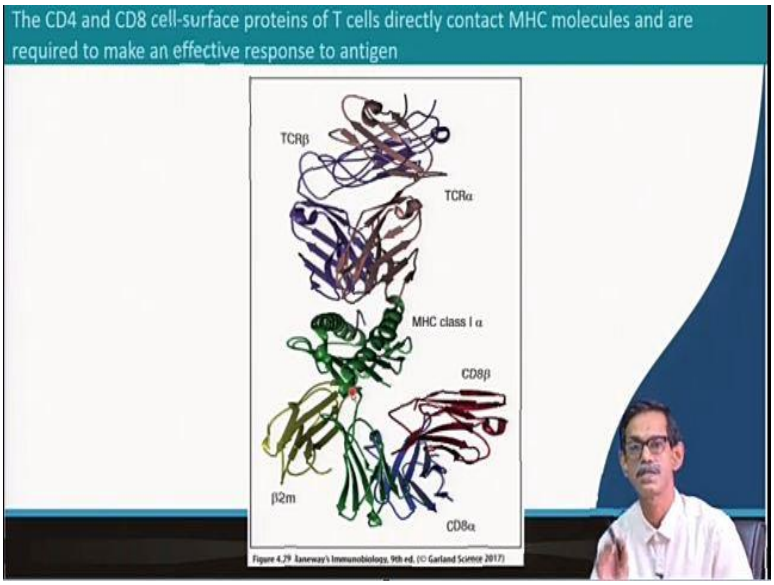

This is a same thing with CD8, like TCR MHC 1 and CD8 in both cases, it is not just a speculation it is fact.

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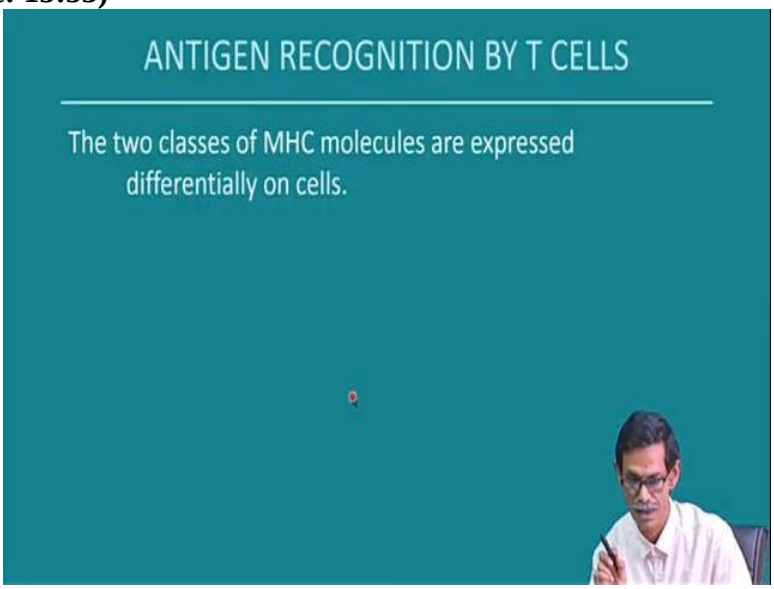

So, these 2 classes now, I mean now, it will be very clear on what I was discussing before these 2 classes of MHC that means MHC 1 and MHC 2 are expressed differently on cells. What that means differently on cells?

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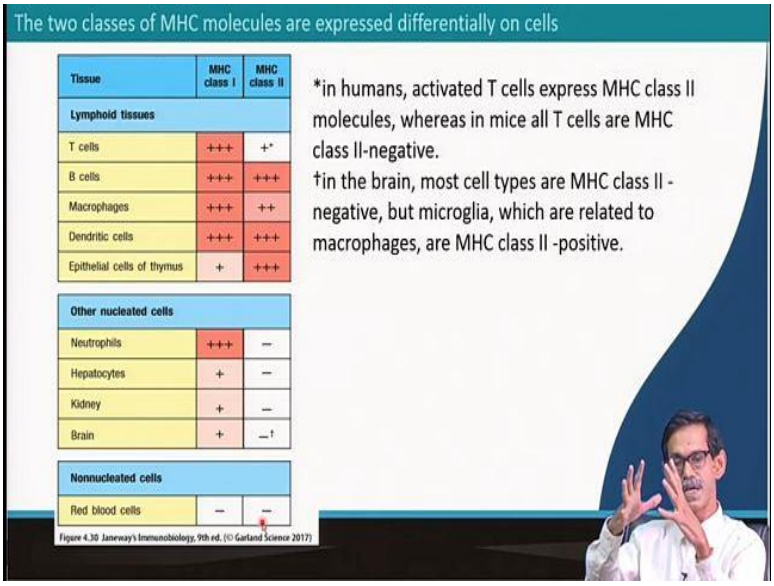

