Immunology
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Lecture No -21
Antigen Recognition By T Cells: Major Histocompatibility Complex (Contd,.)

So welcome, today's lecture we are going to continue on major histocompatibility complex which we were discussing in the last lecture like what is the distribution of the different MHC, MHC 1, and MHC 2 in different type of cells in our body? And we also discussed like how this is like about the malaria parasite have their smart and they can manage to bypass the immune system, I mean what, this is definitely by evolution.

So in last lecture I also told that MHC genes are highly polymorphic and purpose I mean what is the advantage of polymorphism also discussed like very superficially. But today's class we are mostly going to discuss or talk about what is polymorphism and how it is developed and why, how many different type of MHC's are there in so far known actually in human system?

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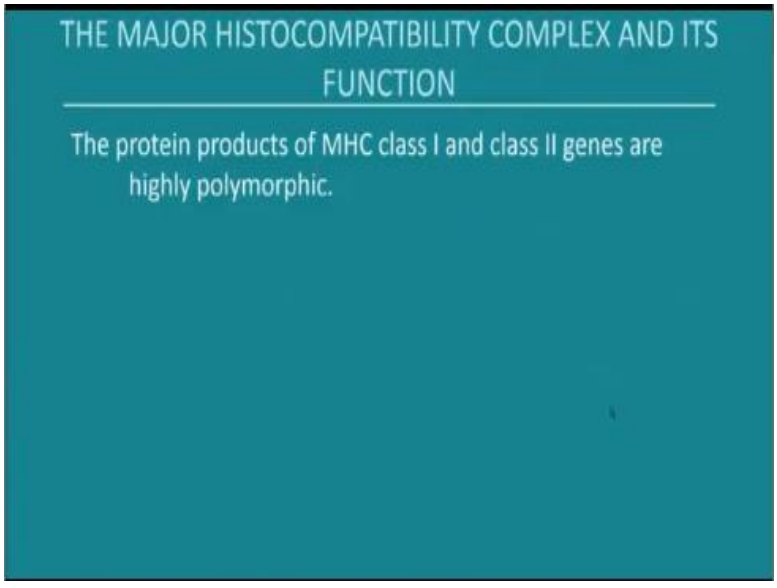

So the protein product of MHC class 1 and class 2 are highly polymorphic. So, if I say this and start with this.

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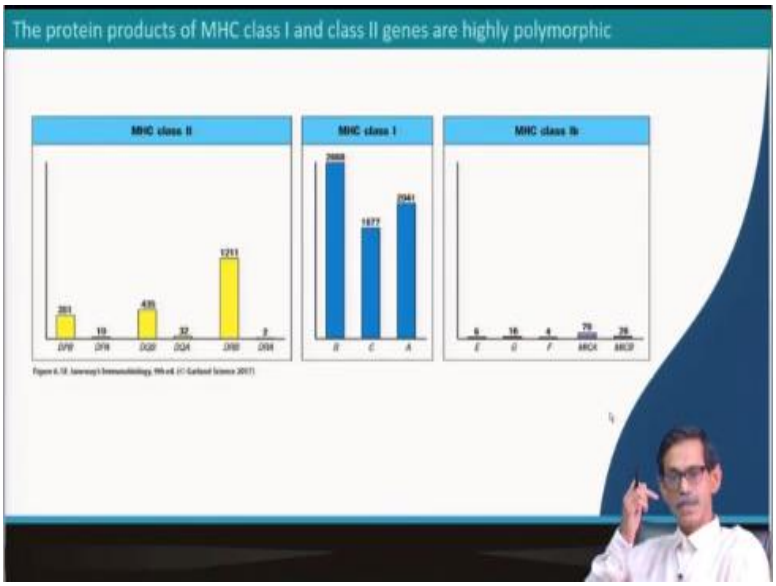

So you see this is the distribution in varieties of in MHC in human. In MHC in human it is actually, MHC major histocompatibility complex is mostly used in case of mouse though we are very commonly used in in human system also, but in human it is called HLA - Human Leukocyte Antigen, I am repeating again, Human Leukocyte Antigen, HLA. That is why many of you might have heard like during transplantation, it is called HLA typing.

