Host-Pathogen Interaction (Immunology)
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Lecture: 56
Adaptive Immunity-T cells and T cell-mediated Immune Responses

Hi so, in previous session you have studied about adaptive immunity various component of adaptive immunity. You have learned about the antigen you have learned the difference between antigen and immunogen and you have learned about antibodies types of antibodies and antibody diversity right. So, in this session let us begin with T cell and T Cell mediator responses I will also touch upon the T Cell diversity.

However, this diversity the phenomena of or the generation of diversity is a similar as antibody diversity. So, I will just show you how this diversity is achieved by the T cells. So, let us begin with this T cells.

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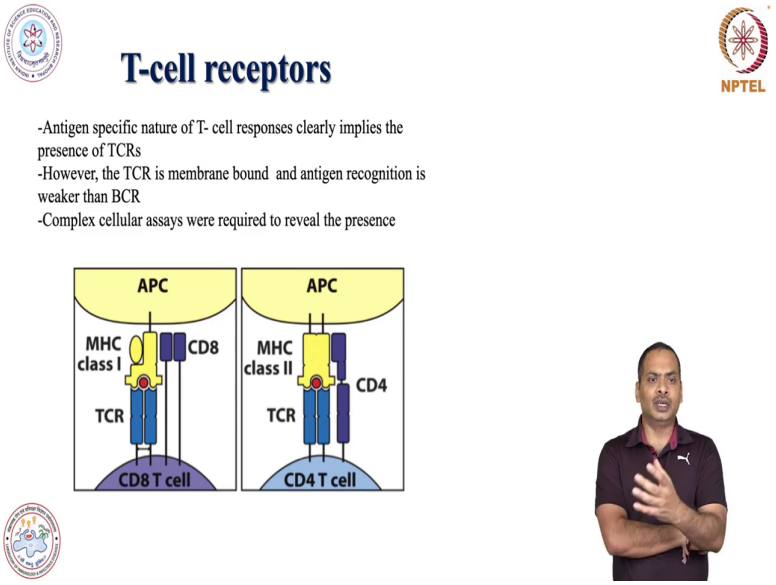

So, this T cells are basically CD3 positive cells. So, all T cells they have a CD3 surface marker and this CD3 marker makes the cells as a T cells. And when there is a when the CD3 is present along with a CD4 then we call it as a T helper cell and when the CD3 is present with CD8 marker then we call it as a cytotoxic T cells, anyway. So, let us look at the T Cell receptor because this T Cell receptor it is better to understand the T Cell receptor here you can see that it is a antigenous specific nature.

So, T cells are antigen specific please note that it is like antibody but there is some differences I am going to tell in next Point. So, antigen specific nature of T Cell response clearly implies the presence of TCR. However the TCR in membrane in membrane bound and antigen recognition is weaker than BCR and BCR stands for B cell receptor. The complex cellular assay were required to reveal the presence of this TCR.

Here you can see I am just putting this a very simple image you can see there is a antigen presenting cells and there is a MHC class 1 molecule in one panel you can see the in first panel you can see there is a MHC class one molecule and the red colour is the antigen and there is a TCR and this TCR is present along with the CD8 molecule. So, here you can see that this CD8 T cell this is a basically cytotoxic T cells.

On another image you can see that there is a MHC Class 2 molecule there is a antigen and then there is a TCR along with a CD4 molecule. So, this is a basically kind of arrangement is there.

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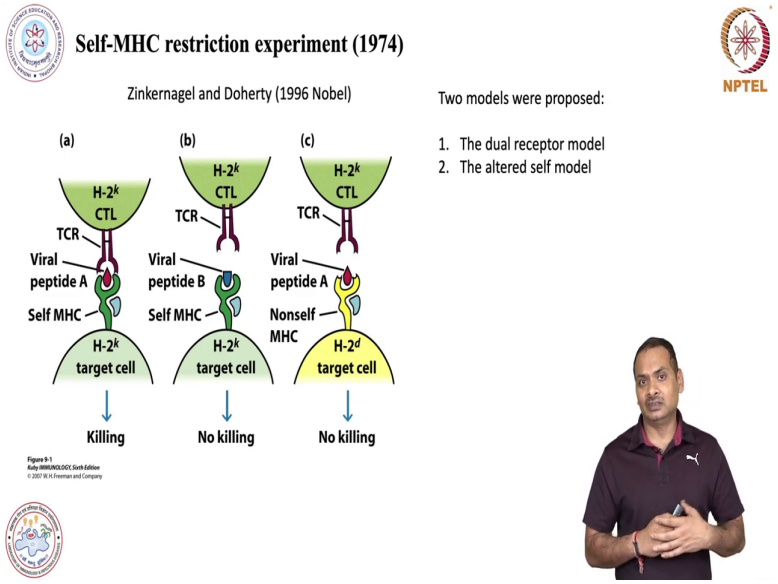

