Immunology
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Lecture - 53
Autoimmunity (Contd.)

So welcome you again. So we are going to continue the same autoimmunity. So in last lecture, we discussed about Graves' disease and myasthenia gravis, right. How the antibody and react with the receptor and cause the disease and their problem. Is very simple I mean they just block the normal activity either by overreacting or just destroying the total function in those case, okay.

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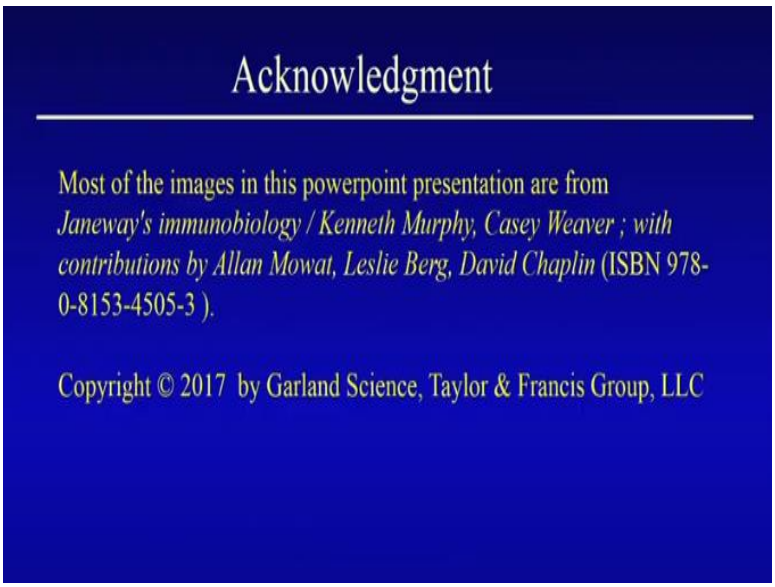

So autoimmunity also today's topic, we are continue few more disease and few more symptoms, what happened and definitely this is also I should acknowledge this book from where the slides are or the photographs or the figures are taken.

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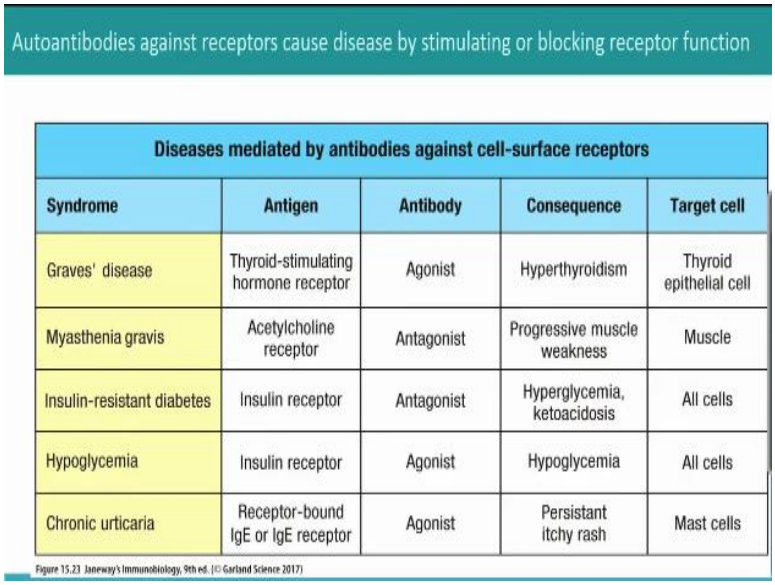

So this Graves' disease, myasthenia gravis, insulin resistance diabetes because the antibodies against the insulin receptor, because what can happen if it blocks insulin receptor that means, antagonist that means insulin will not work. So it will be hyperglycemia. That means blood glucose will be very high. There is no insulin. You know insulin controls the blood sugar.

Similarly, if it is a agonist that means if any antibody binds to insulin receptor in such a way it continuously produce insulin okay as if the positive way that is why the agonist is okay. And if this is the case, so what will happen if this is agonist insulin receptor will continuously produce insulin. As a result, blood glucose will be very low, and that is why hypoglycemia will happen.

So this is like receptor bound IgE, receptor agonist. So this will cause a itchy rash like what we will see. IgE receptor agonist means it will produce hypersensitivity kind of reaction continuous. So these are the different example. We just discussed Graves' disease and myasthenia gravis like how it works and this is some more, okay.

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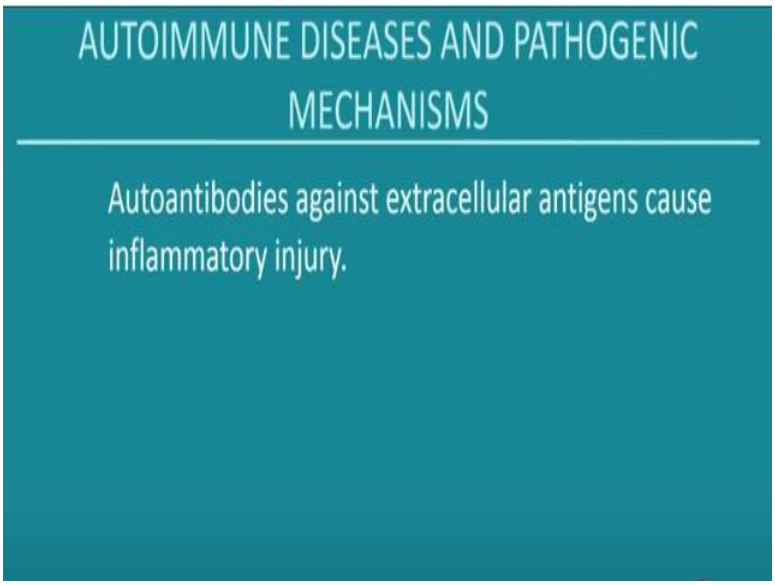

Antibody against extracellular antigen also can cause inflammatory injury. What?

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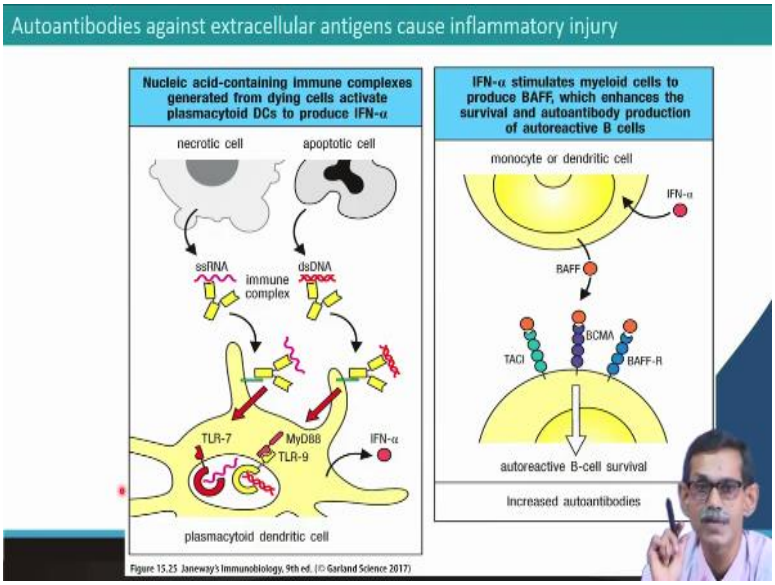

Because many time what happen the cell is dying and macrophage and dendritic cells are eating them, because to clean them. So while their cell is die by necrosis or by apoptosis, there is always a possibility that single stranded RNA or double stranded DNA is released. That we discussed before right in the very first lecture of autoimmunity.

