Immunology
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Lecture - 51
Autoimmunity

You are seeing me after almost three weeks. So by now we already have almost all the basic components and other parts of immunology and in last lecture you have heard the hypersensitivity or allergy. And this allergy or what we are going to discuss today is autoimmunity that both are actually noninfectious, right. So it is not from pathogen.

So from the name autoimmunity you can understand that the immune reaction against our own or self, right. So during the development of T cell, development of B cell or diversity, clonal selection hypothesis, we always continuously said that all the auto reacting receptor containing lymphocytes are eliminated, that is a clonal deletion, okay. Today I am saying that no, it is not completely deleted.

Not only from our self antigen, but you know that we have lot of microbes or microbiota in different parts of our body, particularly in alimentary canal. So that microbes are foreign to us, but immune system, they do not react with them, right. So they are so integrated part of our system, the immune system thinks like they are I mean all the commensal microorganism I am talking about, they are kind of our own part of the body, right.

So autoimmunity when it is developed like immune reaction against our own or cell protein, it is autoimmunity. But if there is any autoimmune reaction or the immune reaction rather against this microbes present in our body different parts, this is called xenoimmunity. But the reaction or the reaction type or the effect or the disease symptoms all are so similar so both we are going to talk almost together, okay.

So you will not differentiate xeno and autoimmunity. So the basic concept or the basic principle why autoimmunity develop is the major part or the major role of immune system when it is not working properly. Major role of immune system is to identify

self and non-self. So what is the procedure that we so far discussed is that somehow immune system learn to tolerate our own protein, own system, own organ.

But if somehow that breaks okay, so then immune system start reacting against our own protein. In fact, if you consider like when I was telling or other Professor, Professor Ganguly was discussing the B cell immunity, and in my lecture I discussed T cell immunity what happen we always say that it is not reacting with our own protein because the cell protein is recognizing receptors of B and T cells are eliminated.

But it is not practically possible. Why? I mean that kind of question might have came to your in your mind that see there are many proteins in our system which is very similar to the foreign pathogen, it is possible. So again this and very similar when a foreign pathogen attack and you know that antigen processing happens. So the overall protein may not be similar to our own protein.

But the after processing the piece of peptide that developed that may be very similar or very, may and very rarely it is identical, but it is possible there are possibilities there. So if all self-reacting antibody or the B cell receptor or the T cell receptor, if it is eliminated from the system, then what will happen the our immune system will be impaired, okay.

It cannot function properly because if there is a commonality between a pathogen antigen, or our own antigen is similar, if the similar one completely eliminated from the system, then what will happen? That pathogen will also be neglected by the immune system because they cannot recognize it. So it is not happened completely. But there is a fantastic balance so that very rarely we have autoimmune disease.

So that means immune system somehow manage that. If anyhow or by any means if that balance is gone or disturbed, then autoimmune disease is happening, okay.

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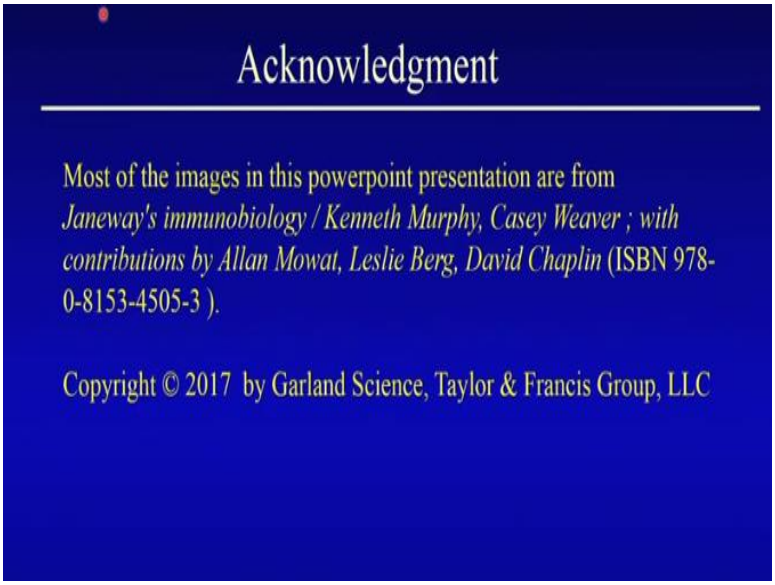

So first what I will do is what I will do is we are going to discuss this autoimmune disease in the first part. There are I will I divided actually in three part. Before that I am supposed to tell like this is the acknowledgement and most of the slides are taken from this Janeway's Immunobiology book ninth edition and which is a copyrighted product.