So, please remember. So, as I told you that this T cells senses the antigen which is presented along with the MHC molecule but there is a one very important point that this MHC should be from the same host if the MHC is from different then it will not recognize the antigen. Here there is a I am just quickly giving an overview of this Zinkernagel and Doherty ~~Zincer Angle and Doherty~~ works who received the Nobel Prize in 1996.

So, and there are before that there was a two model that there is a dual receptor model. Dual receptor model is a just that the T Cell basically recognizes this antigen there must be some receptor which is recognizing antigen and there is some some receptor which is recognizing the MHC molecule. So, this was a dual receptor model people also proposed the another model which is more correct that is all altered self model.

So, altered cells model is that MHC molecule is associated with the antigen where MHC is a little modified and then this complex is sensed by the TCR. So, this is a very simple experiment here you can see that in ~~channel~~penal a please note that H 2 K is MHC and if the MHC molecule is same and it is presented appropriately along with a MHC molecule and along with the antigen then TCR recognized.

And then that will cause the killing of Target cell. Try to understand this T cell is basically cytotoxic T cells. So, in B case here you can see that the antigen is different MHC is same as you can see in T cell and and the target cell the MHC is same but the antigen is different it is the T cell is not that antigen~~ous~~ specific. So, therefore it will not kill the target cell. In third case in C case here you can see that the MHC is different and antigen is same.

In this scenario also the cytotoxic T Cell will not kill the target cell because MHC is different antigen is same but MHC is different. So, all overall if you see this experiment then you can understand that there is a self MHC restriction cytotoxic T cell or here the experiment is with cytotoxic T cells. So, therefore I can say that the cytotoxic T Cell will kill those Target cell which expresses self-image and present the antigen and this is true for T helper cell also.

So, T helper cell will see the antigen presenting cell which is expressing self MHC and it will present the antigen then this T helper cell will proliferate and develop appropriate immune response. So, overall conclusion from this slide is that self MHC is needed in order to activate the T Cell.

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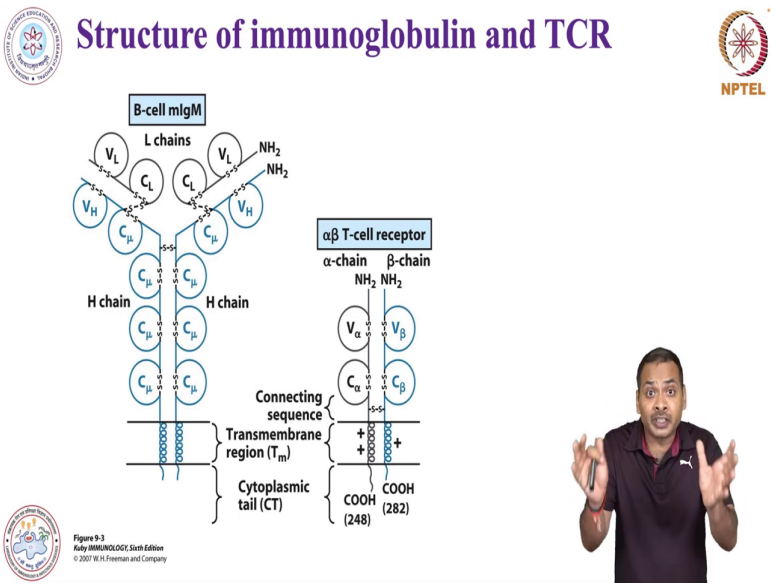

Here this is a comparative structure of immunoglobulin and TCR. Here you can see that there is a light chain there is a heavy chain in case of a B cell membrane-bound immunoglobulin M and these two heavy and light chains are associated with the disulfide linkages. And there is a transmembrane domain which is basically which is anchoring which is act as a anchor for this molecule and there is a also T Cell receptor.