These can internalized by the dendritic cell and is a particular type of dendritic cells, which we discussed during T cell maturation or T cell mediated immunity okay, plasmacytoid dendritic cells and these can internalize and can be activated and can cause inflammatory response. Similarly, this monocytes are the dendritic cells.

After eating that they can stimulate interferon and can release the BAFF that is B cell activating factor which in turn can this is normally not happen. I mean this is only when it happens then the inflammation or the autoimmune induced inflammation is going to happen. So this is that antibody against extracellular antigen okay autoantibody against extracellular antigen it can cause this problem, okay.

This will bind and which will be internalized in turn by opsonization or that receptor mediated opsonization.

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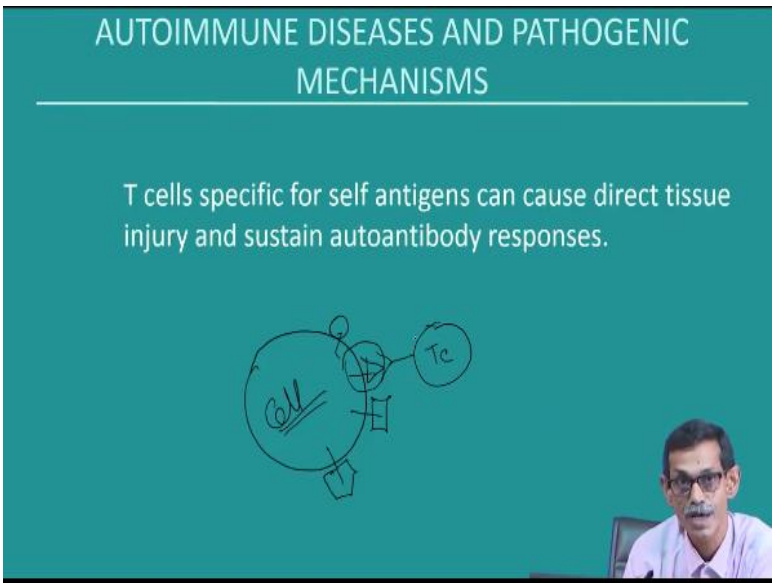

T cell specific for self antigen also can cause problem. If the T cell I mean that we did not discuss so far yet. If the T cell the cytotoxic T cell is activated against any cell receptor protein what will happen? There are many proteins on the cell, right. So there are many proteins around the cell. So if this is the cell, sorry if this is the cell there are many proteins okay. So suppose this is the different proteins.

So any one of the protein how it looks actually, okay. So this is different proteins in the surface and this is any cell, okay. What will happen if any cytotoxic T cell cytotoxic T cell can recognize it. Normally cytotoxic T cell recognize the foreign antigen, viral antigen or the tumor cell. But there are many proteins this cell protein. Normally they do not interact but if they interact what is going to happen?

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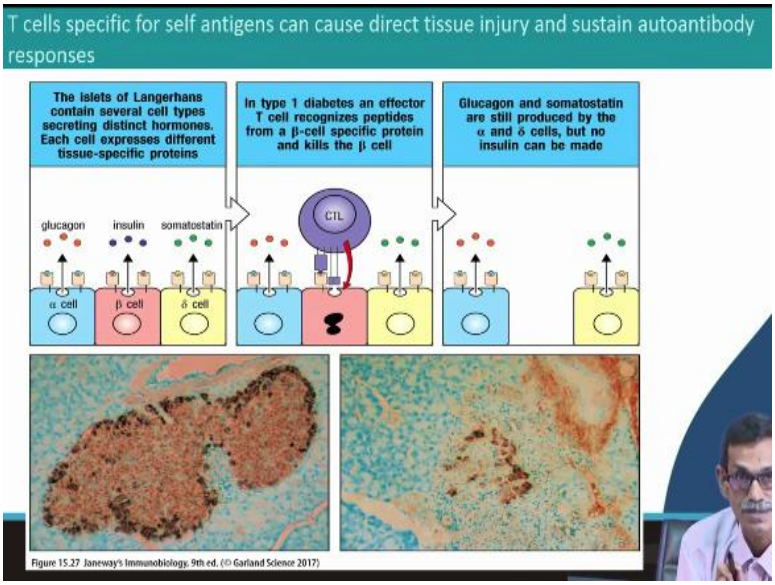

See, you this is again I am coming back to insulin. Insulin anyway insulin is one of my very favorite protein which I can use for explaining many thing. Okay, not only autoimmune disease, the gene expression, regulation everything, this is a wonderful protein that way, okay. It is very important, you can understand now. So in pancreas what happen? In pancreas there are alpha cell there are beta cell and there are delta cells, okay.

Alpha cell is produce glucagon, beta cell is insulin, delta cell is somatostatin. All are hormones. Suppose there are cytotoxic T cell which can recognize some of the surface protein of beta cell which is again presented by MHC I, okay. There are many other proteins presented by MHC on both in alpha and delta cell. But it is recognizing only beta cell protein. What will happen?

It will bind to beta cell, give the signal to die apoptosis because it will not realize whether it is a beta cell important for insulin production or it is viral infected cell. As soon as this interaction happen, it knows I have to kill it, it will kill. As a result, the whole pancreas will not have any beta cell. So what is the ultimate fate? Ultimate fate is no beta cell means that individual will not produce any insulin. So severe diabetes.

But in this case one advantage is there. In this kind of immunity autoimmune diseases one advantage we can supply auto I mean insulin from outside, okay. You can have insulin injection. But if there is antibody against insulin, what is going to be problem?

Because antibody against insulin means it will just neutralize. So then as soon as you inject the insulin antibody will neutralize it.

So there will be no point of applying insulin from outside also. But in this case body is not producing insulin because beta cell is not there. Otherwise, all other functions are normal, okay. So that externally we have to regulate the concentration of insulin, but at least better than antibody generated autoimmunity. Then, but this is also a very severe disease.

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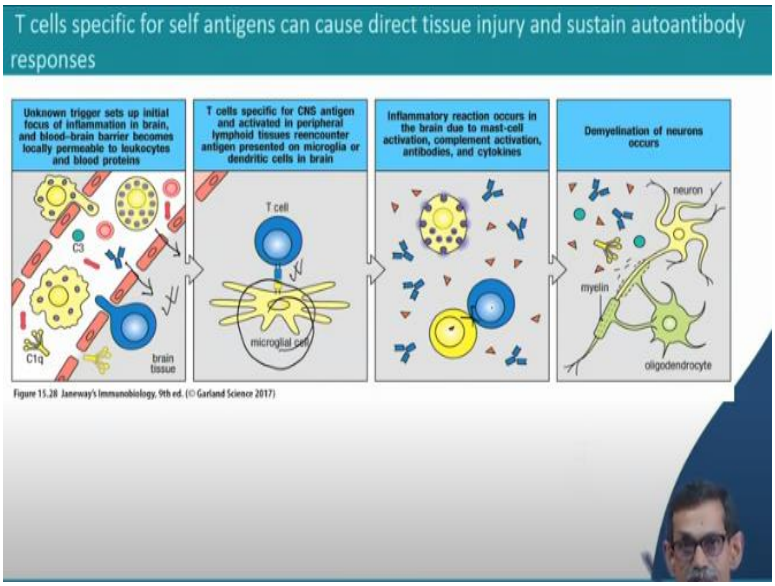

Another autoimmune case is T cell specific for self antigen which can cause direct tissue injury, okay. And what happen? Suppose normally there are some cases. Okay, suppose blood brain barrier. So if this is the brain tissue okay, this is a brain tissue and this is the blood vessels. Normally this neutrophil, macrophage, T cell they cannot enter because this is so tight, right.

