Essentials in Immunology

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Module No. # 17

Lecture No. # 33

Immunodeficiency

So, today's lecture is going to be on immunodeficiency. So, what do we mean by immunodeficiency? So, what happens is you have situations where people or animals are immuno-compromised and that means they lack certain immune functions or immune defects. We have actually in the course of the lectures, we have discussed some of these, but what I will try and do in this lecture is to put it in context of the entire immune response as such ok.

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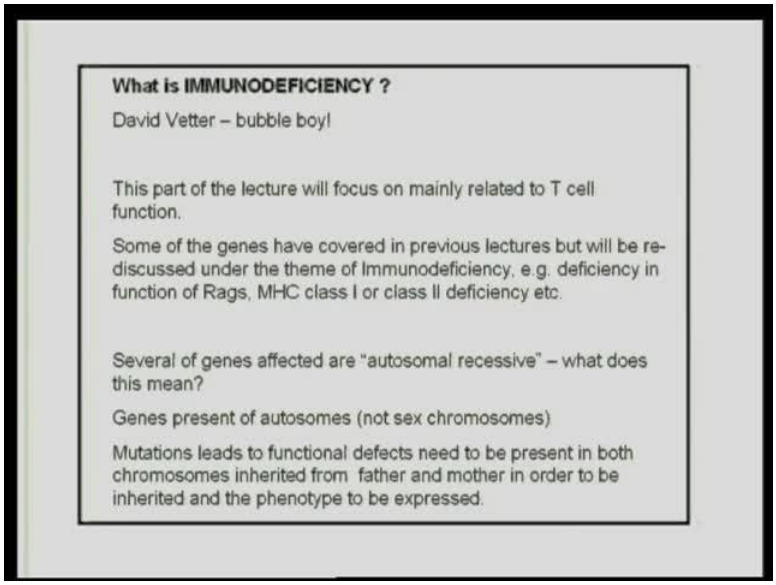

So, in fact in case of immuno-deficiency, one prime example is that of David Vetter who was also known bubble boy and I think all students should be aware of this case. It is an interesting case where David Vetter was diagnosed to be immuno-compromised and from the time he was born and this was a sort of experiment that was done. So, the time he was born he led a sort of sheltered existence and so that he would not come in contact with any sort of

pathogens or even just normal general microbial flora that is usually present. So, everything that was fed to him was auto-clave, was sterile. So, he did not come in contract with any microbes in that both good as well as pathogenic.

So, he lead he was actually his life started off in a bubble and the bubble expanded as he became bigger and this was the idea was that as he would become older, may be some sort of a therapy become available that might help him. So, what happened as a result as he was getting older, he was not in contact with other children of his age and doctors when they had designed this fail to realise the cytological implication of the study. So, at a later stage when they tried to take care of his condition by giving him a bone marrow transplant and the bone marrow transplant was from his sister who was apparently normal but at that time bone marrow transplants where done without checking for whether there are viruses or not.

It so happened that the bone marrow from his sister contains some viruses and because he was immuno-compromised, the virus took over and ultimately he passed away, but his case became very important because you know a lot of publicity was generated about immuno-deficiency. The experiment that was that was done, generated lot of interest because it also talked about the role of scientific research and ethics and also psychological problems with or psychological issues that come up with kids who grow up in a completely isolated environments.

So, it is something that students must look up and read up. It tells us a lot great deal about immuno-deficiency. So, if you are an immuno-deficient, then you are unable to fight just normal flora. If you are not and able to do that what happens is that you come down with recurrent infections. So, one of the common problems with immuno-deficiency is that people come down with recurrent infections and this usually starts off with children because you know that is that is when this sort of phenotype is sort of becomes express. So, what we will do in this lecture? We will discuss some aspects of immuno-deficiency.

What we will, although some aspects of the innate response and the B cell response will be covered. It will be mainly focused on T cell responses. Now, with respect to immuno-deficiency, some we have considered. So, for example what would happen let say if you did not have Rags. Now, what are Rags?

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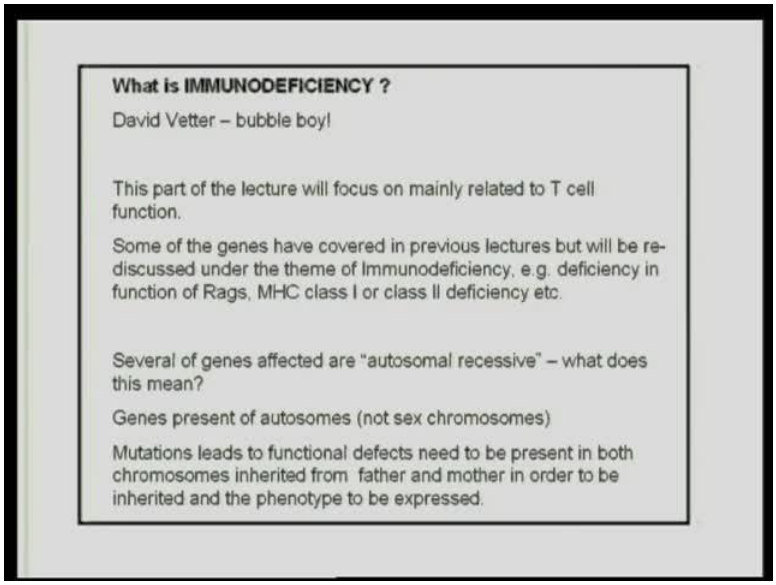

Rags are the enzymes that are responsible for re-combination and the re-combination is for the B cell receptor as well as for the T cell receptor. So, in case there are mutations in Rags, the phenotype is that you are unable to generate functional B cell receptor or T cell receptor. As a result of which, you are severely immuno-compromised because you lack the entire lymphocyte arm or the adaptive arm of the immune response and you can see that this would lead to major problems.

There are other phenotypes also that are observed. So, in case for example you lack MHC class 1 or MHC class 2. Now, if there is MHC class 1 deficiency, what would happen is you would not be able to select for CD8 positive cells. So, those people would have a compromised would lack CD8 positive cells. On the other hand, if there is MHC class 2 deficiency, then it would lead into individuals that lack the CD4 response.

Now, in this case we need to be familiar with certain terms and one of the most important terms that often comes up is that the genes that are affected are autosomal recessive. Now, what do we mean by autosomal recessive? Now, there are two types of chromosomes, one is the sex chromosomes the x and y and the other is the autosomes.

Now, in case of xy if there is a particular gene that is present on the x chromosome and in case of males, if there is a mutation in this and it gets inherited, then it will phenotype itself. However, if in case of females you will have two x's. So, even if there is a mutation in one x, you inherit one from the mother and let us say the other from the father is normal you are probably ok.

So, it is important to realize these aspects that you need often in case of autosomes, especially genes that are present in autosomes. You would need both mutations to be inherited from both the father and the mother in order for the phenotype to be expressed and that is why they are autosomal recessive.

So, there is a distinct difference between autosomal recessive and if they are sex linked. If they are sex linked, you will get different frequency. Whereas, if in case of autosomal frequency the chances are a lot less because you need to inherit both bad copies one from father and one from mother in order for the phenotype to be expressed. I hope this part is familiar with students and this is just simple genetics that I am sure you have sort of learnt previously but it is important for this class that you understand these aspects.

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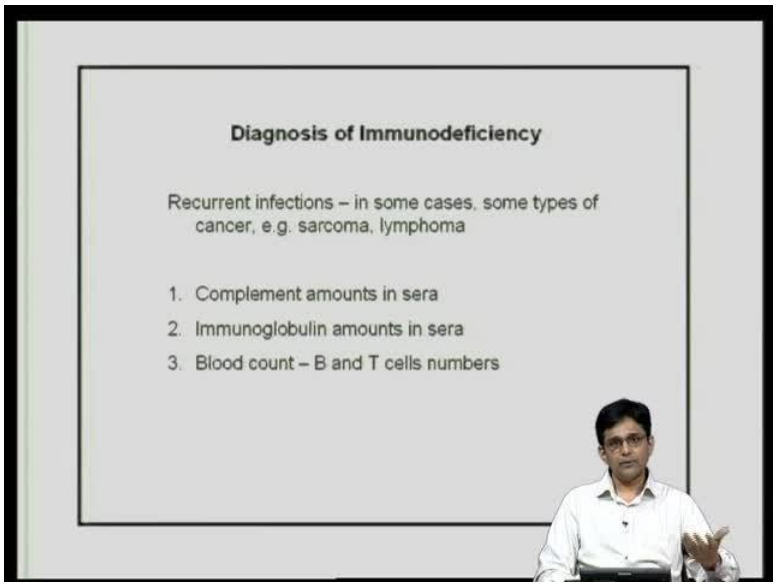

Now, how does one diagnose immuno-deficiency? As was mentioned previously that the most common feature of immuno-deficiency is recurrent infections and it starts off when people are young. So and in some cases, there are cases of cancer, for example Kaposi sarcoma or lymphomas.