And there are two major kind of T cells are there one T Cell we call it as Alpha Beta TCR expressing T cell and another is Gamma Delta TCR expressing T cells. So, here you can see that Alpha Beta TCR. So, Alpha chain is same as a; not same I will say similar as a light chain of antibody. And this also has a one variable regionason as you have noted in case of a light chain in antibody there are there are variable region there are constant regions.

So, Alpha TCR is like a light chain and it has a variable region as well as constant regeionason and beta chain is like a heavy chain in antibody or IgM and here you also you can notice that there is a variable region and there is a constant region and basically this is also inserted in the membrane there is a transmembrane domain. And these TCRSs are always associated with CD3 molecule in order to make it functional I will show you in a next slide.

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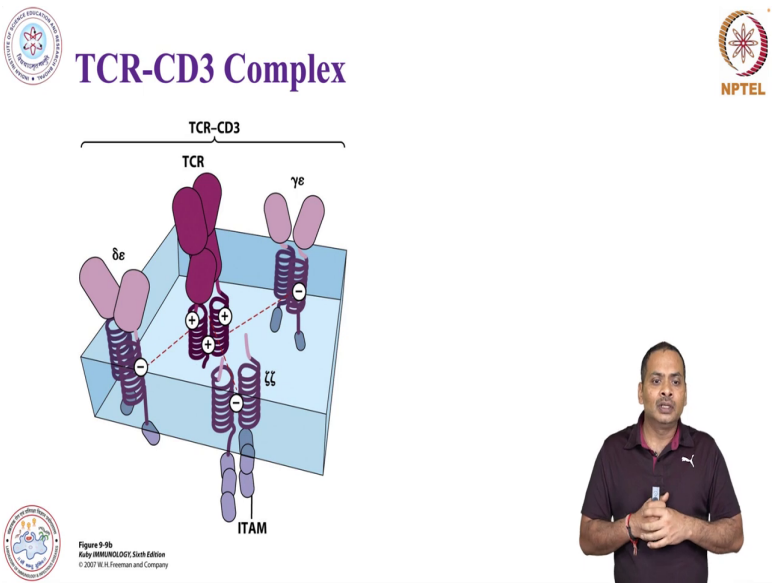

Here you can see that this TCR is always associated with CD3 molecule. There are several polypeptide chains of CD3 molecule here you can see that there is a Zeta chain and there is a Delta chain, Epsilon ~~long~~ chain, gamma chain and if you notice the charges over there the electrostatic charges. So, TCR is having a positive charge and CD3 molecule they have a negatively negative charge therefore they always present together.

And this presence is needed in order to make it functional here you can see there is a one domain or there is a one Motif which you call it as a ITAM.

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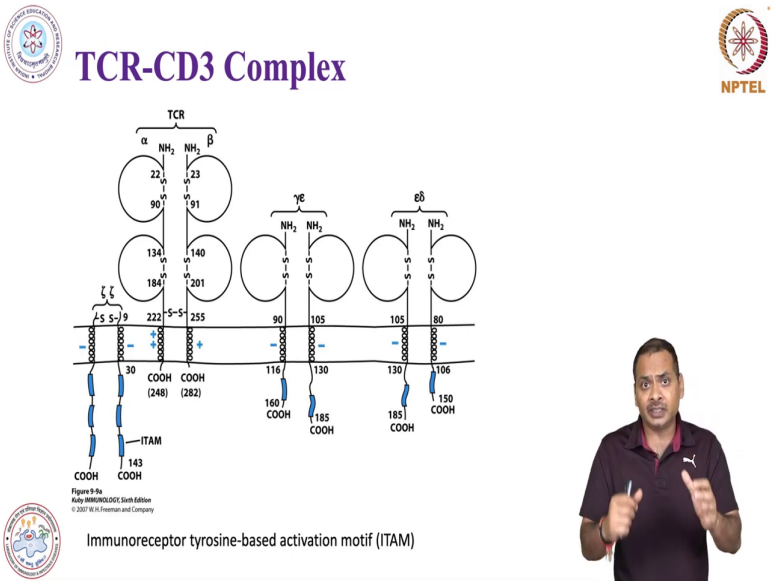

So, in next slide you can see this the TCR CD3 complex try to understand TCR is consists of alpha chain and beta chain or gamma chain and delta chain~~handle touching~~ I will I will show

you in subsequent slide and this TCR either Alpha Beta or Gamma Delta is always associated with the CD3 molecule and ~~see the~~CD-3 molecule is consists of various chain one is Zeta. Zeta has a transmembrane domain which is which is having predominantly negative charge.