I will show you a table. So, if you see this is MHC class 1. So, this column is MHC class 1, these column is MHC class 2, if you use T cell express MHC class 1, heavily MHC class 2 is not that much. Why, because in human cells activated T cells express MHC 2. Whereas in mice, I mean, where it is tested or most of them in expert by immunology experiment was taken and done. In that case, mouse is completely MHC class 2 negative which is also written I kept it in just in case if you forget this.

What does this Asterix means, B cell express both of them highly positive that means they are expressing macrophage expressing MHC 1, very much MHC 2, little less, but they are expressing a very good amount dendritic cells, they are also expressing both MHC 1 and MHC 2 heavily epithelial cell of timers MHC 1 is very little MHC 2 is very high, if you go other nucleated cells, so, what is the similarity of the cells, because they are all immune cells or cells, which are involved in immune system.

But other cells, like normal cells neutrophil is definitely is a part of immune system, they express mostly MHC class 1, not MHC, so, other cells if you see, I mean except this top 5 neutrophil, hepatocytes, kidney brain or you take any somatic cells which present in other parts like skin, you would not see they are expressing MHC class 2 but all of them new trouble is definitely expressing good amount of MHC class 1, but other cells all are expressing MHC 1.

You take any cells from body, most likely they are expressing or all of them are expressing MHC 1, maybe their expression level varies between each other, but MHC 2 is very much restricted to very few cells. If I ignore the T cells because it is only in the activated T cells sometimes expressed that B cells Macrophages dendritic cell and epithelial cell have timers, which is not normally we need it, because timers is only responsible for the development of T cells. And after puberty, timers is disappeared in any adult individual, we do not have timers anymore.

So, this thing if we just ignore the timing, then B cell macrophage, and dendritic cells, these 3 cells are express the MHC 2 at maximum level rest almost no or 0, you know, why this thing happening? What is the role of this B cell macrophage and dendritic cells, B cell, macrophage and dendritic cells are antigen presenting cells, they are professional antigen presenting cells, they have the responsibility or they have the duty to process the antigen and present to MHC 2 to T helper cells and man.

Which in turn helps the B cells to produce antibody. So, major contribution of adaptive immunity or antibody mediated immunity you need that antigen presenting cells. So, antigen presenting cells are B cells, dendritic cells and macrophages. They are the only 3 antigen presenting cells we call it professional antigen present cells, they need MHC 2, because they need to present the processed peptide to T helper cells, rest of the cells, they do not need that because they do not have that response. They do not interact with the TCR.

That so you do not have. Any cells does not have this MHC 2 one thing, we should remember that every cells in our body, they are very economic, economic in that sense, they do not express any protein if they do not need, they do not waste any single ATP if they do not need. So, they are very particular about it. So, if any cell does not require to present the antigen they do not need MHC 2, but why do we need MHC 1 because MHC 1 if you go back to the lecture, early part of this lecture.

What I told is, MHC 1 is responsible to present internal peptide or internal protein in endogenous protein, more specifically, that means the proteins that are synthesized inside the cell are going to be presented by MHC 1. So, all virus infection proteins are expressed inside the cell. If any cell

converted to tumor or cancer cell, they express the protein inside the cell. So, if you think carefully that any part of our body is very much prone to infected with virus.

Like say for example, if I say the hepatocyte, the liver cells, in heypator, sites can be infected by hepatitis virus, hepatitis B, C. So, any cell of our body can be infected to by virus, or any part or any tissue of our body can convert to cancer cells, or can convert to tumor cells so easily need to protect only by cytotoxic T cell to kill them. So, all cells need MHC 1, because all cells of our body can be infected by virus.

Not only that, any part of our body can we convert it to or transform to cancer cells. So, to protect that all cells are expressing MHC 1, because also needed, but MHC 2, we do not need it and that is why it is like distributed automatically by evolution. That way, whenever we do need it is not there. If you see the bottom part the red blood cells, neither MHC 1 nor MHC 2, because RBC you know, human RBC particularly we do not have nucleus see there is no nucleus no protein synthesis.

