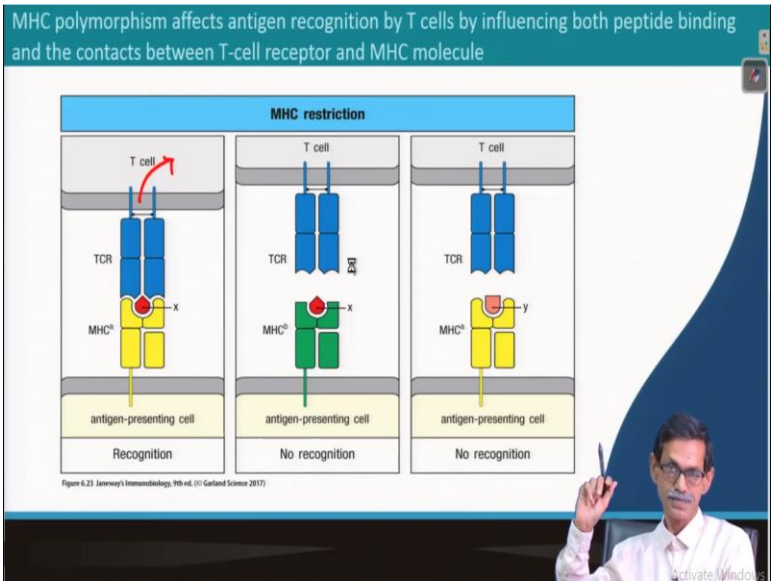
Immunology
Prof. Sudip Kumar Ghosh
Department of Biotechnology
Indian Institute of Technology, Kharagpur

Lecture No -22
Antigen Recognition By T Cells: Major Histocompatibility Complex (Contd.)

So we will start again the Major Histocompatibility Complex, few important thing we need to know and this will continue from last lecture also. So we are going to discuss like what is the recognition of MHC TCR, we are talking about different domain like polymorphism, how it is related to interact with the TCR widening of the MHC part as well as the peptide part inside the MHC how it is interacting.

So this interaction, I mean if you consider, if you understand like MHC with peptide and TCR how they interact, so we have a better picture now.

(Refer Slide Time: 00:57)



So what we can tell is that, this antigen presenting when everything is perfect like TCR is interacting with MHC along with the peptide, you see in this cartoon which is very straight forward not like before the crystal structure. The MHC 1, alpha 1 and alpha 2 presenting antigen x. Here MHCa whatever you are seeing this is just to differentiate between two different MHC, MHCa here, MHCb here. It is not no relation with 1 and 2 all are MHC 1**.**

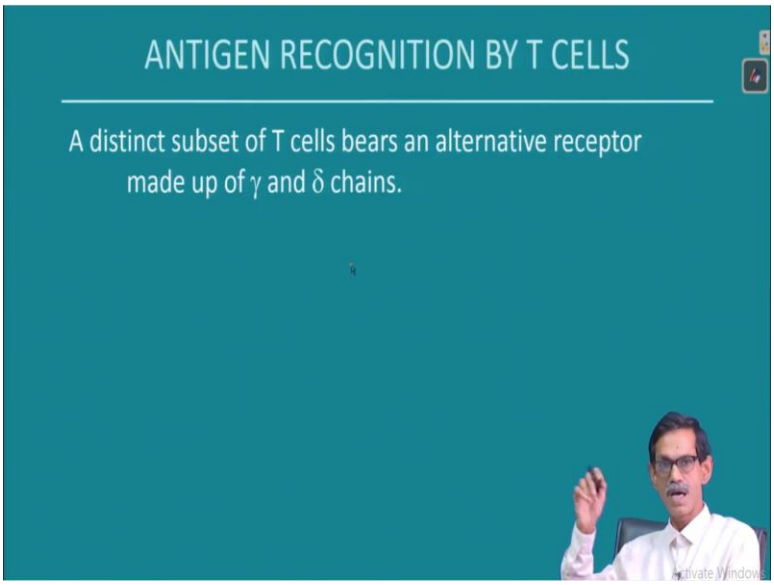
So this MHC 1 is present MHCa type, MHC 1 is presenting x and the n and any particular T cell having a receptor like this is interacting both with MHC nicely as well as with the antigen. So this is the ideal condition for TCR and MHC antigen complex recognition. But if the MHC is different even the antigen is same the x, but TCR it can recognize x, but as it cannot recognize the MHC 1 or B type it there will be no interaction or no recognition.