And TCR is having a positively charge so, this is present in close association. And TCR does not have a long cytoplasmic tail therefore they cannot activate the downstream signalling. In order to activate the downstream signalling they have to associate with the CD3 molecule here you can see that Zeta chain. So, Zeta chain has a long cytoplasmic domain and this domain has a unique Motif which we call it as a ITAM.

It is a immuno receptor tyrosine based activation Motif and it is also present along with gamma Epsilon and Epsilon Delta. So, these are the chains. So, all these things are always present in a complex form and this is needed in order to make it a TCR functional.

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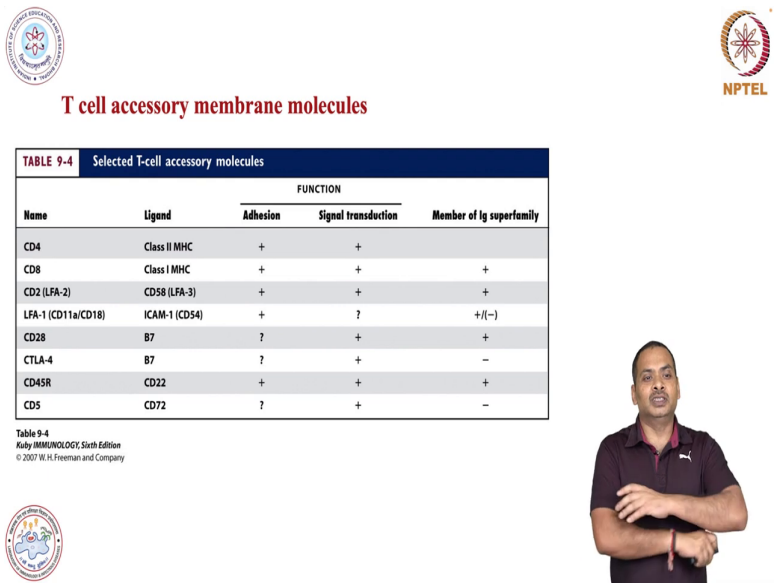

Now I will show you besides this TCR CD3 and MHC cells also needs some more co accessory molecules in order to make this interaction fruitful here you can see that CD4 associate with MHC Class 2 molecule they their main role is adhesion the. So, this will bring the ~~thus the~~ T cells and antigen presenting cells are other nucleated cells. So, if it is a MHC Class 2 molecule.

We can call it as a antigen presenting cells or if it is a CD8 and MHC class one molecule interaction then it is a basically any nucleated cell ~~itself~~. And there is a CD2 this is LFA. So, these are we call it as a co-stimulatory molecules and rest of these molecules are needed in

order to activate the T cell and they are playing important role in Signal transduction as you can see.

And most of these molecule they have a immunoglobulins super family structure. Immunoglobulin super family structure is just there is a presence of disulfide bond and that makes a Immunoglobulin super family.

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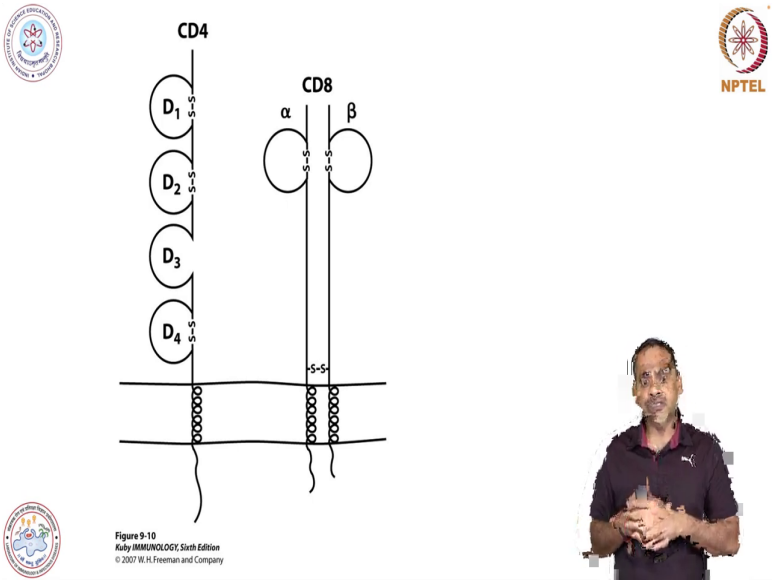