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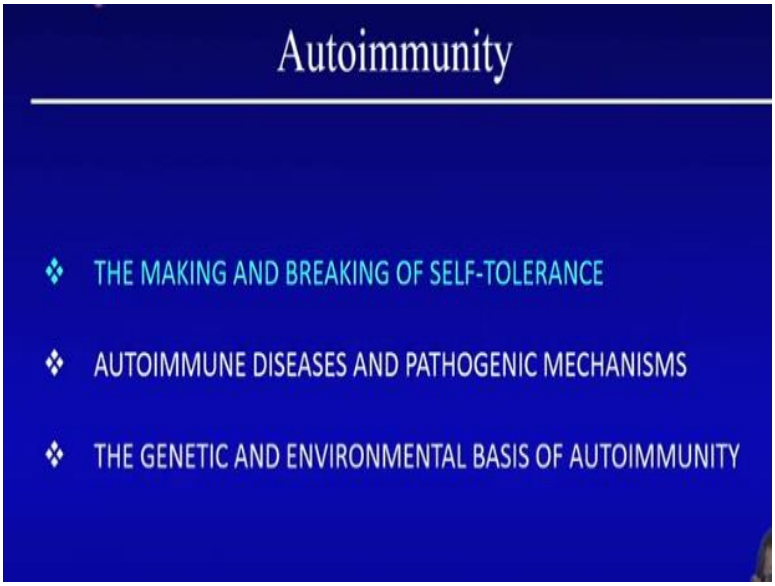

And in autoimmunity we are going to break into three parts actually. The making and breaking of self-tolerance. That what we are just discussing like how these self toleration I mean, we already discussed, we already discussed how this self-tolerance grown or how B cell, T cell develop. So we are going to discuss again. And then autoimmune disease and pathogenic mechanism.

Like how autoimmune diseases developed and what are the pathogenic mechanism, how the disease evolved, what is their symptom? Definitely, we are not going to talk like detail about the disease and all the symptoms and things because this course is not for the medical student.

And third, is there any genetic or environmental basis of autoimmunity so that we can figure it out okay this disease is genetic or environmental or just accidentally it happened okay, in any individual. So first we are going to talk about making and breaking of self-tolerance.

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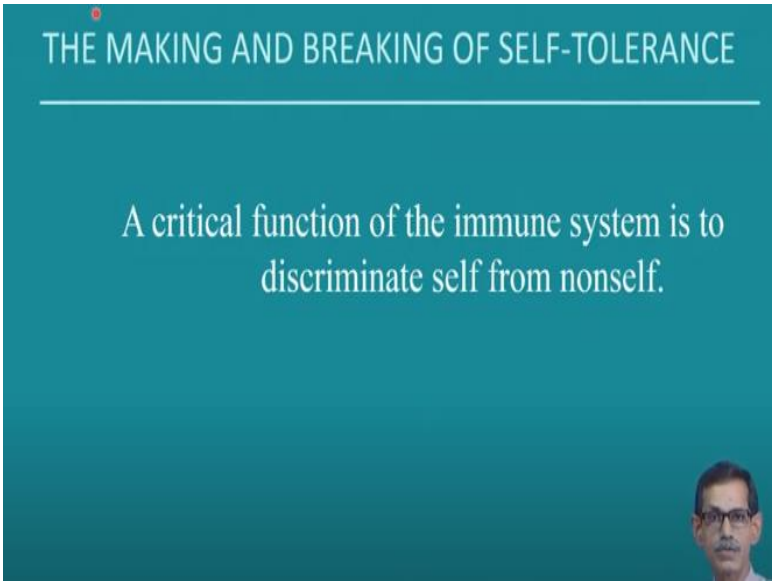

So I already told you, that critical function of the immune system is to discriminate self and non-self, right? So identify the cell, do not do harm. Find the non-cell, clear it or clean it from the system.

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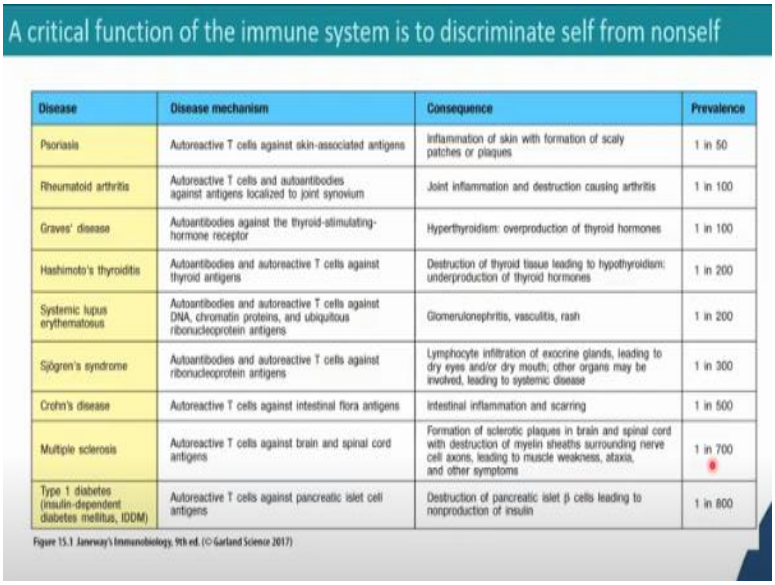

So this is a big table. Okay, you do not have to worry about that. This is what happened there are different disease in this like psoriasis, rheumatoid arthritis, Graves' disease, and Sjogren's syndrome, Crohn's disease, multiple sclerosis, type I diabetes. Here is what I am telling, you do not have to remember all the table like okay you can. Again I am telling you can and you can go through it, you will find many information from here.