HLA and MHC are all synonymous, so in human it is also called HLA. So, different numbers are there. So if we see, so this is MHC class 2. This is a MHC class 2, if we see MHC class 12, you are not familiar with this DPB, DPA, DQB, DQDRB**,** so just assume for the time being that these are different MHC class 2 gene. So A and B stands for alpha and beta, so there are DP set of genes which has DP alpha, DP beta because MHC 2 has both alpha and beta.

And DQ is one class of gene which has alpha and beta and DR is another which has alpha and beta. So if you see, so far variety, I mean a good number of human genome has been sequenced all over the world and after that if you consider all the MHC genes, if you just collect and do the Beinforis analysis, you can see that there are DP type beta gene has 351 variety and DP alpha has 19.

So if you have random combination like how many different variety of DP type MHC 2 is possible you have to just multiply 351 into 19. Same way DQ type 435 and 32, DR the variety is

maximum, 1211 times 2. So this is the different polymorphism, different polymorphic gene has been so far identified and if you have the same genome book or any other book of older version, if you find this number.

You see this number lesser than the or the values are less than the value I am showing here because more and more genome is sequenced, more and more new data will come and that is going to increase the number or increase the polymorphism. Same way MHC class 2, there are 3 genes, 3 types of genes A, B and C and these are the different variety that means one individual can have any of these combination.

It is not that everybody, all of us has all of this. So I may have 200 different MHC class 1, 200 of MHC class 1 if I have, any one of these may contribute little bit. So there may be 100 from the middle, 50 from this one and 50 from this one, so any 50, so that will constitute this 200 variety of my MHC 1 here. So these are the polymorphism, it is very, very unlikely in any other protein so far discovered, that many polymorphism is not known so far.

MHC class 2 gene, I mean class 1b gene is also a group of gene that we will discuss if whenever necessary, it is not that very common in case of MHC 1 and MHC 2 and in the basic part of immunology or basic immunology we do not need to know detail about it.

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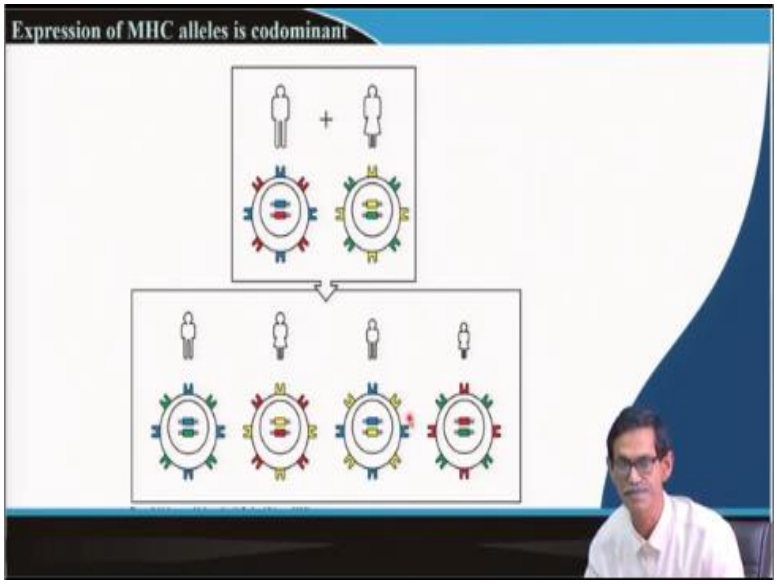

So how this polymorphism evolved and what are the mechanisms like so fast why other genes are not happening this polymorphism but these genes, why? These particular MHC is one of the very rare example of codominance. You know in genetics, even in class 10 when you are reading, studying the Mendelian genetics, there are two very common term called dominant and recessive.