Here this is a structure of CD4 and CD8. So, CD4 is. So, this is the immunoglobulin super family the circle one there is a disulfide linkages. So, CD4 is a single polypeptide chain whereas a CD8 is a two polypeptide chain and both has a immunoglobulin super family structure.

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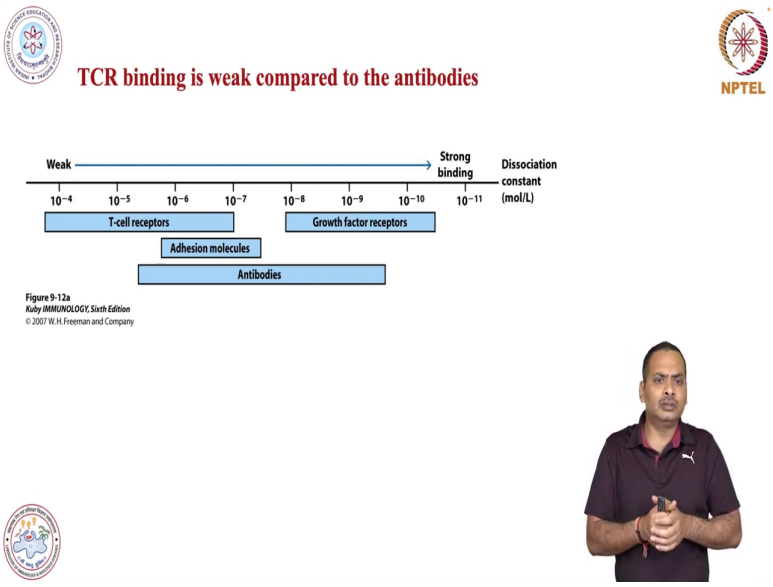

This is a kind of comparison of of the strength of antigen antibody and TCR with MHC and antigen. So, here you can see that this TCR is it is not very strong interaction but if you add this adhesion molecule then this interaction is reasonably strong but on another hand you can see that this antigen antibody interaction is much more strong all depends on the kind of antibody.

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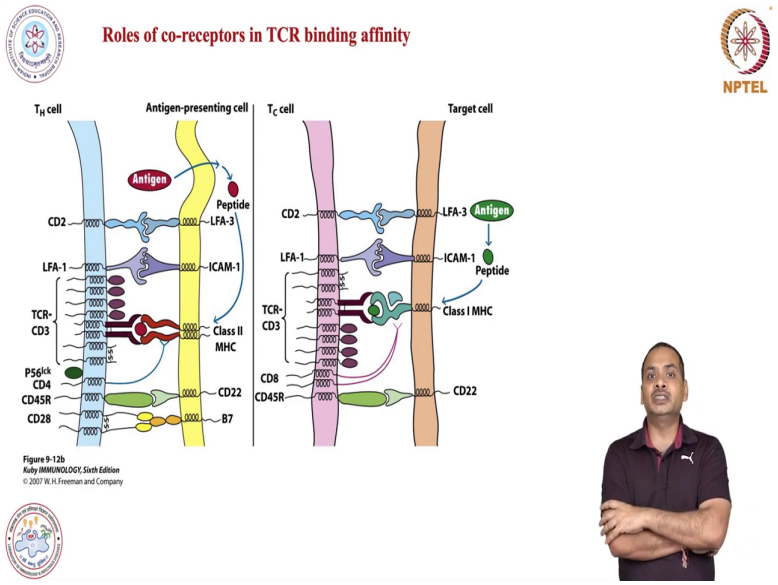

So, this picture will more clearly explain you. So, there is a you can see that there is a T helper cell and there is antigen presenting cell and this antigen from outside it is going in or it is taken up by the antigen presenting cell and it is presented along with MHC Class 2 molecule and this is seen by the TCR and CD3 complex. And this is basically facilitated by the CD4 molecule.