So, if there is no protein synthesis, MHC 1 is not required. There is no proteins in a MHC 1 is not required. If they cannot eat or do phagocytosis or they cannot synthesize the MHC 2 also, so, it is not there. So, this is the general distribution of MHC 1 and MHC 2 and it is also even if you remember this automatically, you can remember their function like whatever is you want MHC to do, or either way, if you remember what is the role of MHC 1, you can remember their disk their distribution in different part of our body or different cell system of our body.

So now I am just seeing the red blood cells. I cannot stop myself to tell you, like, if you remember different pathogens, like our immune system can handle them, if you remember, and most of you know I am sure I am just repeating it again, and those who do not know just for them, malaria parasite, Plasmodium, the Plasmodium falciparum mostly there are vyvanse and others, but Plasmodium falciparum you know, they are growing inside you know, they are growing inside the RBC, imagine how smart they are.

So, first thing they grow inside ourselves, so immune system will not see them. Not only that, that RBC where they are growing and killing one by one and the replicate inside the cell, they cannot express or they do not express, they do not have the machinery to express MHC 1 and MHC 2. So while they are growing inside, if you remember the mycobacteria, which grew inside the macrophage, so this is for initial part of their growth is fine because as long as they are inside the macrophage, our immune system cannot see them.

But eventually they are visible and TH 1 response is there to kill them. But in case of Plasmodium falciparum, I am telling how and how the pathogens are smart and clever to bypass the immune system. So, the malaria parasite grew inside the RBC, which neither express MHC 1 nor express MHC 2. So, while they are growing inside, no way they, are antigen you will be presented on the surface of RBC and as long as they are not presented by MHC 1 or MHC 2 either 1 immune system cannot see them T cell cannot see them.

If T cell cannot see them, even B cells see them cannot do much. So, that way they are they are very, very smart parasite, much smart parasite actually parasitism. We should not blame them, we should blame us actually our evolution rather, because, you see, they are all parasite if I talk the Plasmodium falciparum, this is a protozoa single celled eukaryotic system. So, they evolved long before the human evolved.

So they are surviving. So it is not that they grow I mean they came to me to infect us they were there we came later and unfortunately, we are the host. So, that is why immune system is I mean very find very difficult to find generally most of the intracellular parasite particularly this kind of parasite, which grow inside RBC are even tough. So, you know, the cycle of the parasite in particular the Plasmodium.

So, they infect 1 RBC grow inside then the parts many parasite particle come out and then in fact, multiple new parasite just like spider slices. So, only that period of time. So, when they are inside the RBC, nothing happened we are I mean if someone is infected, then normal as soon as the burst the fever comes chill as severe killing and the fever started and very particular time. So,

this is the symptom of malaria parasite, because you see a fever in a regular interval 12 hours or 24 hours that time actually the burst as long as they are outside the fever is there.

Whenever they found new host they enter again they are secure and immune system cannot see. So, why I am telling all this thing in immunology because we have to know the disease also by immune system or vaccine to protect us. So, if we have to understand their life cycle, we have to know how what is the time span they are staying outside, this is the only time to attack them by immune system.

So, even if we develop a vaccine, we have to be very careful to design that that should be more efficient and they should find that form of because in parasite there are I mean, this particular parasite plasmodium there are 2 form sporozoites and merozoites so that particular time they have to either do have to block the attachment have parasites with the new RBC, so that they even infect but they cannot propagate or we have to kill them or agglutinate them or help them help the macrophages to phagocytosis them.

So, this is so, whenever I mean definitely we are discussing the immune system or immunology, but too apt what is the application of this immunology. So, we have to understand immune system we have to understand the different disease different pathogens, whether it is a bacteria or virus, their life cycle, they are strategy, how they invert their molecule at molecular level then only we can defend. Besides this, they also have another strategy of the malaria parasite which is very common to many other parasites or infectious agent.

They have a surface protein, it is called circumsporozoite protein, which is varied there are at least 200 different genes and every time they affect in new 1, so, even if we introduced 1 antibody which is specific to 1 circumsporozoite protein, they may not be active for the next one or next one they have a multiple copy. So, they express randomly and in one particular cell they have only one type. So, this is another variety you have heard like viruses changing their surface protein that is why antibody is not our vaccine is not working, but malady is like that.

So, all these parameters of the infectious agent we have to know in one hand and other hand we have to know how immune system work and what how we can manipulate and put together if we can manage or manipulate the immune system, then only we can be successful in eradicating the different disease or development of different vaccines. So that way, so these distribution of MHC is very, very important and will tell us what is their role in immune system, so we will talk about I mean still continue the different few things are still there to discuss about MHC they are doing and see you in the next class.