So one will come from father, another will come from mother, so one will be dominant, another will be recessive. So dominant, effect of dominant gene will be seen. Like very, I mean very popular and very classical experiment of Mendel was that tall and dwarf variety of peas plant. So tall and dwarf if you make hybrid, all of them will have both gene from the tall plant and gene from the dwarf plant where all hybrid or F1 generation was tall.

So we see the effect of only tall variety, this is called dominancy. But in case of MHC, these recessive dominant is not visible, they are codominant. What is codominant means? Both the genes, say this is same, Men have two variety of, the one is blue another is red variety of MHC, in the surface both red and green will equally be expressed. In female, this is the green and yellow, both of them are expressed. So if there are 4 offspring here, what is the, what are the possibilities?

The possibilities are, you can see very easily that if this we cross between these and this, these are the different possibilities. If each I am assuming one of each will come, so it may be green and blue, yellow and red, yellow and blue, green and red, all 4 possible combinations are there. So next generation, each one will, I mean all possible variation can be possible in the next generation and in every cases both the alleles will be expressed.

It is not that one is recessive, another is dominant. So whatever MHC genes, this is a very simplest, one of the simplest cartoon, but as many MHC gene I have, I got it from my father and mother, all of them are expressing, so all varieties are expressing to protect me or involve in my immune system.

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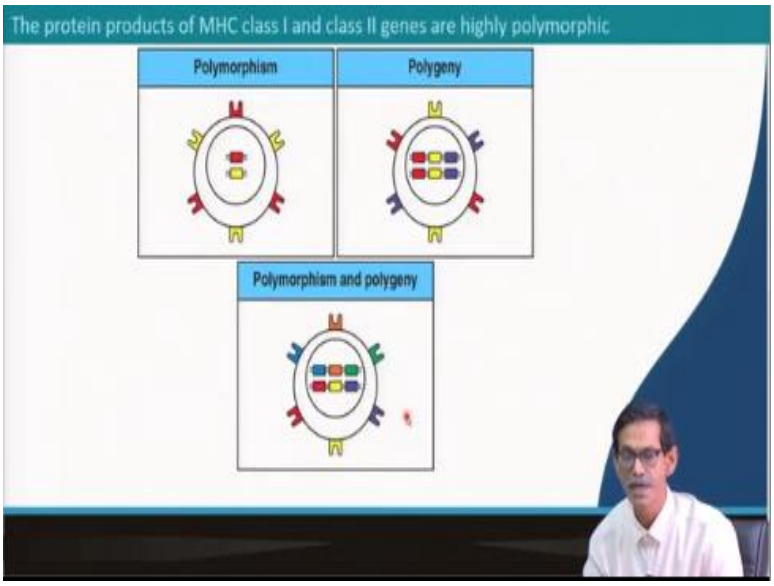

Not only that, for simplest thing was polymorphism, simple thing was polymorphism, two alleles are different expressing two different proteins, both are expressing. That is why the codominance is? Second thing is also there, they are not only one, they are multiple copy. Maybe same type, if you see this is one multiple copy of one gene, there is very common. Multiple copy of one gene if it is there, it is called polygenic, multiple gene is there.

So they are polymorphic, they are polygenic. So this is I am not talking, this is just I am talking about any polygenic gene means they have say one gene multiple copy one is red, yellow and violet, they are very similar, maybe little difference, but their alleles are same. So this is common in living system, polymorphism is also common in living system, many cases we see polymorphism, but in case of MHC what is there?

It is both, so it is not only polymorphic, it is also polygenic, that means it has multiple copy and they all are polymorphic. So even in the simple, one of the simple cartoon what I am showing here, if you see they are polygenic and polymorphic made 6 variety of different MHC molecule. So this is the reason why, why we need variety of MHC molecule that you already know, because we have to present different kind of peptide.

Because all proteins or all antigen coming from different pathogens or different system are not same after processing they will generate different variety of peptide, so to accommodate them we

need multiple type of MHC. So that is requirement is very clear, why we need so many? But how there are so many? 3 things we have to remember, one - they are polygenic that means they have a multiple copy, number 2 they are polymorphic, so all copies are not identical, say even the alleles are different, so that is why polymorphism is.