Now, why is this? This is because the immune response not only takes care of microbes or pathogens but they also take care takes care of tumours that develop and the immune system is very good at trying to control both these two. So, in case the immune system is compromised or deficient, then you will have these other features that are being expressed.

So, in terms of diagnosis what is often done is you one would need to measure the complement amounts in the sera, the immunoglobulin amounts in the sera, especially this is especially true in case of B cell deficiency and then blood counts of B and T cell numbers and in some cases may be functional studies can also be done if required.

So, you may be you know in some cases, you do sufficient number of B cells but in terms of actual antibody production they are deficient and that would show up in terms of lower amounts of immunoglobulin in the sera. If you activate these B cells, you would may be find that even though they look fine they are not actually functioning in the manner that they are supposed to do.

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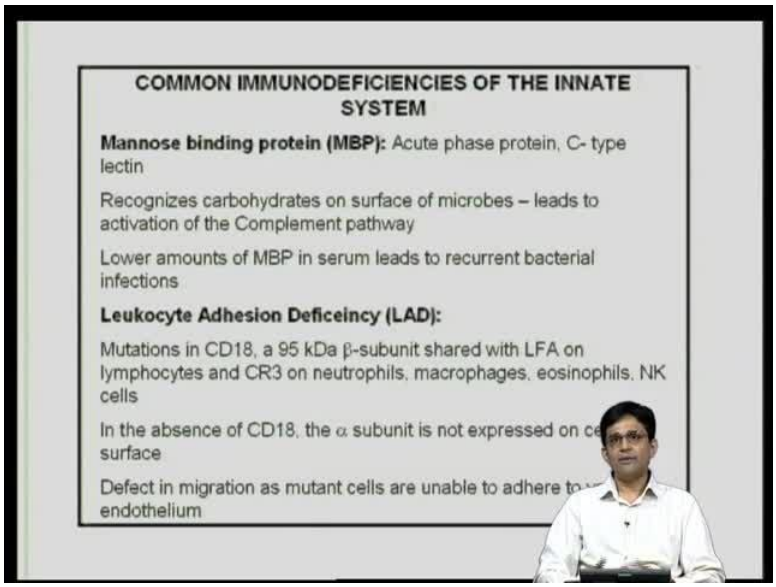

Now, what we will discuss now are what are some of the common immuno-deficiencies of the innate system. Again, these are aspects that we have discussed previously but it is important to put it in this one heading of immuno-deficiency. The one important one is that of mannose binding protein or MBP. This is a common problem or it is a common immuno-deficiency in fact.

Now, MBP is acute phase protein that means as made by the liver in response to inflammatory conditions and the liver makes the lot of these. It is a C-type lectin. What MBP does is that it binds to carbohydrates on surface of microbes, not only does it bind; it also activates the complement cascade.

So, binding as well as activation of the complement cascade is important and what this would do is it results in lysis of the microbes. Consequently, a lower amount of MBP in serum leads to recurrent bacterial infections. MBP is a very common immuno-deficiency that is found and it is very important. It also tells you about the important role of complement proteins or important role of proteins that activate the complement system.

In case, there are deficiencies in this, certain phenotypes will get expressed terms and with MBP what the weight was discovered was if you take serum from the patient, then you are not able to lyse these microbes because you are unable to bind and activate the complement. However, if you mix it with another person, you know who is not suffering from MBP. You are able to ((lye)), so that said that there were some problem or some deficiency in the serum and it turned out to be MBP which was discovered much later on.

The other deficiency that we will talk about is leukocyte adhesion deficiency or LAD. Now, in what happens in LAD is that there are mutations in CD18. Now, CD18 is a beta sub unit and which is shared on LFA on lymphocytes or LFA is a member of the adhesion family of proteins, it is present on lymphocytes. Now, this CD18 associates is the beta chain. It associates with the alpha chain of LFA and this express in the surface of lymphocytes. Now, CD18 is also associated or a part of the complement receptor 3. CR3 is as present on neutrophils, macrophages, eosinophils and NK cells.

Now, what happens is in the absence of CD18, the alpha sub unit is unable to be expressed on cell surface because the alpha sub unit needs the beta, they will join together and they are expressed on the cell surface. Now, what happens if you do not have CD18? If you do not have CD18, there is a defect in migration because in the absence of proper LFA, the cells are unable to adhere to the vascular endothelium and which is a major problem. So, these are two examples that I have taken MBP and LAD to tell you about importance of different aspects of the innate system.

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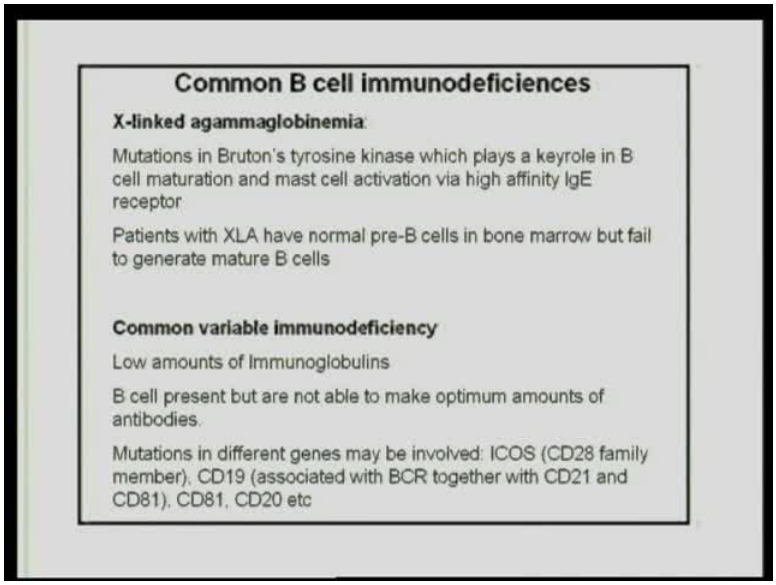

What about the B cell system? Again, in the B cells system, there are two that we will consider but the first one is excellent agammaglobinemia. Now, agammaglobinemia is that agamma means lack of antibodies. The other important aspect over here is that it is X-linked. It is X-linked because the gene that is responsible for this is Bruton's kinase and that is present on the x chromosome. So, that is why it is an important aspect and that is why initially when we discussed autosomes and sex chromosomes this aspect came up.

Now, what happens? Now, Bruton's tyrosine kinase is an important player in B cell maturation and also in the mass cell activation. So, patients who lack or who have mutations in Bruton's tyrosine kinase, they have normal pre-B cells but these pre-B cells do not are not able to mature into functional proper functional B cells. As a result of which you have you have individual without any functional B cells, consequently you will not be able to generate antibodies. So, this is what an excellent agammaglobinemia is.

The other one is common variable immuno-deficiency. Now, over here you have low amounts of immuno-globulins. Now B cells are there but they are unable to make optimal amounts of antibodies. Now, why is it that they are unable to make optimal amounts of antibodies? There are several reasons for this several genes have been implicated. So, unlike the X-linked where you have a single gene that is responsible for it in the CVI or the common variable immuno-deficiency, there are several genes that play a role.

So, for example ICOS. Now, what is ICOS? ICOS is something that we had covered during the course or class on co-stimulation. It is closely, it is family member, it is a CD28 family

member but ICOS comes up later. You will remember that CD28 is expressed on normal T cells but ICOS of the family member is expressed later upon T cell activation. Now, if in individual who lack ICOS, they often show improper or lower amounts of the antibodies perhaps because it probably play some role in controlling B cell activation. So, the phenotype is expressed in that manner.

The other genes that are is CD19. Now, CD19 is associated with the B cell receptor to get the CD21 and CD81. So, consequently if you have mutations in CD19 or in CD81, it results in a common variable immuno-deficiency because in this case, even though you have B cells what is happening is you do not have proper B cell signalling which results in this.