Same way if the this same MHC, MHCa type MHC 1 presenting y molecule because one type of MHC can present a x, y, z different type they are not that restricted that we already know. In that case this TCR which can recognize antigen x, will also not recognize. So that means the image TCR recognition to antigen MHC complex is not either MHC or antigen independently, they should be both antigen and MHC complex, both should be recognized by particular T cell receptor.

So this phenomena is also known as MHC restriction, so neither this case, nor this case, nor this case neither one will have any recognition and if there is no recognition the T cell will not do anything. Because these interaction, strong interaction is very much important, if this interaction happens then only signal will go inside and give the cell response to do next job like proliferation and producing different cytokines to activate B cells and to get.

Sorry to have as this is MHC 1 to be activated by the effector cells, so that it can kill the cytotoxic, these cytotoxic T cells can kill the tumor cells or virus infected cells, but if this one is not so these phenomena again I am repeating is called MHC restriction.

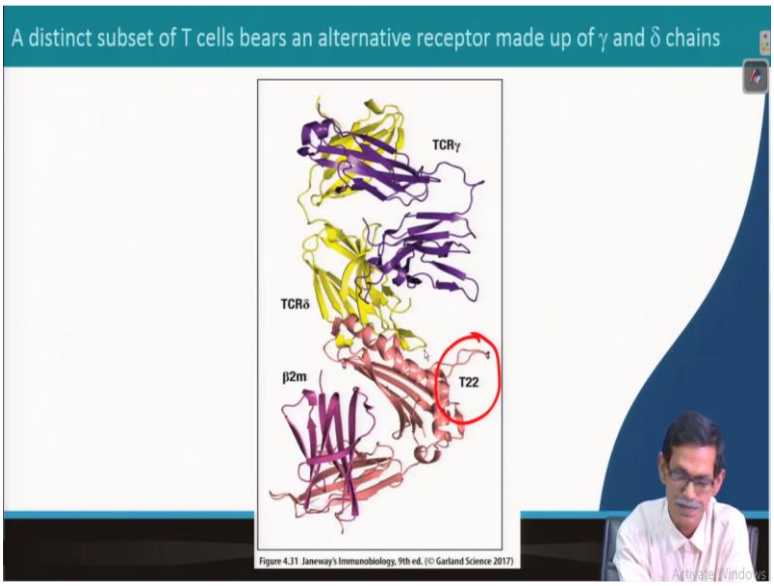
(Refer Slide Time: 04:02)



So we mostly, whole immune system in most of the immunology book, if you find we are talking mostly about alpha and beta type of T cell receptor, gamma and delta T cell receptor is not known as much as we know about the alpha and beta type. We know that it is there we know their function not much research has been on and not much is included in the book. So in basic immunology concept development or the course also we have.

I mean we do not include the gamma delta receptor part that much. But few things we should remember or know that gamma delta chains or the gamma delta T cell receptor is not recognizing that normal MHC 1, MHC 2 present itself. They have a very specific it is different sets of receptor made antigen that they can I will just give you one example here.

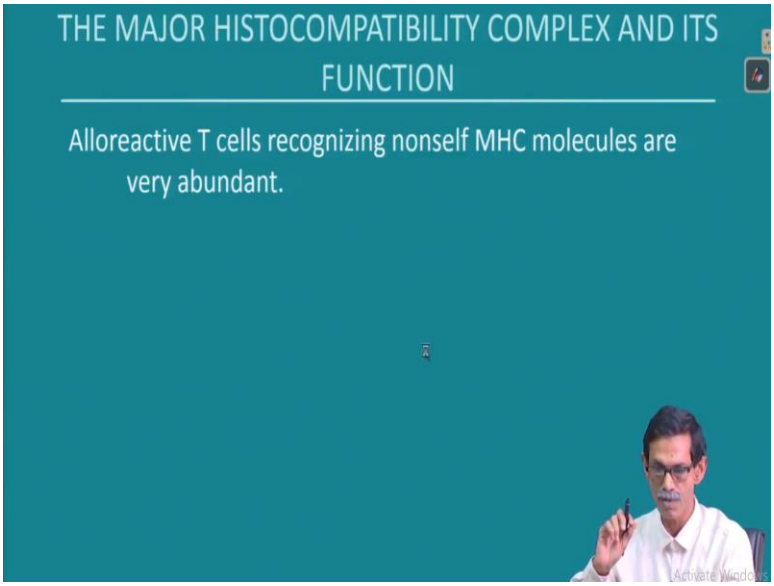
(Refer Slide Time: 05:00)