So this will increase the total number of variety and the third and important point they are codominant, that means whatever possible genes or variety are there, all are expressing and with equal importance. So normally equal importance, but infection make the specificity. Suppose I am, I may come it later again, suppose the product of this blue part, this gene, blue MHC is responsible for presenting some specific antigen and if that pathogen having that antigen in fact what we need?

Suppose all 6 are important, but particular infection maybe the blue is important because blue is presenting the antigen of that particular pathogen. That time expression of blue will increase as long as the infection is there, so that control is also there. So amount of blue MHC will increase and express on the surface to present more and more antigen of that particular pathogen which is at present infect that individual.

Again infection is about, it is going to go and come down. Normally suppose you assume there is no infection, then all 6 here are going to express in equal amount. But in infection or after infection if anyone or to require more to express more protein to give more exposure to the immune system like B cell, more exposure to the T cell, so then that particular MHC will express more.

So that, we can easily see under microscope, different techniques are there and the experiment is very straightforward and simple. If you have a macrophage culture, that means in laboratory if you are growing macrophage, you can see that normal macrophage when they are growing just by normal medium, you are giving them food and they do not have to do anything, so that macrophage will express very low number of MHC on their surface.

But if you give them little few bacteria or add bacteria what will happen? Macrophage will eat them, after eating if you see, after certain time if you can see, assume that there is a device, you do not know that technique may be, assume there is a device by which you can see the MHC on the surface of macrophage, say as red dot. So what you can see? Under microscope, before adding bacteria you can see the numbers of red dots on the surface are very low.

But after bacteria, addition of bacteria say 4, 5, 6, 7 hours depending on the time, you see that red dots are increasing. So which is very easily and clearly visible under the microscope, but you need to do the experiment, you have to have certain system or certain facility, but it is, if you have all this infrastructure, it is very simple experiment to do, clear? So how this polymorphism and polygene, it is a multiple copy, it is always possible.

Many genes depending on the requirement, our system in this is not only true for animal, it is true for plant also. If any protein you need huge amount, if any protein you need huge amount, normally the enzymes we do not need huge amount in cells to perform their function. But if any protein you need huge amount, the cell you need more to prepare. So normally what happened? We need a lot of actin genes.

In many cases like if you see macrophage and the expression of actin much more than any other cells because they are continuously moving, you need a lot of actin there. If you go to amoeba, the entamoeba, the another propagen parasite, they are always moving and doing pseudopodia and eating phagocytes, they need lot of actin, then multiple copy of actin genes. If you go to plant, if you see the seed protein because seed, I mean seed you know there are a lot of storage protein is there in the seed and lot of protein stored in the seed.

So during seed maturation you need lot of production of that particular protein which they will use during germination. So how, one gene may not be enough to produce that much. So automatically what happened? Plant multiplied that gene number so that they can produce. So whenever we need any protein in higher amount in a particular time, we need more copies of genes.

So gene multiplication or duplication is not a rare event. Wherever cell needs or a particular tissue organ or organism need that is automatically evolved with time. So there are many example of such, in this case we need variety of MHC, we need variety of different alleles, so that different variety come, not only in amount, because it is seed storage protein, one type of protein 100 molecule is fine, but here if I have 100 molecules 100 type, it is much better.

So both are accommodate by, accommodated in our immune system by combination of polymorphism, polygenic that multiple copy and codominance. So all three together has served the purpose, that is why we have so many different copy.