So, the other gene that is responsible is CD20. CD20 is again expressed on B cells. CD20 is important because in some cases of myelomas for or B cell lymphomas, CD20 is the target and if you have antibodies in CD20, then you can control these myelomas.

So, it perhaps plays some role but in case you lack CD20, then it results in common variable immuno-deficiency. So, these are two examples that we sort of that are picked in K2 to refer to the importance of B cell immuno-deficiency.

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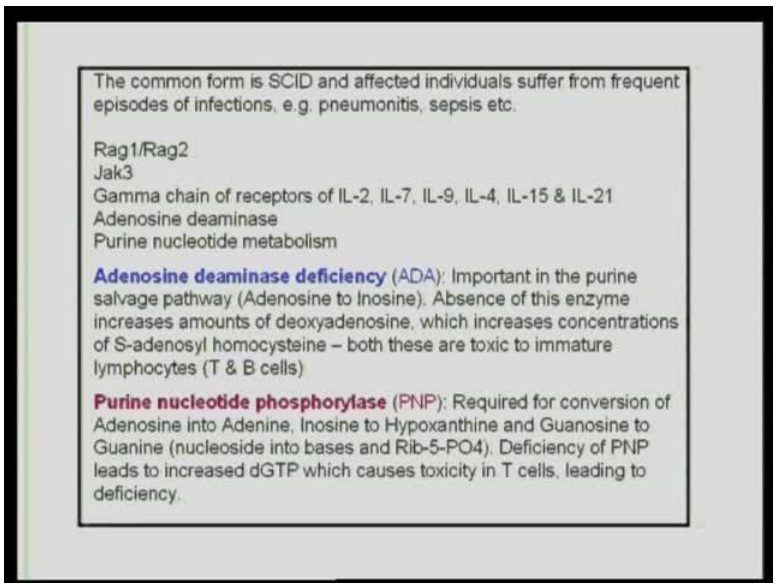

By enlarge you must have heard the term SCID. Now, what SCID refers to is severe combined immuno-deficiency. There are several genes that are involved or that might give rise to the SCID phenotype. The most important one is the Rag 1, Rag 2. Of course, as

mentioned previously Rag 1 Rag 2, you will not generate B cell receptor or the T cell receptor and it will read to these sort of problems.

We will discuss a little bit a little later. On the other one is JAK3 again something that we will see the third one is the gamma chain of common cytokine receptors and there are several of these receptors that utilize the gamma chain. So, for example the gamma chain is common for IL-2, IL-7, IL-9, IL-4, IL-15 and IL-21. Now, this is an aspect that you must have studied while doing the classes on the cytokines, while cytokine receptors. The other two are actually metabolic defects. The first one is adenosine deaminase, so ADA. The other one is purine nucleotide phosphorylase, PNP. So, we will discuss a little bit about this.

So, for individuals who lack adenosine de-aminase, what happens is this enzyme is responsible for converting adenosine into inosine. Now, if this enzyme is not present, you have large amounts of de-oxyadenosine being generated. Now, de-oxy because of large amounts because of accumulation of de-oxyadenosine, it increases concentration of s adenosyl homocysteine and these products are actually toxic to mature lymphocytes both T and B cells. Consequently, the lymphocytes are affected. They die and it results in deficiency of these cells.

Now, in the absence of these cells, obviously it will lead to immuno-deficiency phenotype because here you have case where you do not have B cells or T cells. The other one is remember these are metabolic defects or defects in metabolism. The other one is purine nucleotide phosphorylase. Now, in here this p and p is important in conversion of adenosine into adenine and the ribose 5 phosphate, inosine into hypoxanthine and the ribose 5 phosphate and guanosine into guanine which is the base and ribose 5 phosphate.

Now, deficiency in these leads to increase, you know DGTP this causes toxicity to the T cells leading to deficiency. Again in the absence of T cells, you would have immuno-deficiency because T cells are major players. It would not only affect your CD4 responses which are important in helping B cells, it would affect the CD8 positive response, it would affect the macrophage response because all these cells and all these networks are actually talking to each other and if one important partner is compromised, then it will naturally affect the others which is what is illustrated by these examples.

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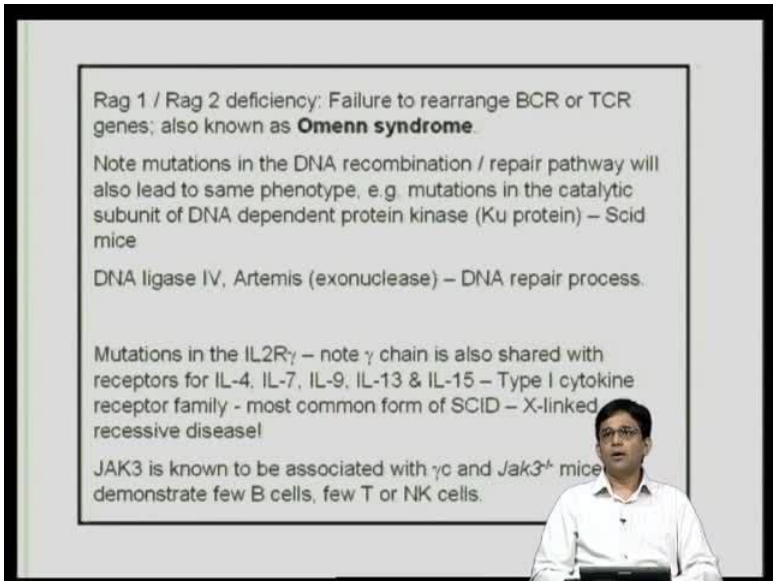

So, I said we would discuss a little bit about this. Now, the failure of Rags would lead to failure to rearrange the B cell receptor or the T cell receptor and this part, this syndrome is known as the Omenn syndrome, very important.

Now, over here this now entire recombination process also involves enzymes that are involved in DNA repair. So, for example if there are mutations in the Rag or in mutations in other proteins that are involved in that repair process, for example DNA dependent protein kinase or DNA ligase 4 or artemis which is an exonuclease. All these would result in a failure to rearrange B cell receptor and T cell receptor, consequently leading to severe immuno-deficiency because you would lack both T cells and B cells.

In fact, in the SCID mice in there is a strain if mice known as the SCID mice. In this the mutation is actually in the DNA dependent protein kinase known as ku, so over here because there is a mutation in these mice are immuno-deficiency. They lack T and B cells which gives it particular phenotype. Again, it illustrates the importance of both recombination and the processes involved in DNA repair which result in these cells. So it is a very important aspect.

The other mutations that we talked about are mutations in the gamma chain and the gamma chain, this particular gamma chain of this receptors, they are shared. So, for example in the IL-2, IL-4, IL-9, IL-13 these all shared this common gamma chain and this in fact, it turns out this is the most common form of SCID. In this case, this gamma chain is again X-linked recessive disease.

Now, along the gamma chain function goes or functions through a protein known as JAK3, so if there are mutations in gamma chain or in JAK3 which is the Janus Kinase 3, you know you would get pretty much the same phenotype. Therefore, JAK3 knockout mice demonstrate very few B cells, very few T cells are NK cells. So, again the lymphocytic arm is sort of affected because these are important in generation of the cells and consequent activation and differentiation of lymphocytes.

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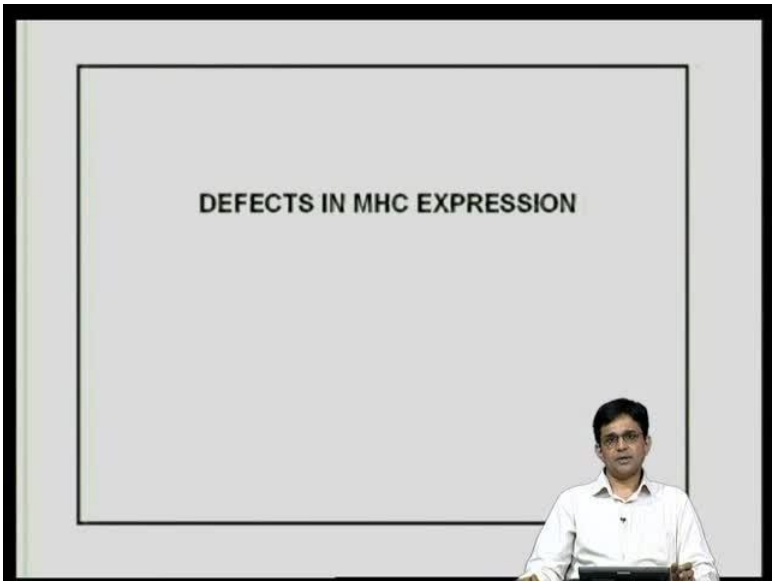

The next one that we will consider is going to be defects in MHC expression.