There is a specific receptor called, this is pacific legend which is T22. I can give you a series or table which is available in net or in book like gamma delta receptor can recognize different type of alternative kind of receptor by which it is recognizing and this x1, a1, 2, 3, 4, 5. So there is no point of remembering all these names at this stage. If you are working or doing research on common delta receptor of T cells in future if you are interested then you will have to know that like what is known what is not known and what you should do.

But at this moment on the alpha beta receptor there concept the immune system is developed and you just for the information you should remember that gamma delta T cell receptor bears an alternative receptor, that made up of the gamma delta chain that can recognize different kind of antigens not the general antigen is processed and presented by MHC 1 and MHC 2.

(Refer Slide Time: 06:07)



So far just we told the MHC restriction that means T cells should recognize the receptor MHC first and then the antigen. But what I did not tell that time I definitely I told you before that this MHC should be self MHC. Self MHC means my T cell receptor will recognize my MHC that is how they can figure out which self which is non-self that is a kind of dress code like military code.

So whoever having that cap is Indian, whoever having that cap is from another country. So seeing the cap or seeing that jersey, so MHC molecule is just like a jersey that we discussed also before to know from far, he is a my team member or member of other team or the player of other team. So you may see the cognition is very, very important. So whatever antigen presented by my MHC I am talking about my MHC, then only T cell receptor can recognize that.

So my T cell receptor will not recognize the antigen presented by somebody else's MHC until unless it is very same or similar. So this kind of training is very important when T cell developed. But even after that it was found that there is some alloreactive T cells which recognize non-self MHC how it is determined. It is determined because if this is true that my T cells cannot particularly the cytotoxic T cells are more important here.

If cytotoxic T cells are not recognizing anybody else's MHC then transplantation should not be a problem. Why we are typing MHC so much? Because if any organ from somebody else is

transplanted to my body T cell will not recognize them because MHC is different and if MHC is different then no immune reaction, but it does not happen. If TCS is not matched properly if MHC is not matching properly or T so typing is not good for whatever reason the transplanted organ will be rejected by our body very short period.

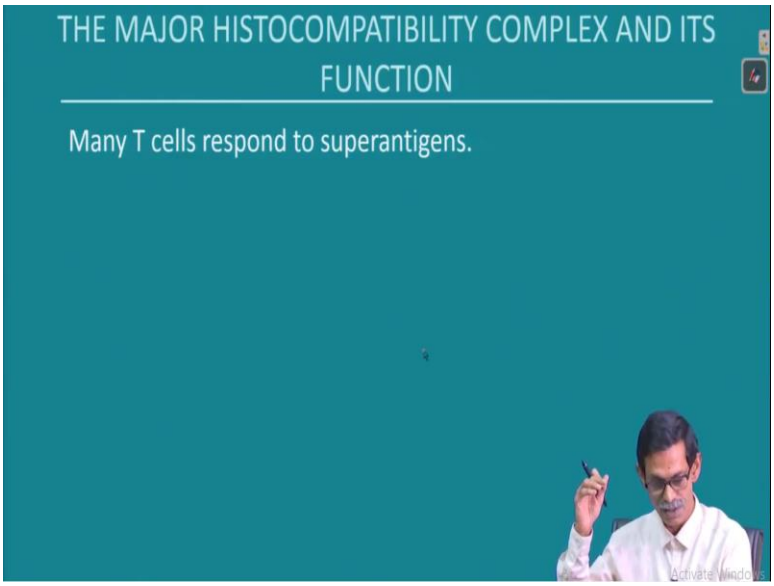
It is just like a regular immune reaction, that will study little bit more detail while discussing the transplantation in the later stage of this course. But for at this moment if understand or believe me that if any organ even a small part of skin from somebody else its transplanted on my body it will be rejected within 7 to 10days. So all cytotoxic T cell will be activated and eat it. So if that statement like my T-cell receptor can recognize only my MHC if it is 100% true, then it should not happen.