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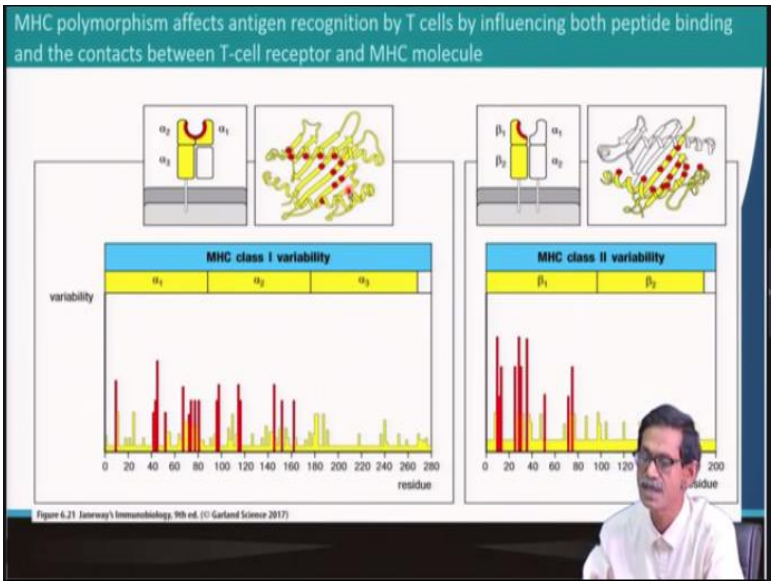

How this thing is originated? That we will see slowly. So now this picture is, now I hope it is familiar this kind of picture is familiar because we have seen this kind of picture in antibody structure also. So when you analyze the sequence in more detail what will see that polymorphism again, so evolution is so precise that did not waste time or waste like unnecessary polymorphism. If you consider this is MHC 1 and this is MHC 2.

If you consider this MHC 1 this red region alpha 1 and alpha 2 is actually the peptide binding cleft that we already know and in MHC 2 half is shown because only beta 1 is shown here in this part. So this is equally true here also. So this part is the peptide binding cleft. So there is no point

of having difference or variation in this region, say beta 2 microglobulin or alpha 2 beta 2 domain or alpha 3 domain, it is no way interacting with antigen.

I mean other way it is interacting with what? It is interacting with cd8. So there should not be much change. If there are a lot of changes here cd8 interaction may not happen. So the interaction in alpha 3 region is not expected. I will not say that it is good. Whereas the peptide binding cleft polymorphism will be helpful or beneficial because more different and more changes are there, more variety of peptide we can accommodate or MHC can accommodate, clear?

So whenever detailed analysis of this MHC polymorphism was studied by sequence or particular residue wise like (())(18:34)) if, you check one by one, you see this is the variability map the same way we discussed in case of antigen binding site of the antibody or T-cell receptor. These variability in antibody or T-cell receptor there are very specific to 3 - cdr1, cdr2 and cdr3, but here it is distributed all over.

But if you go back with this variability, this red portion the hyper variable or more variable region, where they are located? You see they are located mostly in the peptide binding cleft they are located mostly in the peptide binding cleft. Wherever peptide is interacting, it is there. Same way in MHC class 2 also, this variability is mostly because this half is so here the white part is alpha1.

And we are showing here the beta1 and this beta1, beta2 you see variability is almost not there. Again it is important for interaction with the cd4 molecule. So this red domain or the red region that is a most variable region are also present in the antigen binding cleft or the peptide binding cleft. So I personally when I studied all this thing or long back not everyday I am getting surprised, when I studied first time all these things have seen this thing it was really amazing, it is hard to believe that evolution are so specific and so precise.

There is nothing I mean how I mean now today our immune system is so strong and it evolved so many years so many things happened. So evolution of immune system is also a very interesting

thing and it is not easy to discuss in few lectures. So many things you have to know many immune system of many different organisms that is not part, but anybody is interested history of immunology is important that you can study from anywhere, any book.

You can also study the history of evolution of immune system that is also very good. What we are seeing today, what we are discussing today the final product. But how it evolved is really very interesting. So any of one interested definitely you can go on study by yourself. So these thing makes the polymorphism more effective. So in summary what we can say? We can say the polymorphism effects antigen recognition by T-cell influencing both peptide binding and the contact between T-cell and MHC.