But if by any chance if any injury happen or any how this T cell neutrophil all this thing can get in through this what will happen? That T cell specific I mean, they never saw this brain cells or brain protein before, okay. And they have I mean in brain for protection of immune system normally, they are immunologically privileged, but they have some protection, this microbial cell is going to be there.

It is like dendritic cells and they are going to present this thing to T cell and T cell is going to activate it and antibody will be generated because T cell and B cell interact

and antibody will be generated. That antibody will kill all the myelin sheath of the nerve present in the brain. So what will happen? If the myelin sheath of the nerve is not there, the nerve impulse transmission will be defected.

So as a result, what will happen? Brain will not work properly, motor nerve will not work properly. That is one case.

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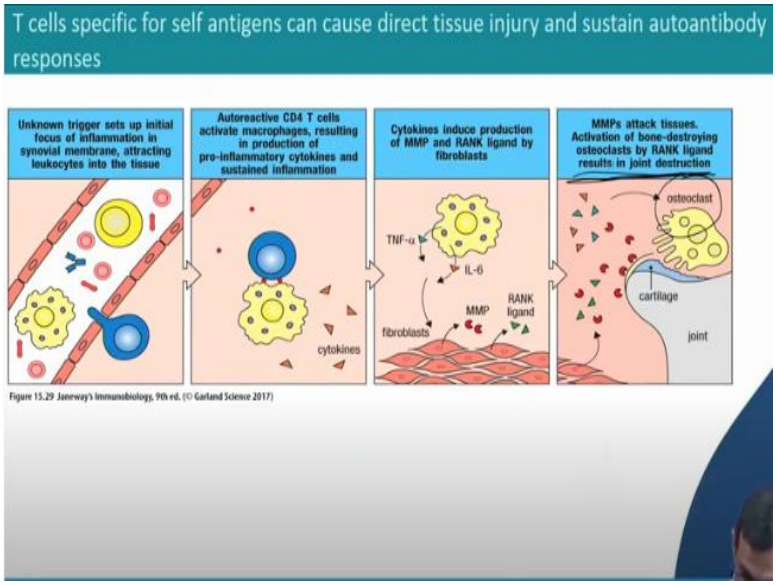

Another case, similar thing can happen in the synovial fluid portion. That means in the joint normally immune part is not there. If any damage happen in any joint what happen? The synovial membrane will be damaged and synovial membrane is damaged means result is I am not going all this detail. The similar I mean normally it is not happening.

If this breakage happen, if T cell can enter into that region they are not supposed to, they start doing all this MMPs, matrix metalloprotease which will start degrading and as a result what will happen different and it will create problem with the osteoblast, which form the bone and there will be result will be joint destruction, okay. So all the joint will be pretty weak. And joint means elbow, knee, everywhere there will be a problem.

So this also kind of this kind of autoimmune disease also possible, but this is again this is accidental injury, tissue injury is very much important, small injury. I mean many times having a very small injury in knee can start this kind of infection. It I

mean it looks very simple and normal just a simple heat, but if injury happen inside autoimmune disease may be activated, okay.

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Now, so this is **this is** part like few example of autoimmunity. I hope you have an idea like what autoimmunity is. Again, I am just summarizing very quickly. Yes, I need to discuss about the third point the genetic and environmental basis of autoimmunity, whether it is there or not. But before that, autoimmunity depends on multiple factor. It may be B cell, it may be T cell and also antibody, right.

It may be automatically generated or the fault of immune system or it may accidentally happen because something was not exposed before but some accident or some injury make them expose to immune systems. The immune system was not ready for that. So they never know that this kind of protein will be there as our own, okay.

Even sometimes some relative if you suppose some relative is very close relative, but you never saw from your childhood suddenly come to your house and you after opening the door you will ask definitely who are you, right. So that kind of thing after but if nobody is there, suppose nobody is there in home to tell okay that anybody knew that person, you will see that you do not know.

So even if your own relative you would not know because you never seen. Same way many proteins are there inside the cell the immune system never know as cell. So they

will I mean as soon as if something happen, they come out nobody will be there to tell them that this is mine and immune system will work against them and disease will happen. There are few example I gave. There are many example.

Lists are shown and given. Anybody is interested go detail and there are a lot of information in the net and any other book. Basic immunology book you may not get lot of information about the disease and their symptoms and the remedy. But just to get an idea, I gave few example of different type. Now I am going to talk about genetic and environmental disease. Is there anything there or not?

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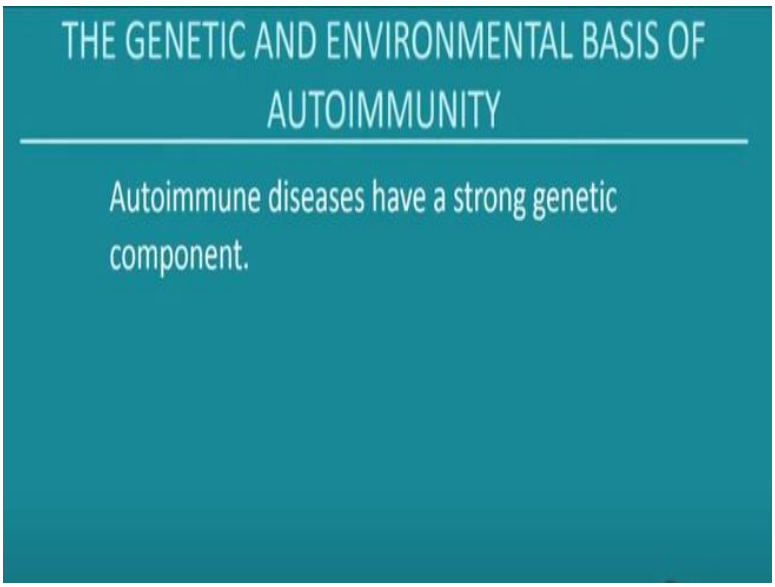

So first point is telling autoimmune disease have a strong genetic component, definitely it is there.

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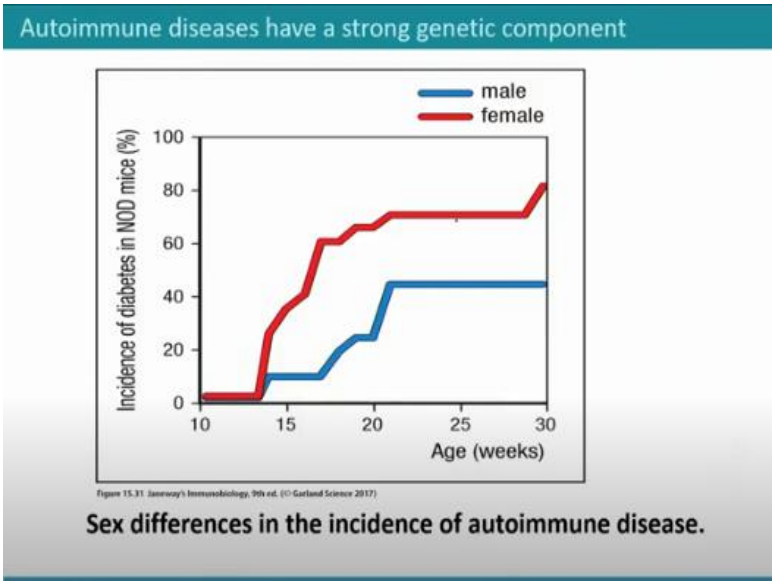

What are those? I mean this is one very simple experiment. So just to see whether this is autoimmune disease is has there any sex specificity, like whether it is more prone to female or more prone to male, what how can I figure it out? So there is a one very simple experiment was done. There is a NOD mice, NOD. NOD stands for non-obese diabetic. Because in mouse model mouse is used for many other many diseases.