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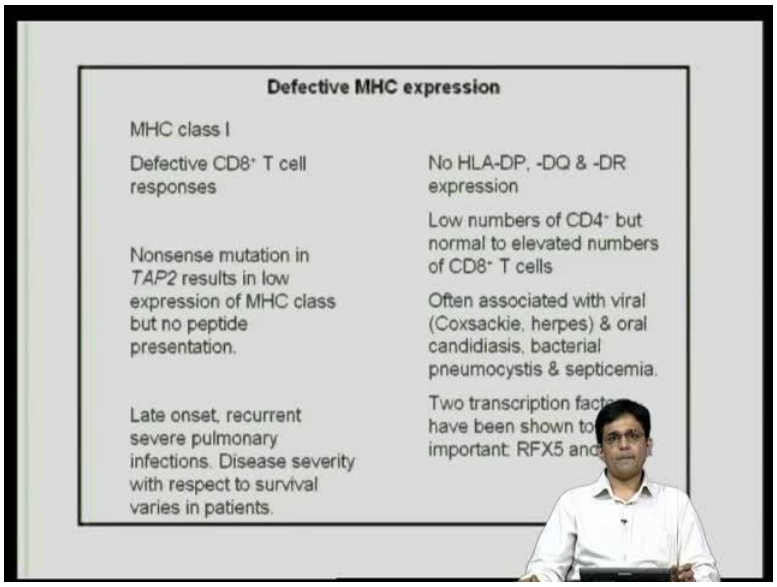

Now, there are two types of MHC, I hope your students will remember. You have MHC; the classical MHC once can be broken down into two MHC class 1 and class 2. You will remember that MHC class 1 you have the heavy chain, you have the beta 2 macroglobulin and the peptides. So, it is a trimer which is important for proper function and cell surface expression.

In case of MHC class 2, it is made of 2 chains, the alpha chain and the beta chain and then the peptide. There are other differences. MHC class 1 is expressed on all nucleated cells whereas MHC class 2 is expressed only on certain cells which are B cells which are macrophages basically, antigen presenting cells, langerhan cells and so on. So, what is important is that the expression of MHC class 2 is in specialized cells, antigen presenting cells, whereas MHC class 1 expression is fairly ubiquitous in all nucleated cells.

So, we will come to this aspect a little bit later. Now, what would happen if you do not express MHC class 1? Now, you need to remember that when we discussed MHC, we had said that MHC proteins are there are three different aspects. They are polygenic that means you have different genes that are responsible for it. They are polymorphic that means within the genes there are certain changes that make them distinct and the third thing is they are inducible with inflammatory cytokines namely interferon gamma would be a good example. Now, the polygenic is important because if you remember in mice you have KD and L in humans you have HLAB and C.

So, if let us say there is a mutation in one, you have other MHC class 1 alleles that can be expressed and so, therefore the chances of MHC class 1 deficiency in this respect is somewhat less. The problem comes is that the heavy chain is associated with beta 2 macroglobulin.

So, if there are mutations in beta 2 macroglobulin for example, so then you have improper folding of the MHC class 1 and you will have improper function of MHC class 1 which will result in MHC class 1 deficiency. Now, there are other reasons also for it. Remember, MHC class 1 molecules bind to peptides in the endoplasmic reticulum and how do they do that because you have transporters that transport these peptides form the cytosol into the er.

Now, if there are mutations in the transporters associated with antigen processing, you will have problems again because in the absence of peptide, the MHC class 1 molecules are not able to fold properly and are not able to reach the cell surface for functional role. So, these

are all problems with this. So, you may result in deficiency in MHC class 1 expression in the assembly factors namely the beta 2 macroglobulin and the transporter associated with antigen processing. In fact, what was shown is nonsense mutation in TAP2 results in low expression of MHC class 1 but and there is no peptide presentation.

Now, what happens if there is no MHC class 1? The most important thing is that proper selection in the thymus is not there as a result of which you do not have the CD8 positive cells. If you are not having the CD8 positives, one important part of your adaptive immune response which is the CTL part is compromised.

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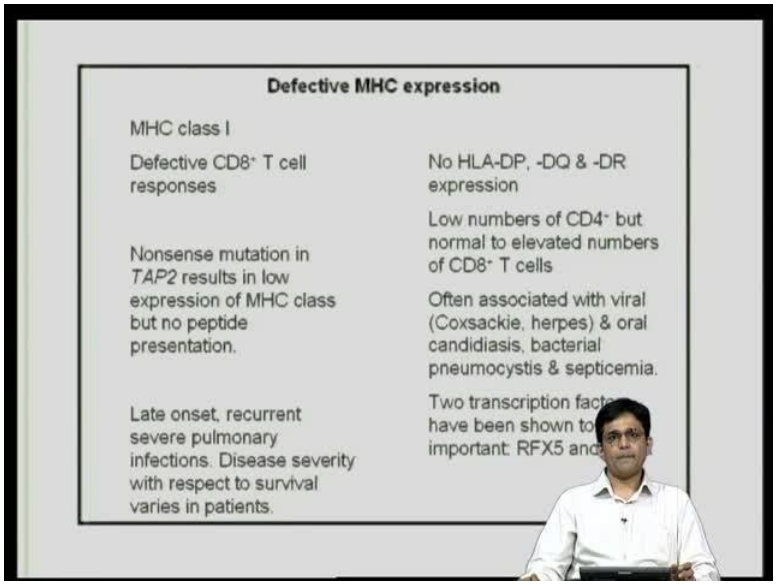

So, consequently you know you have the phenotype is expressed later on because you still have the CD4s and they can do something. They can help those and it is expressed late and it results in recurrent severe pulmonary infection. The busier severity with respect to survival varies with patients and it varies because it depends on where the mutation is, how much of an effect it has you know whether you have, if you have absolutely no MHC class 1 expression. No functional MHC class 1 expression versus low or you know low but there is still good enough to get some sort of responses going. So, that is what it you know there is variability because it just depends on the type of mutation and what is the effect, it finally sheds off.

Now in case of MHC class 2, what would happen is that again you would need now. MHC class 2 is also polygenic, so in case of humans you have DP DQ DR. In case of mice, you

have IA and IE. Therefore, mutations in either of this resulting in absence of MHC class 2 is not going to be all that likely because let say if DP is affected, you know there is DQ and DR that would still take care but over here, the problem in case of MHC class 2 often has to do with expression. It is expression because of some key transcription factor which are important in their expression in certain in these specialized tissues and two of them are C2TA which we had discussed and the RFX5.

So, these are transcription factor which bind to MHC class 2 and MHC class 2 family members like DM so on and are responsible for generation of their transcripts. So, they play an important role in their transcriptional expression and if these transcription factors are compromised, it would result in diminished MHC class 2 expressions.

So, with diminished class 2 expression, what would happen is selection of MHC, CD4 positives would be affected. Therefore, you would have low number of CD4 positives and CD8 to be find and it is often associated this sort of is often associated with viral infections, candidiasis which is the fungal infections bacterial infections and septicaemia.