And in addition to these interaction there is another interaction like interaction between CD2 and LFA3, LFA1 and ICAM one molecule and there is a CD45R which is interacting with CD22, CD28 interact with a B7 molecule. So, other than TCR CD3 and CD4 rest other molecule we call it as a accessory molecule or co-stimulatory molecule. And this interaction is needed if you block these interactions the T Cell will not proliferate or it will not induce the effector response in a very simple term.

On another hand you can see that cytotoxic T cell and Target cell interaction here again you can see that there is a TCR CD3 and CD8 molecules are there besides this there are other molecule like CD2 which is interacting with LFA 3 again. LFA1 is interacting with ICAM1

and there is a CD45R molecule which is interacting with CD22. So, try to understand only this interaction is not sufficient this interaction means TCR CD3 MHC plus CD8.

Only this interaction is not sufficient in addition you need a other interaction if you can perform a very simple exponent if you make the monoclonal antibody and put it in the in the culture which blocks say CD2 or LFA one or other molecule on target cell then you will not see the cytotoxic effect if it is a cytotoxic T cells. So, this is very much needed.

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TABLE 9-2 TCR multigene families in humans

	Gene	Chromosome location	NO. OF GENE SEGMENTS* V	D	J	C
IgL	α Chain	14	54		61	1
IgH	δ Chain†	14	3	3	3	1
IgH	β Chain‡	7	67	2	14	2
IgL	γ Chain§	7	14		5	2

*Not all gene segments listed here give rise to TCR products; pseudo-genes are included in this list.
†The δ-chain gene segments are located between the V_α and J_α segments.
‡There are two repeats, each containing one D_β, six or seven J_β, and one C_β.
§There are two repeats, each containing two or three J_γ and One C_γ.

Table 9-2
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Now there as I told you there are two kinds of T cells one is Alpha Beta T cell and another is Gamma Delta T cells. So, Alpha Beta T cells are major proportion it is about 90 to 99 percent are alpha beta T cells. And only one to ten percent are Gamma Delta T Cell and they have a TCR this V gene germline repertoire. In case of Alpha Beta is a large and in case of Gamma Delta it is a very small repertoire.

Not so, many V genes are there in case of Gamma Delta and you will see in subsequent slide. CD4, CD8 phenotype so, in case of alpha beta in the CD4 marker will be predominant it is about 60 percent CD38 will be less about 30 percent there are some double positive CD4 CD3 double positive cells this is during the development process. So, they will acquire both CD4 and CD8 double positive we call it as a.

And there is a some double negative which is which has which do not have either CD4 or CD8 but their percentage is very low in case of Gamma Delta T cells it is a most of the Gamma Delta T cells are double negative here you can see that 60 percent and some of them

are CD8 positive. So, Gamma Delta T cells are mainly double negative and but a small fraction are having a CD8 molecule MHC restriction you know very well.

In case of a CD4 T cells this will interact with MHC Class 2 molecule and in case of CD8 T cells it will interact with MHC class one molecule but in in case of a Gamma Delta T cells there is a no MHC restriction. Ligands in case of T Cell it will be a protein or which is which is a after processing it will make a peptide and this will be seen by the TCR CD3 complex but in case of Gamma Delta T cells.

I have told you earlier also this basically recognizes a non-conventional antigens like a phospholipid or some lipid derivatives intact protein is also there some in very few cases yes here you can see that in case of Alpha Beta here you can see that there is Alpha and beta. So, their chromosome location is also there. So, in case of Alpha Beta there is a and I told you Alpha is a like a immunoglobulin light chain.

So, I wrote it IgL, IgL stands for immunoglobulin light chain. So, Alpha is similar as a light chain of antibody and if you remember that antibody diversity in case of antibody you probably remember that there is a no diversity region in case of light chain only V J, V J region is there. So, similarly Alpha chain has a only V and J and one constant region and in case of beta this is a you can see that there is a V D J it is same as the heavy chain of antibody.