So in mouse there are model obese mouse model, okay. So that you can and you can induce obesity, you can induce diabetes. So they are these mice is non-obese diabetes. That means you can induce the diabetes by using a specific chemicals. So mouse is normally normal, but you can induce them. But they will not be obese, okay. So they did the experiment.

It was found in non-obese mice when you induce the diabetes, the rate of induction or I mean cases of diabetes is much more in female than male. So this is an indication that means genetic variability or the sex variability is definitely responsible. And it is not like one or two mice. It was number of mice was tested and this is the average like it goes very high and it is there. And the severity or the incidence is also much more.

So it takes more, I mean, humans are more prone so within less time, maybe 13, 14 days it start showing the symptoms of diabetes. For male it is taking longer time and the number is also less. So that means sex differences has some role in autoimmune disease. May not be in all the cases, but at least in diabetes it is there.

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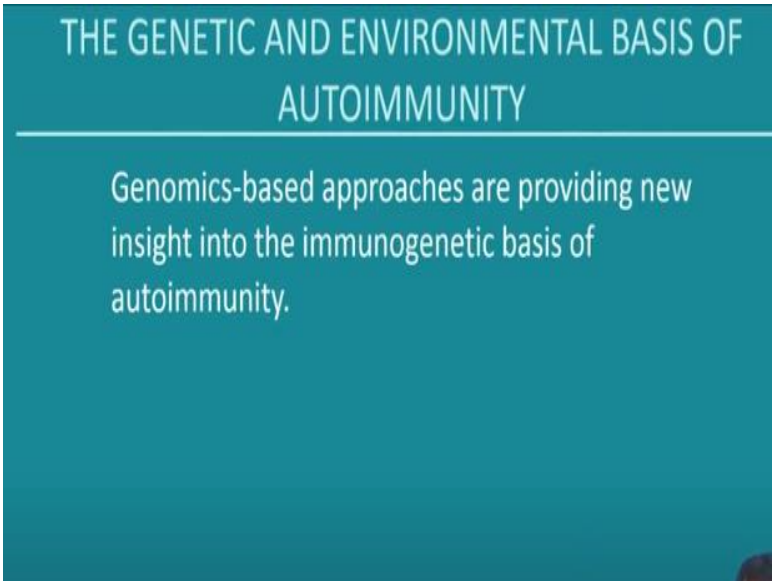

Genomic based approach are providing new insight into you know, genetic basis of that immunity. Because before the human genome project is discovered, we did not know what is what, okay. We have very little information. So this is a patient and we do not know what gene what but now, we have huge data, lot of information. May not be too much information for autoimmune disease.

Because person with autoimmune disease sequence should be in your hand to analyze it. So there are many, I mean, every day new, lot of new information is coming about the human genome, more human genomic sequence, and we are knowing. We have to, in this case we have to just select the genome sequence of or human genome sequence of that individual who has a particular disease and history is known, okay. And that information gives us lot of information.

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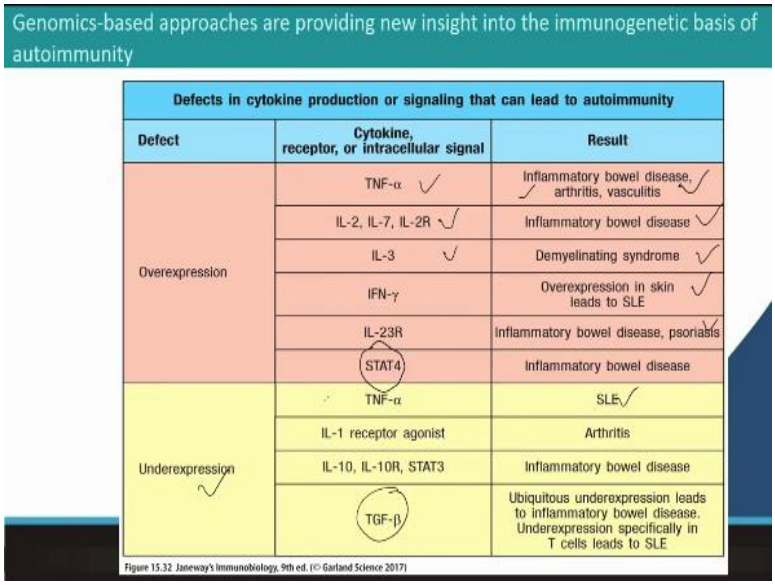

And this is it is showing that what are the gene responsible for different disease, okay? So if you see, I mean, you do not have to again, you just listen what I am telling. I mean, there are lot of names, it is not possible to remember and that is also not important to understand what is the basis of genetics. What is found, there is a multiple genes.

You see, all of them are either transcription factors like STAT 4 or cytokines like TNF alpha, tumor necrosis factor or interferon gamma, IL-23R, 2, 7, 2R, IL-3. So these gene okay all are cytokines, overexpression of these are causing different diseases, okay. Then underexpression. So if some of these genes like TNF alpha, overexpression is causing this inflammatory bowel syndrome.

And underestimation of TNF alpha is called SLE. SLE means systemic erythematosus lupus, which is the antibody against the nucleoprotein complex. TGF beta. So underexpression is also may cause disease. So those who are normal, those were normal they everything is normal, okay. So those who have disease that means it can have either due to overexpression or due to underexpression, clear?

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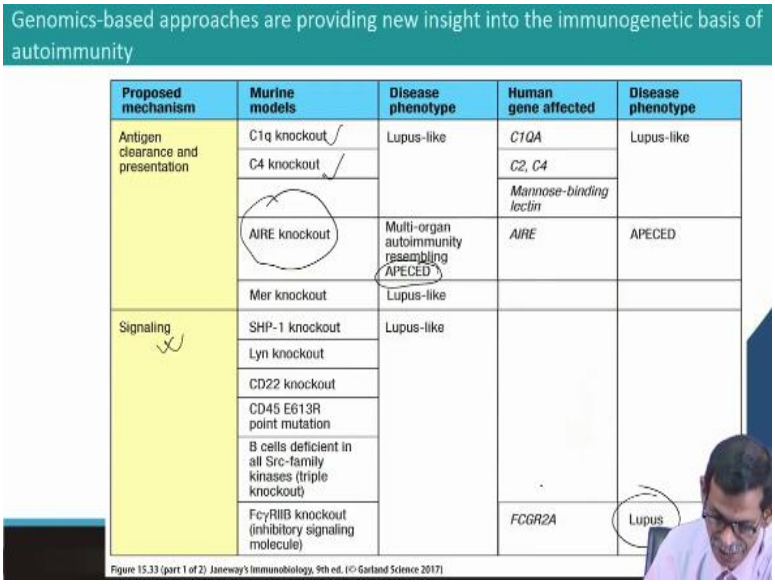

Or antigen presentation may have some problem. Antigen presentation not only this, this is what these are the complement protein, okay. So complement protein can create problem AIRE knockout that we already discussed, okay. That disease in human automatically genetic as well as if you knock out in mice that auto immune regulatory thing that is the transcription factors that can cause this disease.

Signaling protein, these are all different signaling proteins, which is responsible for either B cell development or T cell development or in other different kind of signal transduction process. They can cause disease, okay, that is skin rash.