If I mean just to start that effect like why it is happening it was found that along with that self recognizing T cell resolve a mystery recognizing T cell receptor which we have or which you see along with that there are a another group of T cell receptor which is alloreactive. Alloreactive means which can recognize non-self MHC molecule. That types of alloreactive T cell receptor are basically doing the rejection of the transplant organ or tissue.

It varies from 1 to 10% depending on the individuals. But they are not lesser, 1 and 10% is good enough if you see the total number of T cell present in our body 10% is a good enough number or even 5% is a good enough number. So these alloreactive T cells, so while we are studying the MHC and the T cell recognition or interaction part at this moment, we should remember along with self recognizing MHC, we also have alloreactive T cell.

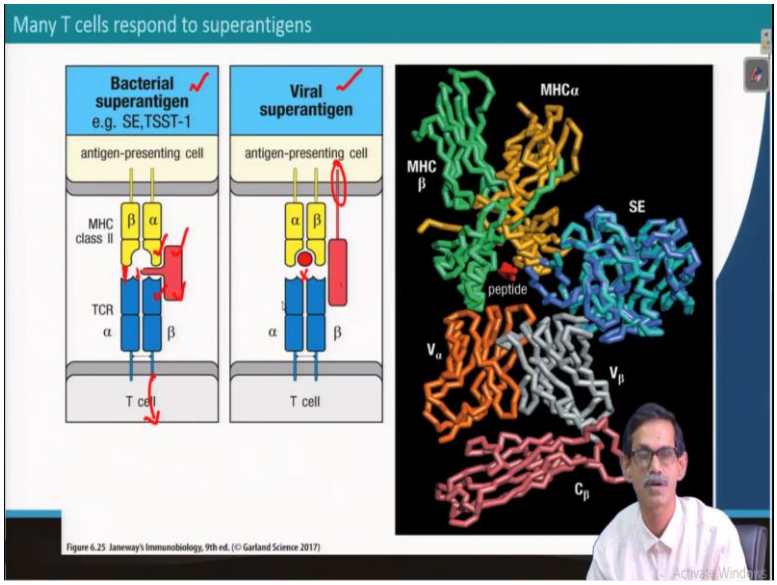
Allo means can recognize some other allel of T cell MHC which is not my cell. Alloreacting T cell recognizing nonself MHC molecules. Generally the percentage varies between 1 to 10% depending on the individuals.

(Refer Slide Time: 10:58)



This is one more information you should remember, another important thing that T cell receptor response superantigens. What is the superantigens? By name you can guess little bit and antigens means which can induce the immune system or which can immune system can recognize them and find them as foreign and there are antigen which is even more powerful called superantigen.

(Refer Slide Time: 11:23)



What is the superantigen? Also the picture it will be clear very much, so if you see this picture normally what happened, this MHC 2 you can recognize by alpha beta 2 chain, alpha and beta domain presenting one antigen, so this is a normal feature. So if T cell receptor can recognize it, so in that case if you remember the MHC restriction what is going to happen this T cell receptor will recognize this part and also this part and this part through antigens.

So this can happen and this is very specific if you just go back or remembers that image statistics and slides where we saw that MHCa, where everything is perfect so interaction is there or no recognition is there in one case. MHC is not matching another case antigen is not matching in both case it has no recognition, but here what will happen there are certain antigen which is called superantigen.

They do not need the presentation by MHC they are even smart enough. That is why they are superantigen. In case of bacterial superantigen, you can understand from this light like there are two type one is bacterial another is Viral. So not all the antigens from bacterial are superantigens, certain bacteria produce some proteins which act as superantigen, similarly some Viral proteins are act like superantigens.