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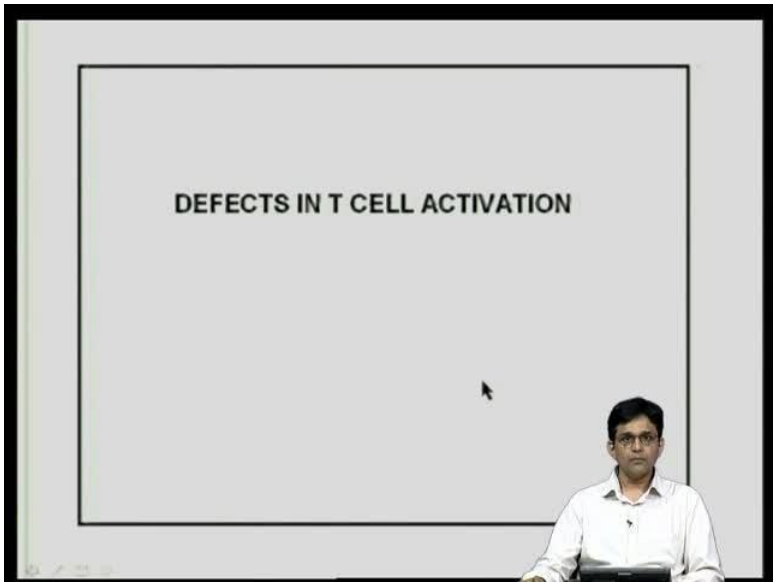

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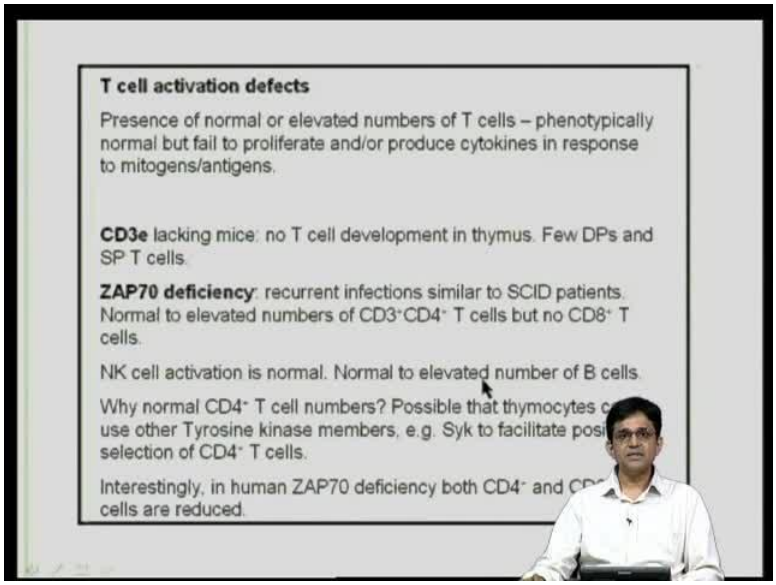

Now, defects in T cell activation, now in this if you have T cell activation defects you would have presence of normal or elevated number of cells but they would fail to proliferate or produce cytokines in response to mitogens and antigens. So, in this case the a the absence of T cells and then the absence of proper activation are good examples.

So, some of the ones are in fact, if you have the CD3 epsilon, remember the T cell receptor is there, it is associated with the CD3 proteins. If the CD3 epsilon is not there, then what happens is the for the T cell receptor you need the T cell receptor and the CD3 to properly to be expressed as the multi-protein complex and this multi-protein receptor complex, then goes up to the cell surface. If some of the components are not there, then there is improper assembly of the T cell receptor, it cannot go up to the cell surface and so this is what happens in CD3 epsilon lacking mice. You have no T cell development in the thymus. We have very few double positives and single positive T cells.

Then the other example is ZAP70 deficiency. What is ZAP70? ZAP70 is data associated protein and the molecular weight is 70 KDA which is what which is why it is it has been given the term as ZAP70.

So, in this case again you have recurrent infection similar to SCID patients. You have normal or elevated numbers of CD3 positives and which are that CD4 but there are no CD8 positive T cells. Now, this in case on humans in fact what is seen is there is efficiency in both CD4 and CD8. So, the question then becomes is why is it that you have normal CD4 numbers in case of mouse? Now, what is possible is that you know in the thymus may be some other

tyrosine kinase member like Syk something could bind and it could result in selection of CD4s whereas in humans that sort of is not the human ones are not able to be able to complement that. As a result of which you do not have you see deficiency in both CD4 and CD8. In case of mouse, there are some differences as a result of which you will get some selection of CD4s in the absence of ZAP70.

So, there are these clear differences between in some cases between mouse and humans and this is a good example of that but nevertheless the fact is ZAP70 is a major player and it leads to this sort of deficiency. The other one, the other T cell activation defect which results in immuno-compromise individuals is going to be your mutations in your stim 1 and orai proteins. Now, you will remember that stim and orai are important in mobilization of calcium into T cells and you need proper for proper T cell activation you need a spike in calcium, intercellular calcium but calcium amounts need to be sustained over a period of time, so that there is sufficient calcium to activate calcineurin, to activate NFAT. So, you can turn on the signals and there is proper gene expression.

So, an individual who lack who has mutations in stim or an orai, stim is a sensor, orai is a calcium channel which allows extracellular calcium to enter into T cells. You will have mutations in these so something that is important for you all to think through and also the fact that this aspect was sort of discussed in the T cell activation class and it is better that you are again you familiarize yourself with this aspect.

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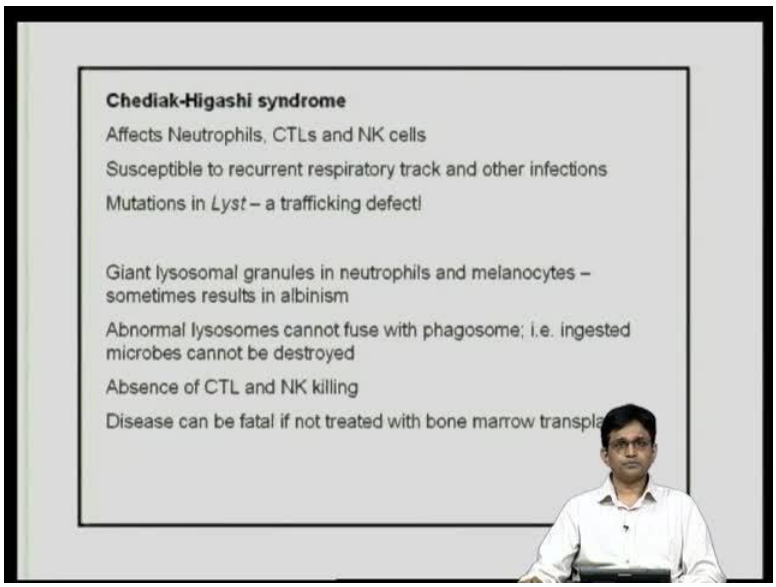

The other one that I would talk about is the Chediak-Higashi syndrome. Now, the Chediak-Higashi syndrome is a very important cell biology aspect. Now, over here there is a problem with trafficking. Now, as a result of which you know it affects neutrophils; it affects cytotoxic t lymphocytes and NK cells.

Again, the phenotype you know these people these are susceptible to recurrent respiratory track and other infections and mutation is in Lyst which is a trafficking defect. Because of this what happens is you have joint lysosomal granules in neutrophils and melanocytes sometimes resulting in albinism.

Albinism means melamine is degraded. As a result of which you know you have white patches. Abnormal and these abnormal lysosomes cannot fuse with phagosomes. These ingested microbes cannot be destroyed; there is an absence of CTL and NK killing. Remember, the granules are affected because of the trafficking problem and since, the proper formation and the granules are not there. There is improper CTL and NK cell killing and the disease can be fatal if you do not treat with bone marrow transplant and this is something that we will see.

Immuno-deficiency the only way that you can really treat immuno-deficiency is going to be through bone marrow transplants. I mean whether it is David Vetter who was the bone marrow was failed because that time viruses in the donor transplants could not be detected but now they are able to detect. So, at least you know chances are reduced but this is an important aspect that you know transplants bone marrow transplants is unfortunately the way to go about it and perhaps the only real practical solution.

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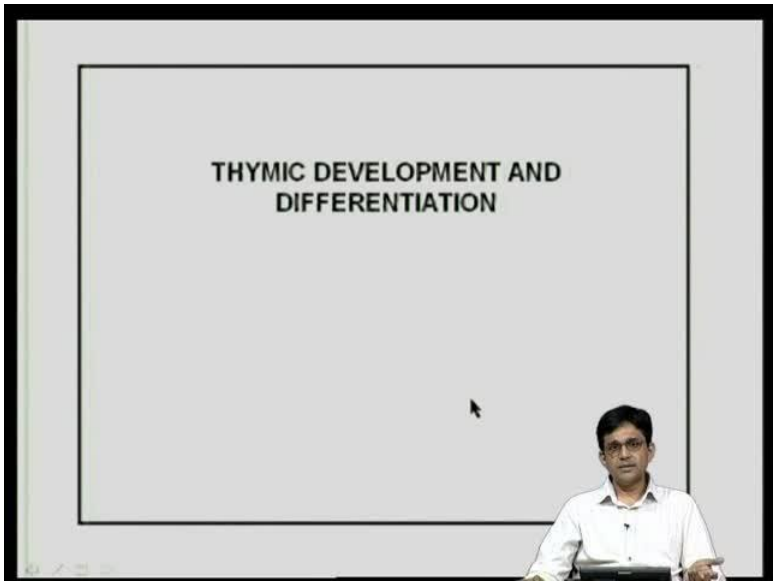