So, here you can see that there is a lot of variable Gene segment about 67 you can see and there is a very few diversity region that is two and there is a joining reason which is about 14 in case of Gamma Delta T cells if you see the gamma chain is like a light chain of antibody and here you can see there is a there is a 14 only 14 V region is there and five J region is there and in case of Delta it is very few it is only 3 variable 3 diversity and 3 joining region.

So, here I am I am trying to compare with antibody diversity with the T Cell diversity. So, they also have a light chain and heavy chain and their diversity is also like that and there further processes are also like that antibody diversity. So, I will not talk in more detail about the T Cell diversity.

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TABLE 9-3 Sources of possible diversity in mouse immunoglobulin and TCR genes

Mechanism of diversity	IMMUNOGLOBULINS: H Chain	IMMUNOGLOBULINS: κ Chain	αβ T-CELL RECEPTOR: α Chain	αβ T-CELL RECEPTOR: β Chain	γδ T-CELL RECEPTOR: γ Chain	γδ T-CELL RECEPTOR: δ Chain
ESTIMATED NUMBER OF FUNCTIONAL GENE SEGMENTS*						
V	101	85	79	21	7	6
D	13	0	0	2	0	2
J	4	4	38	11	3	2
POSSIBLE NUMBER OF COMBINATIONS†						
Combinatorial V-J	101 × 13 × 4	85 × 4	79 × 38	21 × 2 × 11	7 × 3	6 × 2 × 2
and V-D-J joining	5.3×10^3	3.4×10^2	3.0×10^3	4.6×10^2	21	24
Alternative joining of D gene segments	-	-	-	+ (some)	-	+ (often)
Junctional flexibility	+	+	+	+	+	+
N-region nucleotide addition‡	+	-	+	+	+	+
P-region nucleotide addition	+	+	+	+	+	+
Somatic mutation	+	+	-	-	-	-
Combinatorial association of chains	+		+		+	

*Immunoglobulin data from Table 5-2; TCR data from Baum et al., 2004, *Nucleic Acids Research* 32:D51.
†A plus sign (+) indicates mechanism makes a significant contribution to diversity but to an unknown extent. A minus sign (−) indicates mechanism does not operate.
‡See Figure 9-8d for theoretical number of combinations generated by N-region addition.

Table 9-3
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Here you can see that by simple mathematics there is a possibility of generation of a huge diversity in T cell in both Alpha Beta T cells as well as Gamma Delta T cells. And it is compared with the immunoglobulin here you can see that this diversity is basically achieved by these different permutation combination of V D J, V J recombination.

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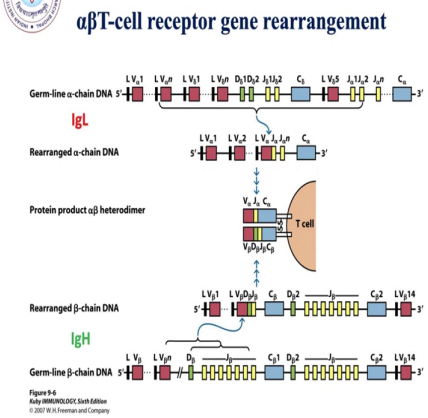

Here I am just for your quick understanding I am showing the gene rearrangement in case of Alpha Beta T Cell receptor. Here you can see that there is a alpha which is like a immunoglobulin light chain and there is a beta which is like a immunoglobulin heavy chain and there will be a recombination as I explained you in case of B cells it is called similar. And then the mature Alpha Beta TCR will be appear on the T cells.

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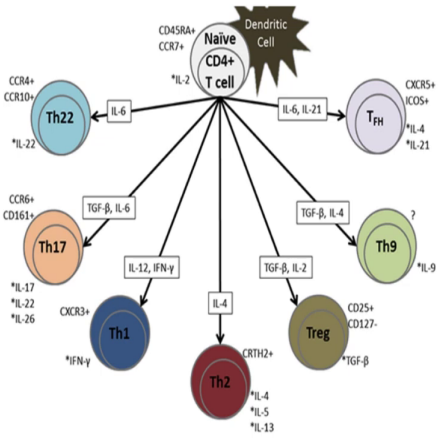

Here I just want to tell the there are various kind of T helper cell and they play a role in different kind of phenomena as you can see that there is a TH1 cell which plays important role against the intracellular pathogen elimination. There is a TH2 it induces antibody responses and Allergy responses there is a TH17 cells this TH17 cells plays a very important role in inducing inflammation and it promotes the autoimmune disease.