Why contact between T-cell and MHC? Because this alpha helix part is mostly interacting with the T-cell receptor of MHC and this internal side where the peptide is cleft, this is T-cell middle portion of the T-cell actually central portion of the T-cell if you consider the 3 dimensional structure are interacting. This MHC both side are interacting with T-cell in general. So it is not peptide specific.

So both are actually hampered here this polymorphism, both T-cell interaction as well as peptide binding site of the T-cell, that part is mostly affected rest of the part is not.

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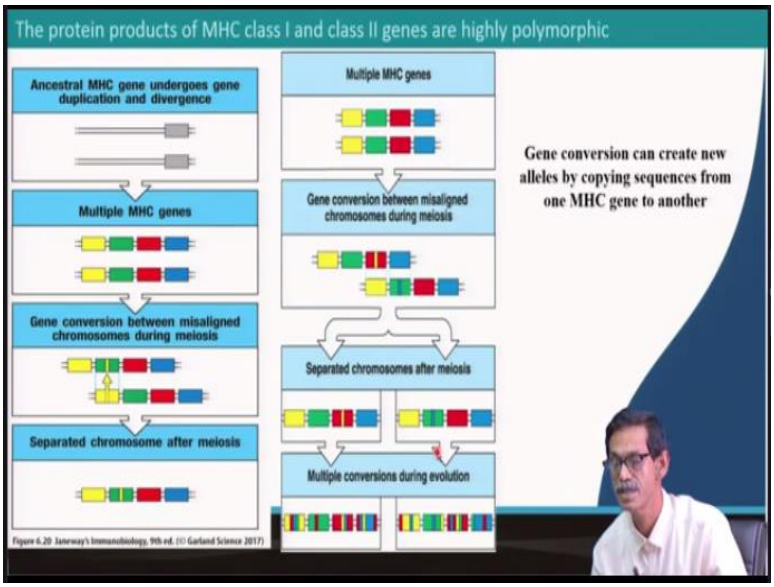

So how this polymorphism or how this varieties. So many varieties of T-cell or MHC are generated. So we could have stopped there. But what I thought let us see like just spend few minutes and how, what are the possible mechanisms of unknown that, what is the origin of this so many variety? This picture looks very cumbersome but it is very simple and straightforward. I hope you will understand very quickly.

Do not look at the other part of them, whatever I am pointing out look at that part. Suppose at the very beginning when immune system started there is only 1 gene. As I just told in case of plant or many other cases, if we need more protein we need more copy of gene because we need more mRNA. So depending on the need this gene duplicated, multiple copies. So there was 1 at the beginning, then it become 4.

There is no polymorphism, so therefore is a polygenic now. When the similar gene, very similar gene their structures and their sequence are very much identical there may be little different what happened during cell division? You know 2 chromosomes are crossing over time they may misaligned. They may misaligned, it is not a recombination. Before recombination they may misalign 2 chromosome.

They are so similar, they may misalign and this misalignment may cause some change just or exchange of genetic material and eventually they can produce this kind of product after meiosis. Where small part of this green is changed to yellow. Yellow means from these gene it is replaced and other one you will see a small part of the green is inserted into this yellow. So it is not 1 side only.

So what will happen in next generation where in the sperm cell or xCell you have instead of just pure blue, green, red and blue you will have a mix of this. This exchange of genetic material by this misalignment of this method is called gene conversion. It is not gene recombination it is gene conversion which is resulted by misalignment of chromosome during meiosis. So if you can understand this part in 1, then I am going from here to here again.

So it is multiple MHC gene, multiple MHC gene. So, that multiple MHC gene if they misalign like this, so there are 2 transfer is possible; so one from between red and yellow, another between blue and green. So, as a result 2 things will happen. So some blue will come within green and some red will come within red, yellow will come within red. So this is just a single case, independently there is single case.

So if you understand this thing and with generation after generation, every time if this kind of slow or but steady way if this genetic conversions keep continuing with evolution what will see? You will see a multicolor this. Every time a small part is changing, every time small part is changing. So if anyone is not good it will be automatically ruled out from the system. So we are selecting better is better and better whichever is better and we are getting a varieties of MHC molecule and that is why we have so many when you are showing the bar graph that.