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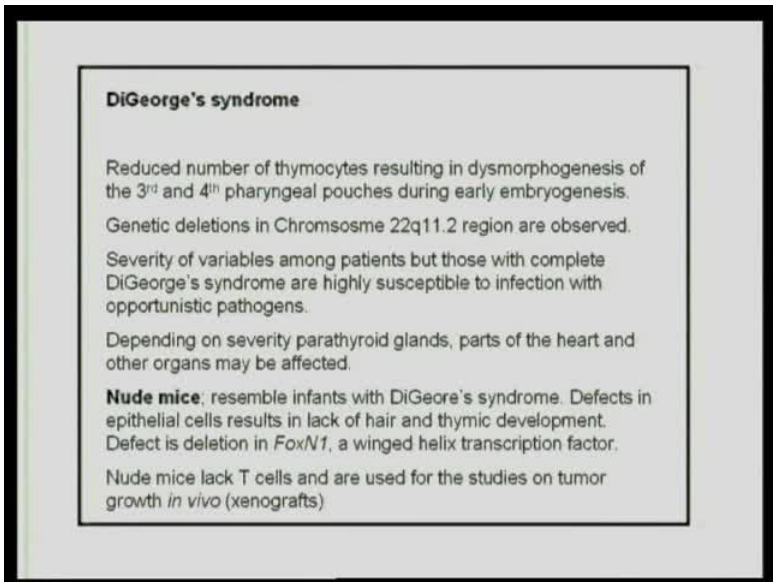

The other is the thymic development and differentiation. Now, over here we will discuss DiGeorge's syndrome. DiGeorge's syndrome results in reduced number of thymocytes and resulting in improper formation of the third and the fourth pharyngeal pouch during early embryogenesis that means during development you know you have improper formation of this region which contributes to the thymus which and other parts, so including the heart.

So, if DiGeorge's syndrome is because of deletions in a particular region in the chromosome which is chromosome 22q and there are several phenotypes and observe because this again would depend on the types of mutations that are observed. It affects and depending on the

kind of mutations, it will affect the thymus, it will affect parathyroid glands and it will affect parts of the heart which are all closed by linked.

Remember, the thymus, it is right on top of the heart. So, the parathyroid, thymus, heart they are all sort of linked and they come through a common developmental thing which is the third and the fourth pharyngeal pouch which gives rise to these organs. So, if there is a development defect because of some mutations in chromosomal 22q, then these sorts of things are resulted.

So, the closest to DiGeorge's syndrome in terms of a mouse phenotype is that of the nude mice. Now, why is it called nude? It is called nude because these mice lack hair, so their skin lacks hair. So, you know it gives them that is why then name nude. So, these mice have two phenotypic defects. One is you know of the nude phenotype lack of hair, the second is the absence of a thymus. Now, in the absence of a thymus what would happen? You would you would not be able to generate sufficient number of T cells now and why is this? The mutation has been found there is a defect in a transcription factor known as FoxN1 which belongs to a family of a winged helix transcription factor.

Now, nude mice are extremely useful in terms of immunology. They are extremely useful because in the absence of a good T cell response, what you could do is you could do allographs or even in some cases even xenografts.

So, you can take transplant tumours, especially you know tumours from others strains of mice or even human cells. If you want to study whether their chances of developing tumours these can be transplanted on to nude mice and then you see if these develop tumours are not remember. In case of tumour, the T cell response plays an important role and so you are able to now check or study if something that you can actually culture these cells to find out which indeed are cells that would ultimately turn into tumours, especially in terms of human cancer studies, it becomes difficult to do this in vivo.

So, a good way to study is to use nude mice and so these are done because and you are able to do it because you are because the nude mice because it lacks T cell. Response will not be able to generate a good allograft or good anti-allograft or good anti-xenografts response and so people have made use of his or scientists have made use of his to use as models for growth of tumour cells.

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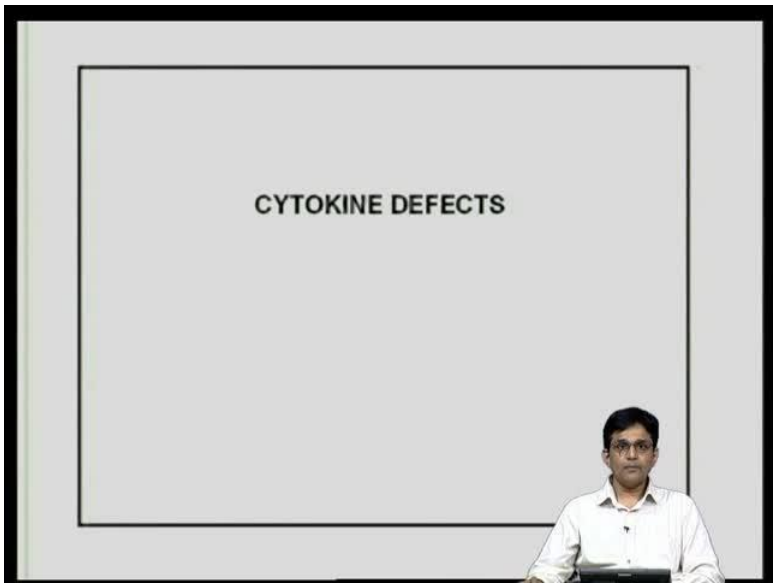

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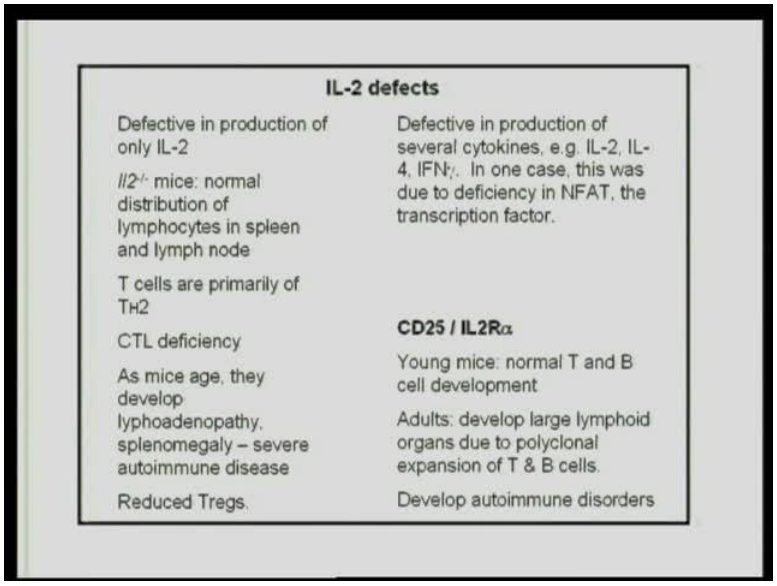

Cytokine defects, now in this case we will discuss some important cytokines. IL-2 is clearly an important one. Now there are two types of mutations that need to be thought about one is defective in production of IL-2. So, for some reason there is a defect in production of IL-2 and what has been found is what one would expect with the IL-2 knockout mice is that because they cannot produce IL-2. There would be some problem in generation of immune response. In fact, what was found in the IL-2 knockout mice is that you have auto-immune like situation. You have hyper proliferation of T cells and the T cells are primarily of TH2 type. There is a deficiency in CTL function.

Now, initially were these mice develop as they are as the age, they develop this auto-immune syndrome and why is it that they are able to do it then? Here, we have discussed this aspect before is IL-2 is important for the survival and maintenance of T regulatory cells. So, with time as T regulatory cells decrease, you have an increase in auto-immunity because the normal suppression is that the T Rags do are not being done. Consequently, you have increase in auto-immunity. So, this is one aspect.

Now, this is also seen in cases of where you lack CD25 or the IL-2 receptor alpha. Now, CD25 you may remember is rapidly induced upon T cell activation. It is a good marker for T cell activation and what was seen in mice that lack CD25, again young mice, they have normal B cells. Now adults, you have large lymphoid organs because of polyclonal expansion of T and B cells and they develop auto-immunity.