Why they are called superantigen, because there is no need to be processed and presented by MHC. What they are doing, they have some sequence which nicely interact with the alpha 1 domain with super antigen as well as beta chain, which is a variable beta domain and this. So this part without going to proper channel they can interact sidewise. And these sidewise interaction what they are doing even antigen is not there suppose there is no peptide here this red is not there.

If that red is not there, if suppose if there is no red here even after that it will interact with the MHC and T cell. They will bring them together and make a strong interaction, say like T cell or any other cell that we have you know said, they do not have any eye right. They see only by each other, they talk between each other they give signal to nearest cell or the neighboring cells by protein-protein interaction only.

So as soon as this interaction happened T cell will realize or think that some antigen is presented and I am interacting, even there is no antigen this interaction may be there. So this interaction in presence of antigen or in absence of antigen will bring MHC class 2 and T cell receptor together and T cell will think that enough binding with enough strength is there, so signal should go

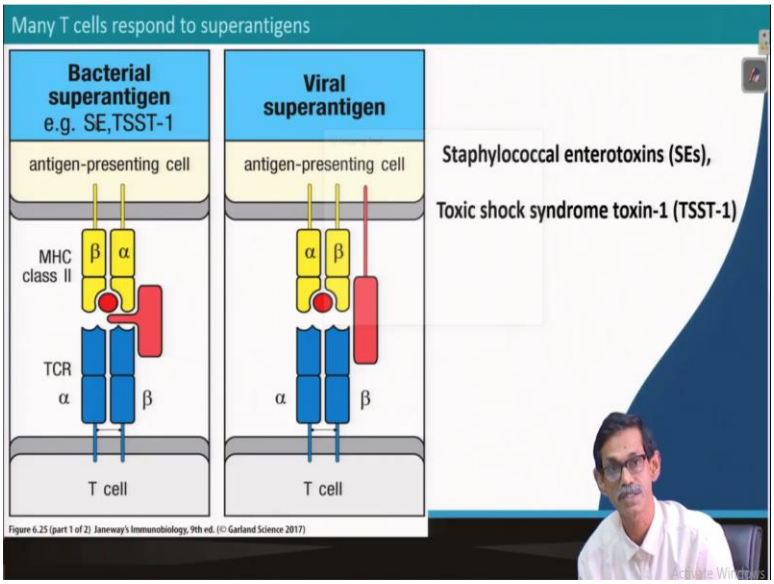
inside and then we proliferated and that proliferation will increase the numbers. So what you can understand, I mean you can guess, I will tell the answer after discussing the viral one.

You see the viral one is doing the same thing, but in case of viral one, one more thing is there the viral one, the viral antigen should be integrated this is one difference normally and here you see interaction between alpha, alpha chain of MHC and beta chain of T cell. In this case what happened both are beta, so beta chain of T cell and beta chain of antigen presenting cells. So, antigen presenting cell is infected with virus, mostly dendritic cells happen.

They express the viral antigen which will bring the T cell even without any proper interaction in this case. So both the cases whether either it is a virus or bacterial antigen, both the cases T cell and MHC come together without or with proper interaction. See if the proper introduction is there so antigen recognition is there it will come automatically we do not need super antigen. But even if it is not there they come closer and interact and signal will go to the T cell for proliferation.

So this kind of superantigen what they are doing it is a general inflammation kind of thing so whole T cell population wherever they will find interact that T cell non-specifically will be get activated and proliferate.

(Refer Slide Time: 17:06)



So these this is and two examples are here, I mean here one is Staphylococcal enterotoxin, this one SE stands for Staphylococcal enterotoxin and other one is Toxic shock syndrome toxin and this is also Staphylococcal (())(17:16)), also produced by the Staphylococcal toxic. Both the cases these two proteins can act as superantigen many viral protein can act as super antigen. But how this evolution or this kind of interaction helps were is in negative flip interact or they block the T-cell.

And what is the effect of this production of superantigen by this bacteria or virus is not very clear in case of pathology. It is not known much, but this is a very common and this the superantigen can cause some general fever, some because it will cause lot of different immune reaction and as it is already some site expression like we can feel fever or something can happen. But scientists are scientists, as soon as they saw this the super antigen is have a general capability or capacity to activate the immune system in general.