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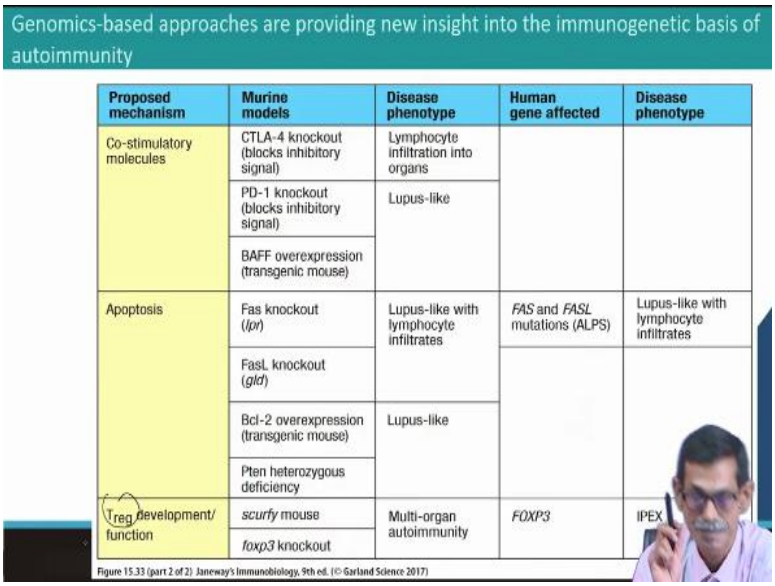

Similarly co-stimulatory molecule, apoptosis inducing molecular, apoptosis regulatory molecule, Treg development function. If the T regulatory gene function

proteins are not there, that means auto I mean, they are basically controlling all the self-reacting T cells. By mistake if anything happen immediately Treg will suppress them, do not do anything. Just telling them this is mine.

The way I was saying like any relative come you do not know but somebody from our from your home came and recognize him and say okay, please come. So that is this Treg is saying that okay. Do not do any harm, this is our own self. If T regulatory function is disturbed, so lot of autoimmunity can happen, okay.

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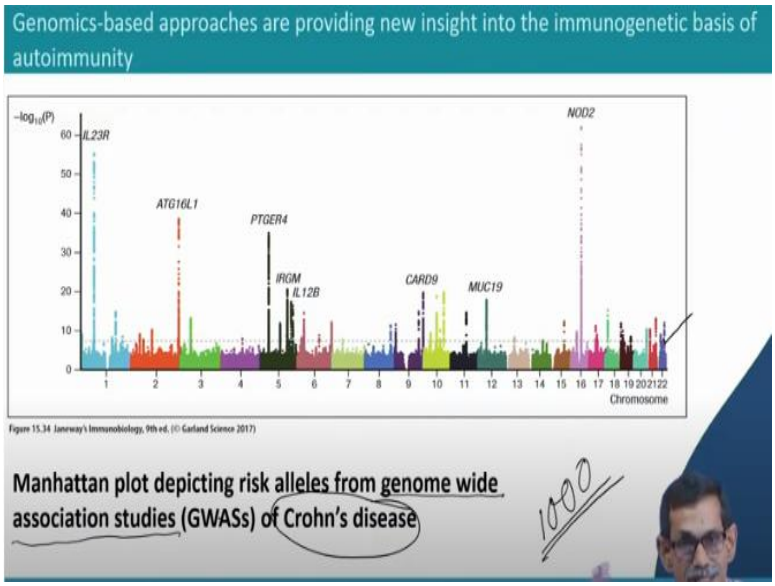

So these, these were this study when it is done now there is another way we can represent. What is called? It is called Manhattan plot. What? It is genome wide association studies. So what is doing when you have sequence like this, I was telling in the previous slide or these slides, I am telling you the name and which gene is there. So this is saying okay, I have one patient one sequence one thing.

And you can tell okay that may not be true because there are so many different kind of population, so many different kinds of variations. So same thing may not happen with somebody else. So then to say and this is all I am talking about the bioinformatic analysis. So when say gene analysis, we are doing we can do individual level like 5, 10, 20 or we can do 1000 okay.

So when we do genome wide association studies, it is generally at least we do thousand individual gene analysis. And then we study the frequency. Suppose

thousand individual with this disease okay, with these disease, Crohn's disease and see their genome profile. Now on not only sequence not only DNA sequence okay, because DNA sequence cannot tell which genes are overexpressing which gene are underexpressing.

What you would like to know there? To see the gene expression, we have to have the RNA sequence analysis, okay. Now there are lot of nice sequencing techniques like next gen sequencing is there which can sequence you very quickly. Now we will I mean, when we started like RNA expression analysis, we used to have different cDNA library and then northern blot which is very small scale thing, okay.

I mean, you see you can count. But now, we used to do real time PCR okay just to see what is the copy number of that gene. But that is also individual level, but now RNA sequencing can tell you how many exactly how many copies of your gene of interest mRNA is there. So if some mRNA is 10 and some mRNA is 100, you can always say that 100 is more. So this is for two genes, say gene 1 10 copy, gene 2 100 copy.

I can say gene 2 is more active. But for gene 1, if I take two individuals say person 1 and person 2 for gene 1 or gene x if person 1 is expressing 10 copy and person 2 is expressing 50 copy and this person is having autoimmune disease, I can say that particular gene, gene x may be responsible for that disease. But that this is a guess. Guess means that many thing else I may not seen because there are around 30,000 genes.

So one gene expression means overexpression does not I cannot tell that okay this gene is only responsible. But if I see that out of 100 people 75% people are having this gene is overexpressed than the control or underexpressed than the control, then I can say this gene has certain role or association with that disease, okay. So that is why I mean when you say genome wide analysis, then we can see for this particular disease, these are the different genes.

You see IL-23, ATG. ATG actually, they are very good marker of auto phagosome. Okay, ATG are the auto phagosome. So and then these different genes. We do not have to see their name or do not know all the functions. But the thing is, you can see

not I mean this there is a baseline, is the dotted line or the baseline okay. So this dotted line if you see baseline. So most of the genes are here, okay.

And this bottom means the chromosome number 1, 2, 3, 4, 5 this 22 is the chromosome number. So you can understand X and Y chromosome is not included here, particularly this is not for this disease. So you see in chromosome number 1 only one gene is overexpressed in case of this disease. Chromosome number 2 one gene, 4 there is no gene. Many chromosome there is not much.

But some chromosome it is see this there are lot of hikes, okay. That means in this particular case, this gene is overexpressed. Okay, that is called genome wide. So now, I mean even if these data I mean without knowing any information about the disease, if I know okay, this is x and this is the pattern and picture showed me, I can tell okay, for this disease x, these genes are mostly responsible. So this is the initiation.

Now what I will do, I will knock out this gene, I will overexpress gene, I will make some find some inhibitor of this gene so to develop a drug against that, many things are there. And that is where the biotechnology or the drug discovery is depending on or the research. This is the initial information that in this case, this is happening, okay. And I will just also inform you many of you may not know why it is called Manhattan plot?

Because it is just like a skyscraper in New York City Manhattan, like there are a lot of high-rise building. So it looks like that. That is why it is called Manhattan plot. And this is this genome wide or GWAS, this is not only used for autoimmune disease, you can apply for any kind of gene analysis for any kind of genetic disease or any other disease or any other say development I would like to see, cancer this is very common now because we have lot of information.