We have so many MHC 1 ABC type and DR, DQ, DB that alpha beta genes it is because of this reason, it is because of this reason. So what if I come back to somebody genetic this is again why this polymorphism arise, genetic conversion which is one of the more or major reason for so many variety of major histocompatibility complex.

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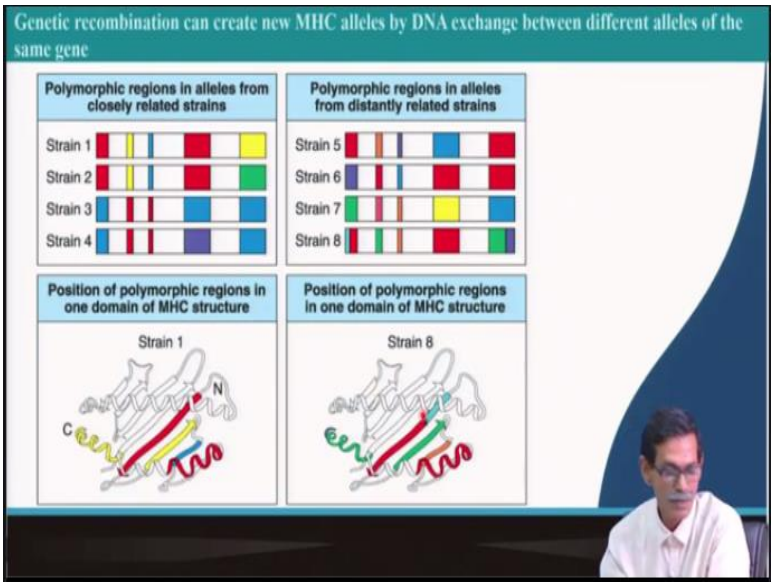

Not only this, this say along with that normal recombination is already there, right? This is gene conversion but normal recombination during cell division is already there. So, that also

contributes some variation in the polymorphism. Genetic recombination also create can create the variety of different variety of MHC molecule. And here are some polymorphism closely related alleles. How it will look?

So strain 1 and strain 2 if you see compare they are very much similar everywhere. So up to here the red, red, yellow, blue, red again is same but only this part is slightly different. If you see the strain 3 and 4, you see almost same except this region is different. This is we are talking about closely related strains. This is done in Mouse. When I am saying strains normally you understand it is Mouse.

Normally we do not say human as strain 1, strain 2. So now if you see where this polymorphism located rest, white part is very much identical that is why it is not shown. In this gene white part is very much identical. So if you convert to in this ribbon structure we will see that majority of this polymorphism are in the either T-cell binding site or in the cleft where is the peptide binding site.

That specification is still maintained and same thing if it is a different related or distant related strain, that they do not match most of the part. You can say there this is just a color code, you can make like your choice anything. But whatever the color you give does not matter but it contributes again the different part of the peptide and T-cell binding sites only. It is not hampering other part like which is not interacting with the peptide like alpha 3 or in case of beta 2 or alpha 2 domain of MHC 2.

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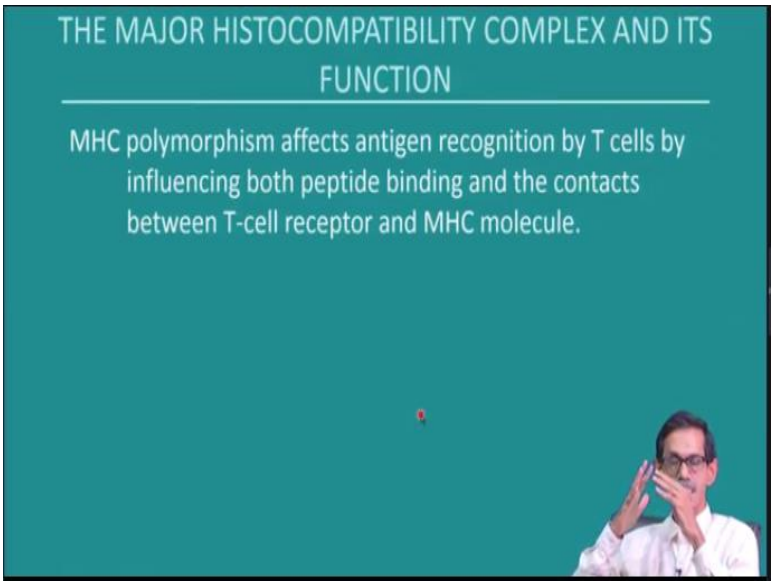