The T-cell will be activated they started thinking how can we exploit this property and do something. That is where the knowledge of regular system like even in biology most of the; whatever you say biotechnology kind of development or anything. So biological system is doing something for their own survival, for their own fitness to this system, because they have to fit themselves best so that they can survive so many you know.

So but scientists are you, all of you are welcome just whenever you see something any effect if you start thinking how you can use this for our day-to-day life. Maybe medical maybe something else not everything is or not all technologies and medicals not everybody's probably helping the production of medicine or developing drug or developing vaccines, something else also can be possible.

So there are many such example I am not going to go that so to do biotechnology these kind of information, so this is the place of information like there are superantigen if I tell you what can be done. There are super antigen present, in some bacteria also some viral protein are also acts as separate region which induce the T-cell population non-specifically. So the overall T-cell population so how can be used, so I am given I mean I am telling you because it is already

known. This is used during immunization what happened, people used to give the whole bacteria.

So if you inject a proper antigen for vaccination, what will happen that definitely it will go activate the immune system produce some memory cells which will remember. Next time if the disease real disease happens that will protect us that is a normal primary and secondary infection. So during primary infection what we mix with the vaccine is that we will discuss when you will discuss the vaccine.

Some material which that particular antigen which I want to raise the immunity or the interested particularly that antigen of interest is definitely there, along with that if I make some superantigen what will happen. If I mix some pure antigen that I would like to raise immunity against that definitely it will be there along in that little bit this superantigen molecule I just mix an inject what will happen.

Superantigen will activate the immune system, suppose somebody's immune system is going down or not good or not very effective to that antigen, that will not we do not have to think about that because these superantigens will activate the T-cell particularly the T helper cell you can see both of them are reacting with MHC 2. T helper cell will be activated when all T helper cell will be activated, the whole immune system will be very active.

And that among this all possible T helper cells some of them which is very specific to the antigen that I injected along with the superantigen that will also be activated. So more immune response against that indigenous interest will be much more right. So that is the reason why we use the superantigen. So that is a kind of information in immune system exploited in the regular technology, like how we can very simple information.

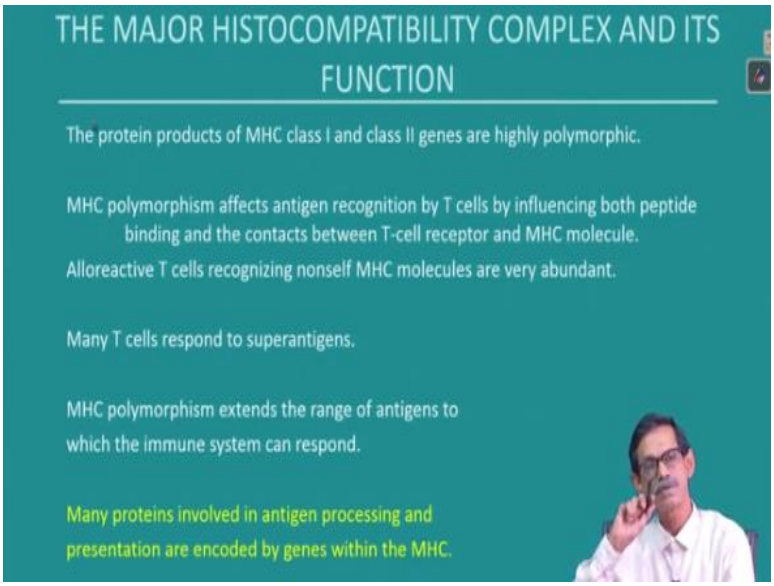
But someone thought and in what nice and there are a lot of superantigen or superantigen type so we use during immunization our various immunization that's going on to induce the immune system as a whole actually, for the first time remember we do not use superantigen every booster

dose. Booster dose I told in the last, the first injection is a primary injection and then second one second one injection is called first booster.