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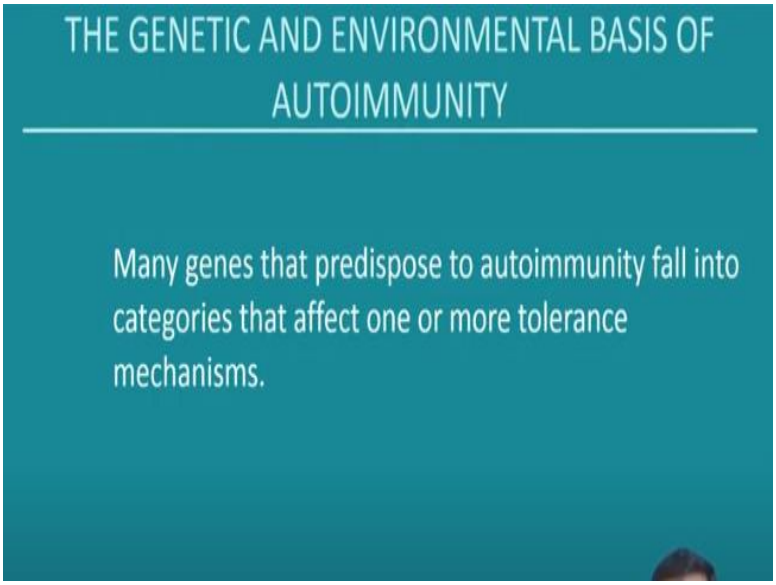

Many genes that predispose to autoimmunity fall into categories that affect one or more tolerance mechanism.

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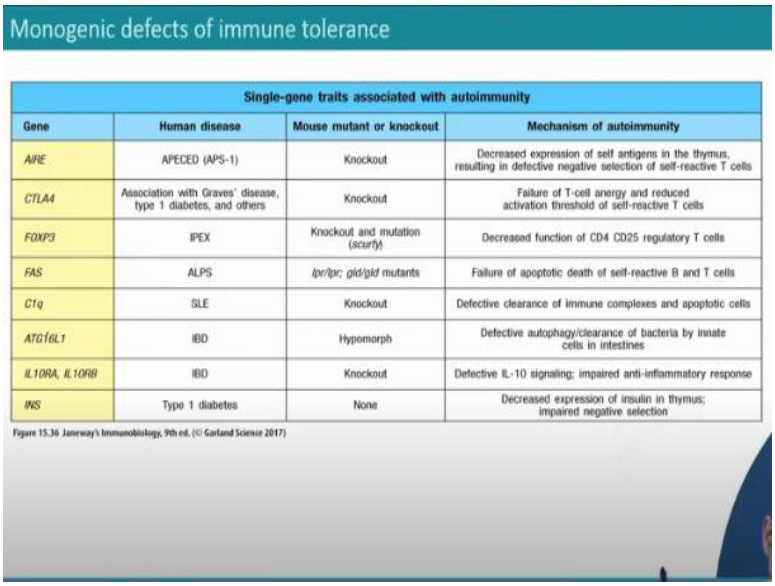

What we can tell is that most of the gene that are found the responsible the disease, they are very common in immune system like CTLA4. You know what is that. This is a negative regulator of T cells. If it is not there, then T cell will be continuously active. So all these gene is listed in the left column, or left most column is what? It is responsible for immune system general regulation, okay.

And if there is a failure, that means autoimmunity. That means self-tolerance is broken.

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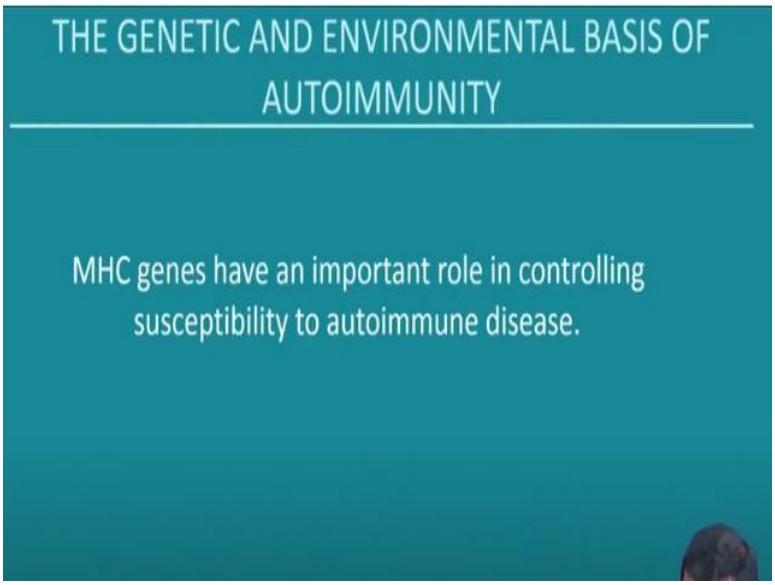

MHC gene also responsible. How MHC is responsible, I will go quickly because you do not have to remember all this.

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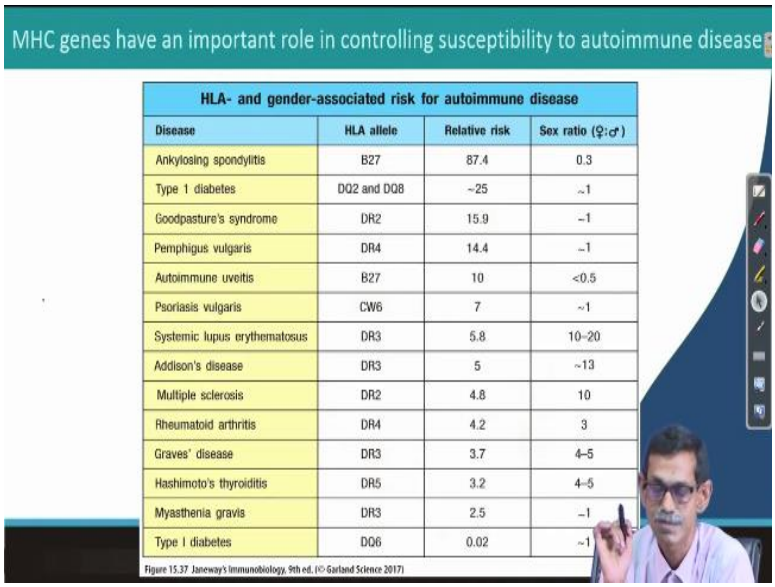

HLA- and gender-associated risk for autoimmune disease

Disease	HLA allele	Relative risk	Sex ratio (♀:♂)
Ankylosing spondylitis	B27	87.4	0.3
Type 1 diabetes	DQ2 and DQ8	~25	~1
Goodpasture's syndrome	DR2	15.9	~1
Pemphigus vulgaris	DR4	14.4	~1
Autoimmune uveitis	B27	10	<0.5
Psoriasis vulgaris	CW6	7	~1
Systemic lupus erythematosus	DR3	5.8	10–20
Addison's disease	DR3	5	~13
Multiple sclerosis	DR2	4.8	10
Rheumatoid arthritis	DR4	4.2	3
Graves' disease	DR3	3.7	4–5
Hashimoto's thyroiditis	DR5	3.2	4–5
Myasthenia gravis	DR3	2.5	~1
Type I diabetes	DQ6	0.02	~1

Figure 15.37 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

So these are the name of the disease, okay. So this is the name of the disease, okay. These are the name of the disease. This is the different HLA. HLA you know, MHC in human, I am reminding an HLA is a MHC in human we call human leukocyte antigen. So this is the different HLA allele. In MHC, if you remember the MHC class or you can go back and check we have seen there are lot of variation in the different alleles and this is the link.

So suppose type 1 diabetes. DQ2 and DQ8 HLA allele is there. So wherever DQ2 and DQ8 is there relative risk is 25%, okay. Sex ratio that means male, female is almost 1.

So there is no variation, particularly this one. If you see the Graves' disease, if somebody has DR3 that means more chance, okay. What is the ratio? 4 to 5. That means, if I say 4 or 5 that means, one there are five times more chance for the women, okay.

So that means it is sex wise is also not all, some most many of them are 1 that means equal opportunity and many of them female are more prone to autoimmune disease, okay. If you consider overall except this first one, they all are and this also all our male are more I mean, more prone to autoimmune disease.