So, the phenotype that is shown by IL-2 knockout mice and CD25 are reasonably same. Now, the same does not hold true for the IL-2 receptor gamma. Now, gamma IL-2 receptor gamma was pointed out results in severe SCID phenotype that is because the gamma is shared by different cytokine receptor. So, just so that you know I mention this just for that students do not get too confuse and they realise difference between CD25 which is IL-2 receptor alpha and the IL-2 receptor gamma, you get a more severe phenotype and that is because the gamma is shared by the cytokine receptors.

Now, in some cases you may have situations where not only IL-2 but other cytokines are not produced like for example, IL-4 IFN gamma. Now, in this case what was been shown is that this is deficiency in the NFAT or the nuclear factor present in activated T cell which is induced upon T cell activation and which is important not only in production of IL-2 but of other cytokine. In the absence of this cytokine, you have defect in production several cytokines which gives you a major phenotype.

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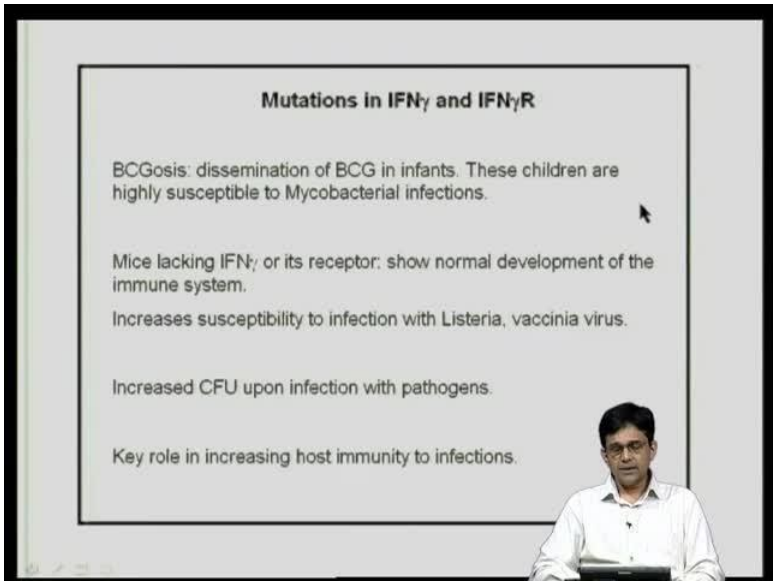

Then the second one we will discuss are mutations in interferon gamma and its receptor. Now, these uncovered especially in cases of young infants who have given BCG. Now, if infants who lack interferon gamma or interferon gamma receptor or in actually if they lack IL-12 or IL-12 receptor they are the same phenotype. Now, BCG is a live attenuated vaccine. It is a good paediatric vaccine against tuberculosis and when given if the person is or the infant is immuno-compromise and lacks these important cytokines, it is unable to find BCG and there is disseminated disease.

So, and which diseases known as BCGosis and the children are highly susceptible to micro bacterial infection. In fact, in mice lacking interferon gamma or its receptor show normal development of the immune system but they are very sensitive to infections with microbes. So, for example listeria vaccine virus, intercellular, other intercellular pathogens so on. What you see is there is increased CFU upon infections, these pathogens and this sort of illustrates important role of interferon gamma interferon gamma receptor in and actually, also IL-12 and IL-12 receptor in playing a key role in increasing host immunity to infections.

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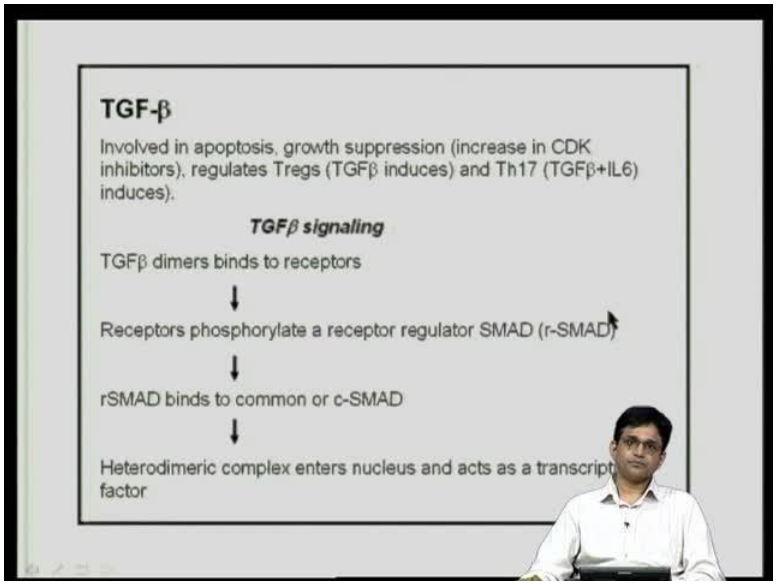

Now, there are two cytokines that we had, that we had discussed but not studied in greater detail and I thought we would we would do that. So, in fact both these cytokines actually do not result in what can be considered as immuno-deficiency. They are like IL-2 in that respect in the sense that there is an auto-immune phenotype that they display but this is an aspect because we are studying role of different cytokines. So, I thought I would put them over here.

Now, TGF data and IL-10 other ones that I have in mind, it is very interesting because both come under the category of immuno-suppressive cytokine. Both TGF beta and IL-10 would be once that are well known to sort of down modulate responses and but the phenotypes of this are very distinct. TGF beta is involved in apoptosis growth suppression because it increases the production of the cyclin inhibitors, it regulates T Rags. In fact, TGF beta alone induces is responsible for the generation of T Rags.

Now, however if TGF beta plus IL-6, then you will have different type of cells coming up and those are the TH17 cells that is an aspect that we have studied during our class on T cells sub cells. So, very interesting TGF beta alone increases T Rags because that is important but if the TGF beta is given in combination or is present in combination with IL-6, then it gives an advantage for the TH17 in positive TH17 group of cells to develop.

In case of little bit about TGF beta signalling again, this is an aspect which we have not looked in or studied and the TGF beta dimers into cell receptor. These receptors phosphorylate a receptor a regulator SMAD and this is known as the r-SMAD and now the r-SMAD goes and binds to a common order c-SMAD. Together, these heterodimer enters the

nucleus and acts as the transcription factor and which gives rise to you know the different affects that it has in apoptosis growth suppression so on. So, that is the primary way by which TGF beta functions.

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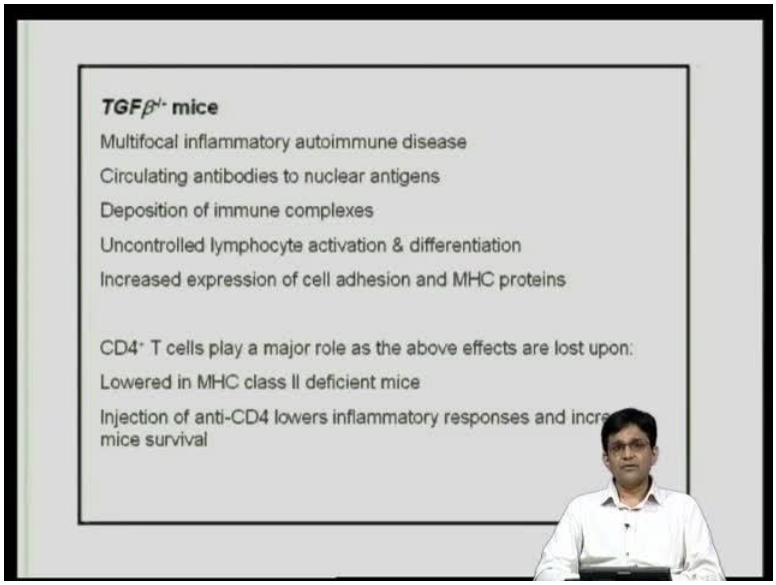

The phenotype of TGF data knockout mice is that it results in systemic auto-immune disease. It has multi-focal means at different places inflammatory auto-immune disease. You have increased circulating anti-bodies to nuclear antigens deposition of immune complexes. This uncontrolled lymphocyte activation differentiation increase expression of (()) and MHC proteins.

Now, in this it turns out that the CD4 positive cells play an important role. Now, what is the evidence for that? There are two ways that is if you breed now the TGF data knockout mice with the MHC class to deficient mice, then a lot of these inflammatory symptoms that are seen are reduced. The other way is if you inject anti-CD4 which means you deplete the CD4 population, then you lower inflammatory responses.

So, this sort of tells us that this heighten inflammatory responses that are seen in TGF beta knock out are due to the uncontrolled proliferation of CD4 positive T cells. So, again TGF beta is immuno-suppressive cytokine. It sort of reduces inflammation and this is just proved by the TGF beta knockout mice.