So first injection then first booster second booster third boosters something like that. It is not the first one is the first booster, first one is the first administration of the antigen, second administration is the first booster, so first administration time only we give this superantigen. But once it is already activated against that next time or not we do not use it so that is the process of immunization that in one of the classes when we will discuss what is vaccine how we can develop?

That time will say again this one may be little with more detail so this is superantigen which is normally present on present in nature but can be exploited for our own purpose or some development of vaccine or immunization process.

(Refer Slide Time: 23:39)



Now this is a kind of summary what we have discussed so far. There is no point of reading all this again. It is written here but as just to mention here if there is anything I missed also the protein product of MHC class 1 and class 2 genes are highly polymorphic. I am sure you have no doubt about it right now. MHC polymorphism effects antigen recognition by T-cell influencing both peptide binding and the contact between T-cell receptor and MHC molecule which indicate that the polymorphism given only change a different colors in the binding, cleft**.**

We see 1 and MHC 2 I saw to you the alpha chain only. So that part alloreactive T cells recognizing nonself MHC are very abundant that we just showed. So and we also told that this one is responsible for rejection of the transplant organ or host versus graft rejection or reaction. Many T cells can respond superantigen that we just discussed. MHC polymorphism extend the range of antigen and which other system can respond.

So importance of polymorphism, so why this polymorphism evolved what is the mechanism why not other genes many things could have happened. But this polymorphism how it is helpful that we already discussed, because different kind of and peptide we can MHC can fit into it. So if you have multiple variety of peptide can be displayed. Polygenic which is not written here, polygenic is also important because I have said 200 different genes, if one gene does not work or by some infection or somehow something happened 1 or 2 genes somehow blocked my whole immune system will not be 0.

So still I will have many other copies of MHC so multiple copy of a MHC is also very important not written here, but it is we should remember. Now the last thing is many proteins involved in antigen processing and presentation are encoded by genes within MHC. I am repeating again many protein genes involved in antigen processing and presentation are encoded by genes within MHC, this part we have not discussed yet.

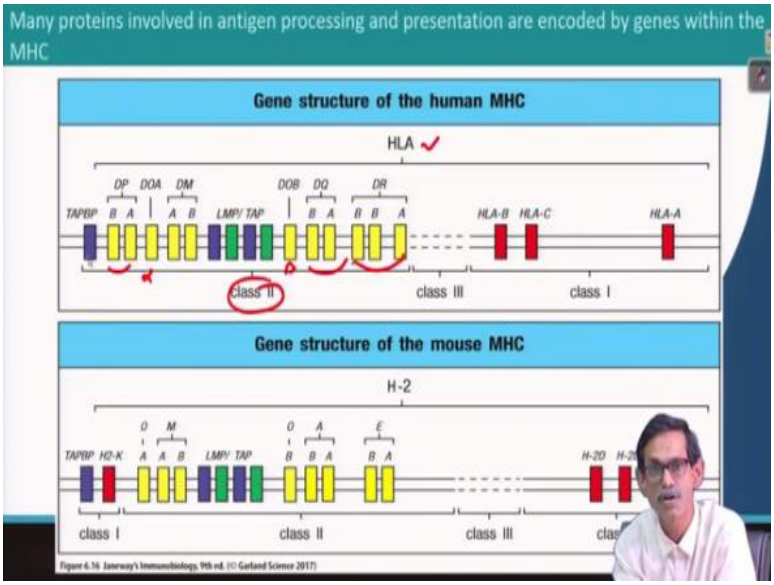
So far whatever we are discussing, we are discussing about structure of MHC, how it looks where is the difference between MHC 1 and MHC 2 hope all of everything you remember. So when when the question may come right in your exam in different form in different national level test, compression is all matching something some way or some other way if the question can come like what I mean how they are similar how they are different.

So compare means both you have to tell similarity and dissimilarity and difference mean only dissimilarity that I am sure you know and when MHC1 and MHC1 will be asked you have to tell both they are structural similarity and dissimilarity as well as functional similarity and

dissimilarity including binding to CD 8 and CD 4 that MHC 1 binds to CD 8, MHC 2 binds to CD 4.