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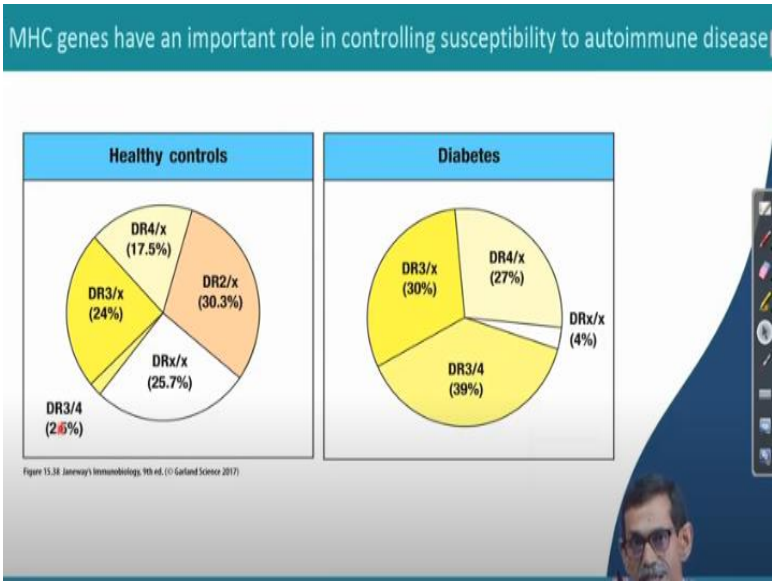

And this is the pie diagram. This is the healthy control, again with the MAC gene with autoimmune disease for diabetes. This is healthy control and this is diabetes. You see that DR3, DR3 is almost same. But wherever this DR3/x means any other gene except DR3 and 4. So you see these this one is not here at all, okay. So this DR3 allele if it is present or 4 allele in case of diabetes patient, 39% cases it was found that HLA type having this is having diabetes.

So these indicate these indicate and in this in the control healthy control it is very little 2.5% okay. So which can tell us like MHC or the HLA of a particular allele are responsible for this autoimmune diabetes. So this is in other way saying that these autoimmune disease also have some genetic contribution.

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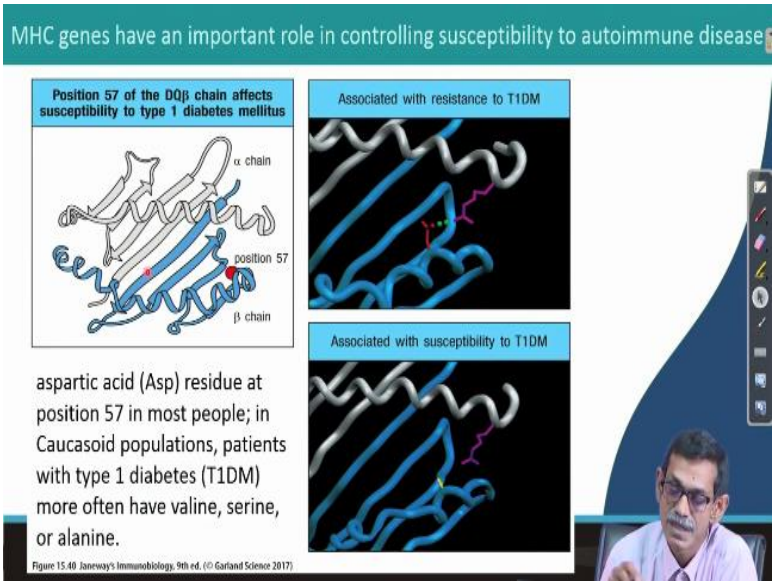

And it is found that in the peptide binding cleft, there is a particular position called position 57. In normal individual it is aspartic acid, okay. But in case of disease or the who has the disease in that case, this aspartic acid is mutated and what is there it is valine, serine or alanine. So that means, this particular position is also important. So such is also they are not only HLA is important, a particular point mutation is also important, clear?

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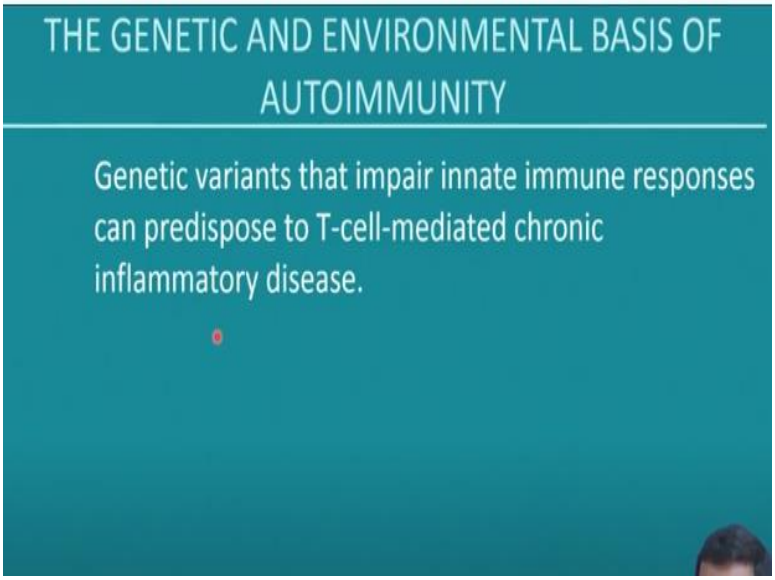

Genetic variation that impair innate immune response is also responsible. So whatever we said mostly autoimmune disease is adaptive part.

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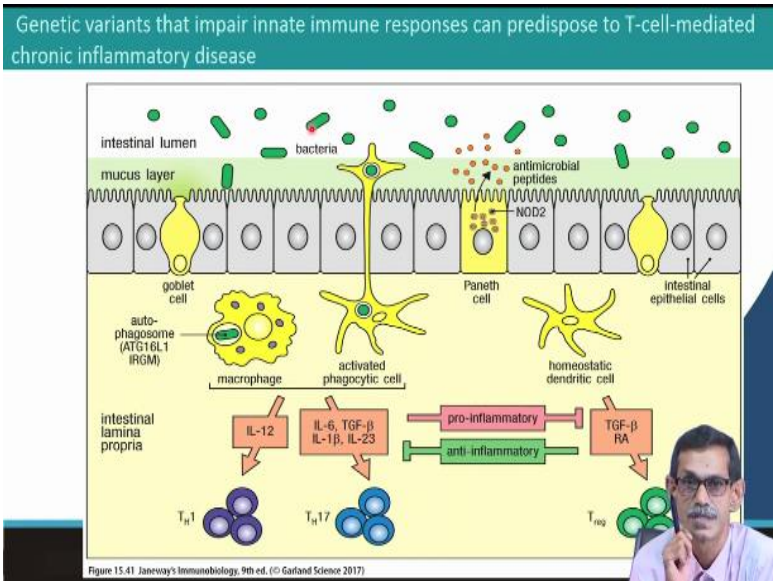

Autoimmunity in innate part is also responsible. What happen? Normally, so this is the intestinal lumen okay, this is intestinal lumen where lots of varieties of commensal bacteria are there and they are doing helping us. But the immune system do not react with them. Because there are some dendritic cells, that dendritic cells even if they get that they activate this T regulatory cells and these that we already discussed.

These T regulatory cells use anti-inflammatory. So TH1, TH17 cannot work. You remember in the second lecture, we discussed that, right. So T regulatory cell stop them, okay. Even they found this commensal bacteria is acting. But somehow if it is this control is gone and some injury happened so that this bacteria, which is supposed to stay on in the alimentary canal enter inside and taken by macrophage or some activated phagocytic cell can take from outside inside you can see these.