So; MHC polymorphism affects antigen recognition by T-cell influencing both peptide binding and contacts between T-cell receptor and MHC molecule. So these change, okay, these change whatever we see or mechanism or the reason like polymorphism, polygenic, co-dominance these 3 this change is changing what? This is changing the T-cell interaction along with the peptide molecule.

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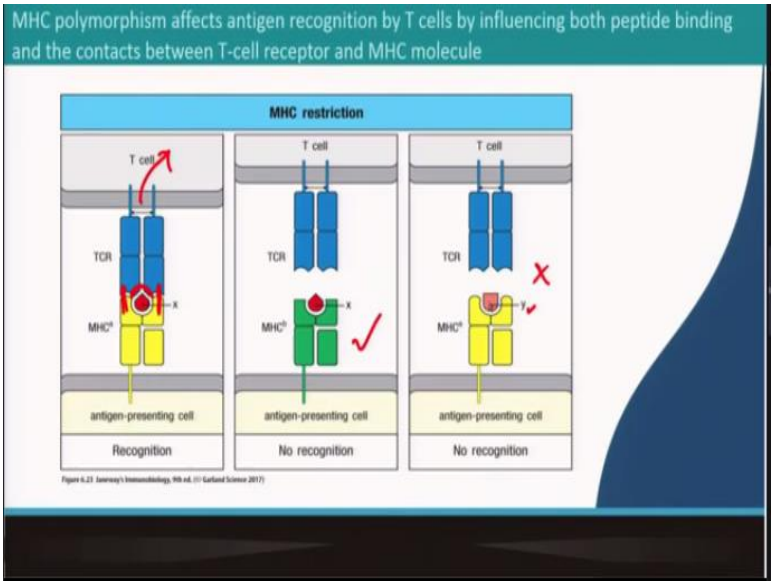

So this is called MHC restriction. What is MHC restriction? MHC restriction, this is the nice picture, say this is MHC 1 which is presenting an antigen name x. This is MHC 1, you know by this yellow line or single transmembrane domain and the T-cell have the T-cell receptor which is

interacting you see this part with, let me change this, this part with this part, this part with this part and the central part is interacting with antigen.

So this interaction is not possible with this T-cell if the MHC is different type. You see how it is different in this case, the green part it is flat instead of it is oval. The T-cell even the same antigen X is there, T-cell will not interact or same MHC but different antigen why? This T-cell which can recognize X will not interact. So these phenomena like T-cell should recognize the MHC as well as the peptide to interact.

So T-cell should know which MHC it is. So this part if this is T-cell receptor and this is MHC, it should interact the T-cell receptor first. If it is does not interact even the antigen specificity is there it will not interact which is the middle case. Antigen specificity is there, but it is not interacting because it is not, this T-cell is not recognizing this green one which is MHC B, this is MHC A, just to differentiate between 2 different MHC.

Even these same MHC A which T-cell can recognize, but this T-cell cannot recognize the antigen why? It will not interacting. This phenomena is called MHC restriction, that means T-cell should recognize MHC as well as the peptide presented by the MHC. If all both interaction is perfect then only TCR will get the interact with this, then I mean which is not shown here, then only signal goes inside and say T-cell what to do, what not to do.

No recognition can happen either due to MHC or maybe by antigen. This is called MHC restriction. So today I will end this lecture here and again some part of MHC is still left, very little will discuss in the next part of the lecture or next lecture. Thank you for then.