There is a TH22 cells this TH22 cells plays a very important role in mucosal immunity inflammatory diseases and barrier defense. There is a TSFH cells and these TSFH cells are playing a important role in antigen~~ous~~ specific B cell immunity. TH9 cells they are playing important role in some or other aspects of tumor basically they are anti-tumor in nature. Besides this humeral immunity through the B cell interaction this promotes.

And function on many cell type including ~~muscle~~Mast cells. So, they modulate the mast cell and other CD4 positive T cells there is a T-reg~~Rex~~ cell. So, T-~~Rex~~reg cell is a basically regulatory T cells and this regulatory T cells plays a important role in kind of a damping of a T cell mediated immune responses.

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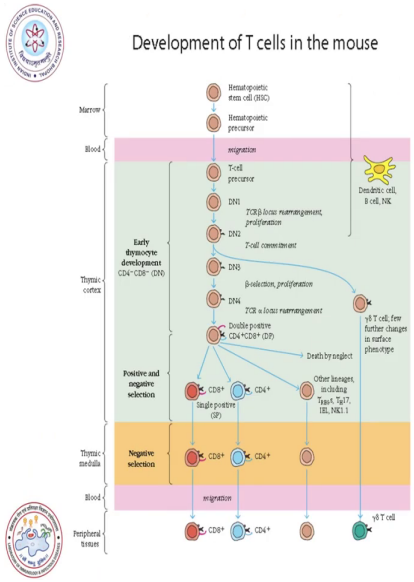

Here I am showing you the quick snapshot of how the T Cell development is taking place. So, here you can see that hematopoietic stem cell is coming from the bone marrow then through blood it moved to the thymus and thymus plays a very important role in T Cell development. I have told you when I have discussed the thymus the new organ. So, this will reach to the thymic cortex and over there here you can see that there are different stages of T cells.

There are double negative one double negative two double negative 3 4 and then there will be a double positive T cells. And then there will be this maturation process is taking place in first in cortex then medulla and then there will be a generation of CD8 and CD4 T cells and then this will migrate through the blood and reach to the peripheral tissues. And over there they will see the antigen and then there will be a development of antigen specific T cells.

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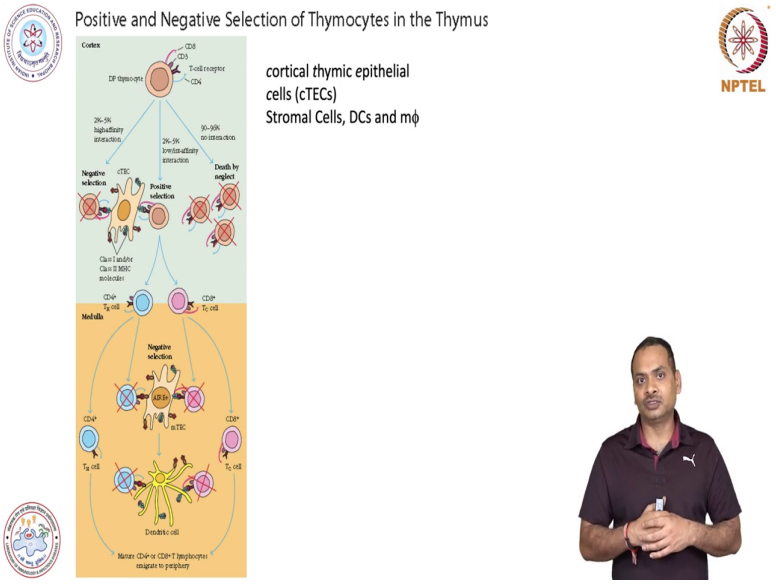

There is a phenomena of positive selection and negative selection which I have explained you earlier. Positive selections is basically the only those cells which is a immunocompetent naive immunocompetent T cells they will proliferate and all those auto reactive T cells and other cells in which there is no fruitful recombination are taking place all those cells will be clonally deleted that we call it as a positive selection and negative selection.

So, this is all about the T cells and now with this I am finishing the week 8 and thereafter we will move to the another topic we will talk about the viruses and so on and so forth, thank you.