So what happen, these get activated okay, they get activated. So T regulatory cell cannot do much. Then if it is activated, it gives inhibitory effect to T regulatory cells. And this which is normally not going to cause disease, and they got continuous inflammation in the alimentary canal. And as a result we have will have a chronic inflammatory disease, okay.

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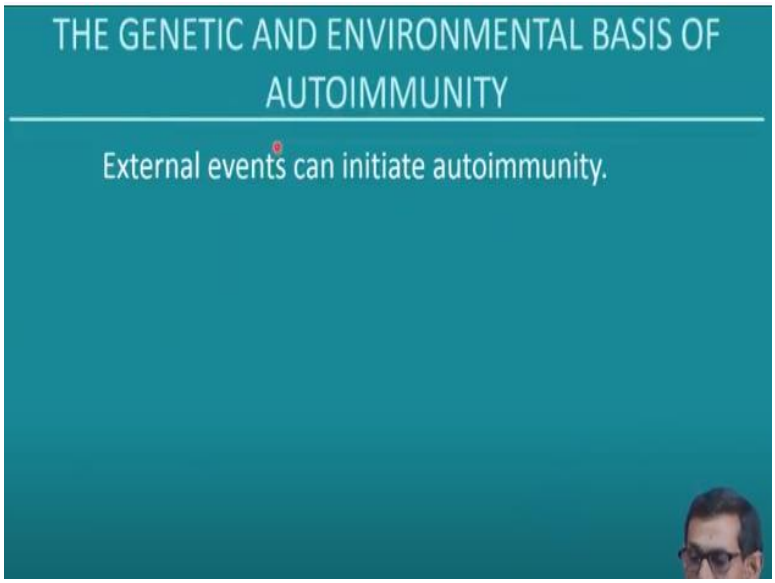

An external event can also initiate immunity. That I will quickly go through.

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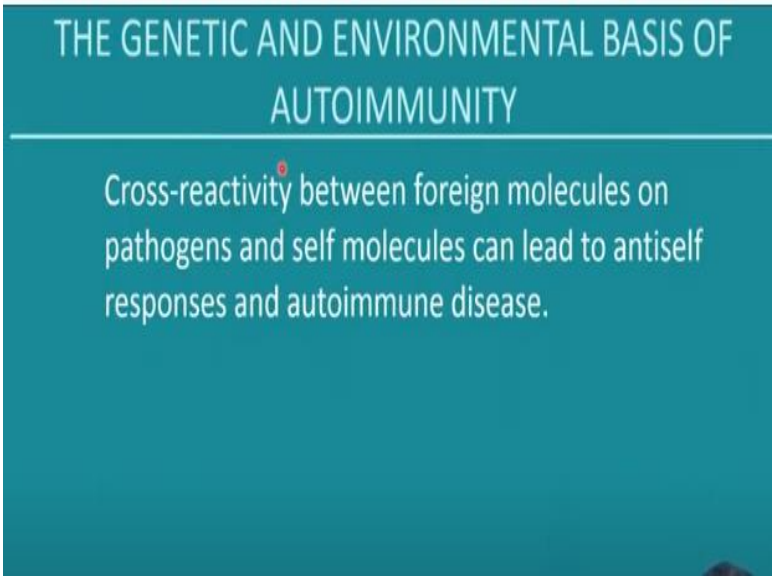

And cross reactivity foreign molecules, pathogen, self antigen can lead to antiself response. I am giving example.

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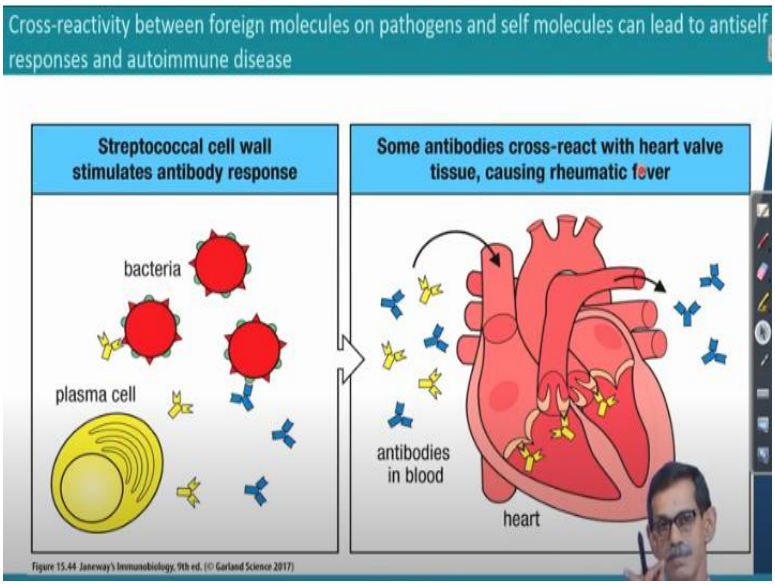

And this is what, what happens? Streptococcal cell wall when there is a Streptococcus infection, Streptococcal cell wall is foreign, antibody developed against it, okay. So these antibody developed against the Streptococcal cell wall protein has some similarity with some protein present in heart. See, this is a molecular mimicry. That cost so it is normal. So infection is also important.

So it was normally fine. So infection happened, that infection produce some antibody or immune system produce some antibody against that infection and somehow the cell wall protein and some protein in heart are similar or has some similarity. So these antibody because all blood will go through heart anyway. So this will go and heart and binds there and cause some disease. And what is the disease?

It is the rheumatic fever because heart will not function properly, okay. So that is also, there are many other infection which cause this molecular mimicry and antibody raised against the infectious agent and that find similarity with our own protein and create some problem. That most of the time it is temporary, but it may be chronic also, okay.

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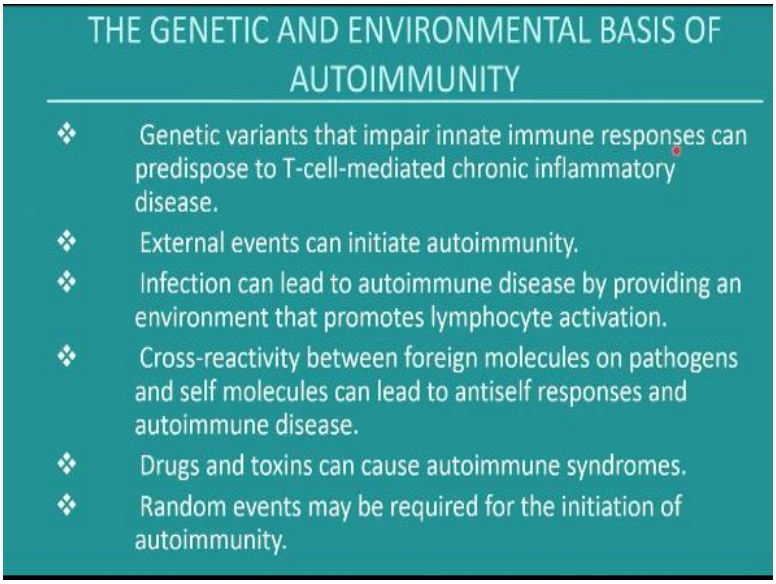

So this is the summary. I am just showing you for a minute. So you can have, stop it. And whatever I told so far about this generic information, this is just summarized here, okay. This is one and this is the other point. So these are the thing which I already told in different way and this and cause the disease. Drug and toxin also can cause autoimmune disease. Same way, this is external.

So if you take a drug, immune system will react against it, produce antibody. That will find similarity with our own protein. So it can always even and run now events may be required to initiation autoimmunity. Many things are not known, okay. So this is a end of autoimmunity chapter and next lecture we are going to discuss transplantation. Till then see you. Thank you all.