It presents the endogenous antigen peptide and it presents the external peptides or protein which is taken from outside, so that we are already seen but these all these should be there. But this last line which is written in yellow the many proteins involving antigen processing that we have not studied may be in the next lecture we will start that we name its antigen processing.

(Refer Slide Time: 28:04)

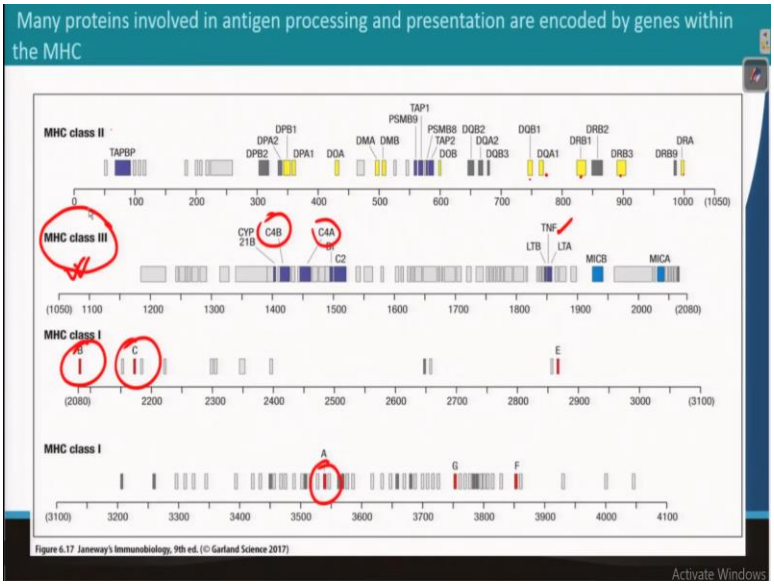


So many proteins involving antigen processing how they are located in MHC they are encoded within MSC so let us see whatever gene we are told M is shown how they organized this is the gene organization of messages you remember that the bar diagram of different genes like their polymorphism is very high some are very low so these are the genes actually DP, DM, A means alpha and B means beta there are DQ, DR there are two different DR.

Beta say gene two copies na and these are the class 2 you see here it is class 2, so this is one class 2 DQ DR. So DP DO is also there one alpha is here and beta is here and if you see the MHC class 1 this is there are 3 genes A, B and C polymorphism is there. So in chromosome it looks like this, this is for human is C this is called HLA and repeating again in human it is called human leukocyte antigen and in mouse it is called MHC.

In mouse also they are different class 2 genes but why we are saying that different antigen processing genes are in between because these genes LMP TAP which responsible for antigen processing are present within this region. So which you don't know now but we will discuss what is this TAP what is this LMP what is this TAP BP. So if you go to the detail chromosome map of human right.

(Refer Slide Time: 29:55)



The human chromosome genome organization if you see this that was the cartoon and this is the same map we you can all this just this all this are you yellow here like DQ, DR, DRB3, DRA. So all this yellow part is MHC 2 genes is a 7 c, class 2 which has this again tap 1, tap 2. Clear this tap 1, tap 2 is very important some of you may know will discuss again, MHC class 3, I will come later MHC class 1 genes B, C and A is here.

So A, B and C there are some other genes a GF they are important but not even a class 1 if you remember, the other which will it is not discussed much MHC class C genes are actually very tricky we do not have any messy class 3 like MHC 1 and MHC 2. There is no MHC class 3 but there are many genes like you can see the complement genes are here which is you were going to learn very soon.

That complement genes compliment 4 and there are some cytokines like TNF tumor necrosis factor T and F which is a cytokine, so these genes are present in between this MHC class 2 and

class 1, there are very important in which is required for MHC activation or the processing of antigen. So these genes which helping this antigen processing or immune system and activated along with them SC they are known as but they are not MHC directly like a MHC 1 and MHC 2 they are together all together they are called MHC class 3.

It is again I am repeating MHC, it is MHC class 3 it is not like a specific type of protein like MHC 1 and 2 there is no relation with the presentation or T-cell interaction. It is many proteins which involve in immune system cytokines complement and other proteins which activate the different process of antigen processing, so these genes are known as MHC class 3. So in next class we will see how the antigen process and antigen processing starts thank you very much.