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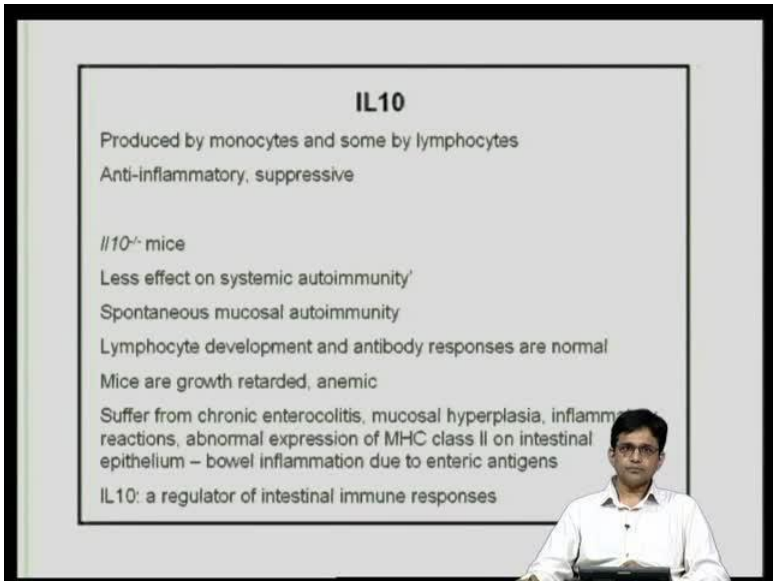

What about IL-10? Very interesting, now IL-10 is produced by monocytes and some amounts are produced by lymphocytes. It is anti-inflammative and it is a suppressive. Now, in IL-10 there is less effect on systemic auto-immunity. By systemic auto-immunity means like for example, integer beta you know such a inflammatory reaction that in fact inflammatory responses that are seen by the mice. That sort of is not seen such a dramatic response is not seen by the IL-10 knockout mice. In fact, what is seen is that it has it has causes spontaneous mucosal autoimmunity.

In fact, it turns out that it is a T regulator intestinal immune response and why do we say that? Because the immune the lymphocyte development and antibody responses are normal but the mice are growth retarded and anaemic. Why is it, because they suffer from chronic enterocolitis colitis means inflammation of the colon. There is mucosal hyperplasia of the intestine. Hyperplasia is proliferation, the inflammatory reactions abnormal expression of MHC class 2 on intestinal epithelium. This bowel inflammation due to enteric antigen and this you can sort of reduce it if the mice are sort of breed in again in sort of bubble chamber is where they are not exposed to normal flora that we sort of live in with.

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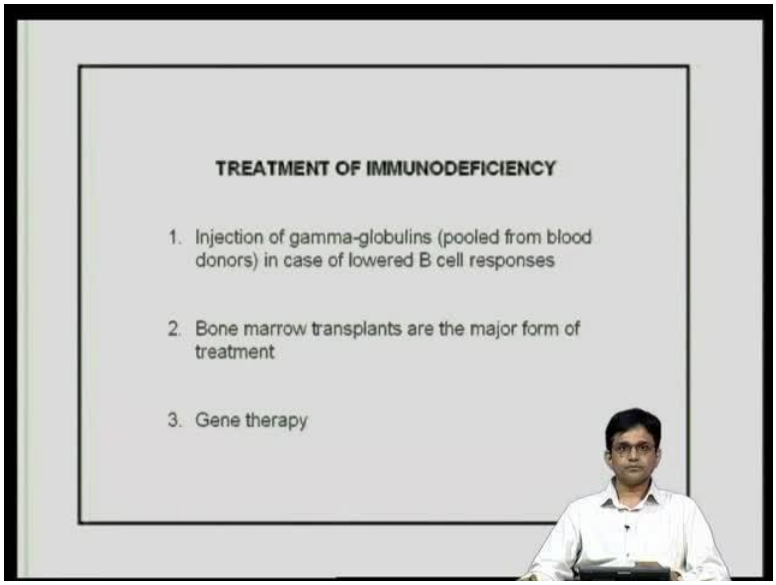

So, how does one treat immuno-deficiency? Especially, in cases of B cell immuno-deficiency is like excellent agammaglobulne due to mutations and Bruton tyrosine kinase or the common variable immuno-deficiency. There is you know patients are injected with gamma globulins and so these gamma globulins are got from pool blood donors and so this is sort of helpful. Then in the other case as I have said in terms of immuno-deficiency, the practical mode of treatment is bone marrow transplant and bone marrow transplant under careful conditions. These days you know this is possible because medical technology has improved a great deal since the days of David Vetter.

So, that is this the bone marrow transplant is the real practical sort of solution to immuno-deficiency which can be really life threatening because all the time you know you are coming down with infections. If it is a really if you are infected with the extremely pathogenic, then it can be severely life threatening. Then there is gene therapy but as I have said how much gene therapy is applicable in practical terms is not clear but bone marrow transplant is perhaps the way to go about it.

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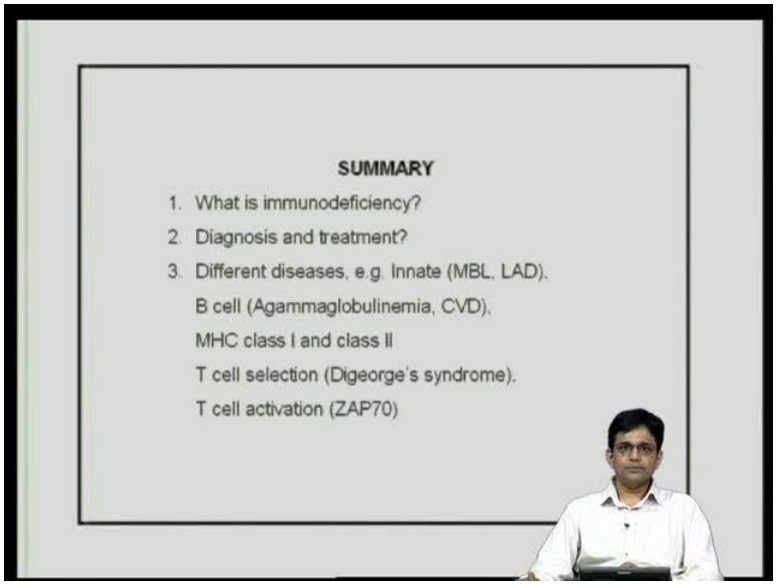

So, we will we will summarize this lecture. So, we started off with what is an immuno-deficiency and over here, it is the absence of a large part of the immune response. So, for example if you have Rags, then you have obviously a major hole in the immune response or you have smaller ones like mannose binding lectin, a key protein that is important but nevertheless the phenotypes are you know depending on the mutations. The phenotypes often the most common one are recurrent bacterial infections and these can be diagnosed. You can diagnose, you can check your complement levels, you can check your MBP levels, you can check for antibody, what is your B cell antibody.

If your B cell antibody levels are really low, then perhaps as the B cell deficiency, then you can finally actually check for numbers of T cells, B cells neutrophils so on. Also, check for function and the treatment as mentioned at most likely treatment or most practical solution is going to be that involving bone marrow transplants.

We discussed different diseases, so we discussed in innate. We discussed the MBP and the leukocyte adhesion deficiency and B cells. We discussed the Bruton tyrosine kinase and the other the common variable immuno-deficiency. Now common variable immuno-deficiency that are several reasons for it which and the several genes involved ICOS, CD81, CD20 so on.

We discussed the bare lymphocytes syndrome. Bare lymphocytes because lymphocytes there are less number of lymphocytes, lymphocytes are bare and that is because you lack MHC class 1 or MHC class 2. The reasons for that are once that we discussed in case of MHC class

1.You lack beta 2 macroglobulin or the TAP transporters. In MHC class 2, the specialized expressions are responsible for certain transcription factor, c2ta is really a key player in that and you have the other one also which plays an important role.

We discussed T cell selection in which case DiGeorge's syndrome which is actually a developmental defect and in T cell activation we and we discussed ZAP70. There we also discussed the Chediak-Higashi disease which affects the trafficking defects and so the proper granule formation of proper lysosomal formation is not there. As a result, it affects CTL and NK function.

So, overall in terms of immuno-deficiencies are really important and what immuno-deficiencies have done is that, it has told us about the importance of the proteins that play such an important role in the immune system.

Thank you