What it is telling is this these are the disease and this is the disease mechanism. So if you see that it is mostly whatever is written here is either antibody or T cell mediated, right. And this is a consequence what happened to this disease. Okay say Graves' disease. What is happening, it is hyperthyroidism. That means over production of the thyroid hormones okay. And this last column is the prevalence.

And it is actually not alphabetical. It is according to the prevalence of the disease. So you can see this psoriasis is 1 in 50 maximum frequency and type I diabetes is 1 in 100, okay. That means this disease we do not see many, but it is not that rare also. Many cases it is very common to many of us. That means our immune system is not working properly or active in all possible it is correctly in all the individuals, okay.

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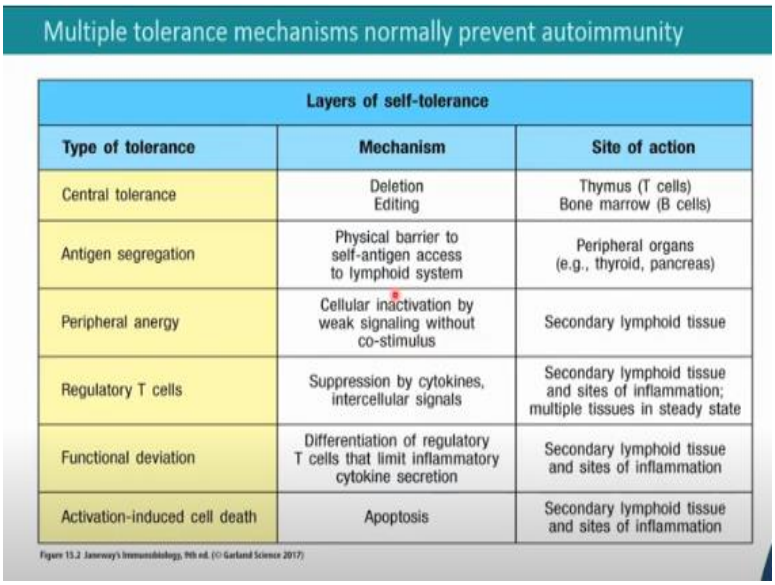

So what, I mean this is a summary slide what we already discussed in previous all the lectures, okay, except if you just ignore the hypersensitivity all these are already discussed. How immune system tolerate our own protein or own antigen? Because there is a central tolerance. What is that central tolerance? That is the deletion, editing. That means, B cell and T cell receptors are deleted.

I mean B cell and T cell containing receptor which interact with our own protein will be deleted, okay. That we are telling from the very beginning, clonal deletion method. And this happen where? It happen in thymus and bone marrow, okay. Then antigen segregation. Because all antigen are not exposed to the immune system like there is a physical barrier, okay.

And most of the time what happen, the immune reaction is happened in lymph node or spleen in the secondary lymphoid organ. And secondary lymphoid organ do not have the access to all the organs like they do not see the pancreas, they do not see our retina, okay. So there are many specified organ where immune system where the reaction happen actually, they do not see each other, okay.

So like here the thyroid, pancreas there are many other such organ. Then peripheral anergy that we have already discussed. Like even after the central tolerance, when it is eliminated during the development either for B cell in bone marrow or T cell in thymus after that what happen they come to the peripheral blood. In peripheral blood or peripheral system also they interact with many cell protein.

But if the interaction is not very strong, okay that we discussed during T cell development. If the interaction is not very strong, if it is weak then they survive, okay. If the interaction is very strong, then they die. They die by apoptosis. So that is clear. So not only the central tolerance, there is also peripheral tolerance also.

So after coming to the periphery, if B cell and T cell can interact with our own protein or own cell so they are not going to be activated and if it is a single interaction just like B cell receptor interacting with a protein only, no T cell is involved or only T cell receptor interacting like cytotoxic T cell receptor interacting, so they are supposed to kill it.

No, it needs another activation, right. So the antigen presenting cells should give the co-stimulatory signal to activate. If you remember the T cell activation, there are three signals are required 1, 2, 3 right. And there is one signal by T cell MHC, second signal by B7 and CD28. And the third signal by the cytokines. I am repeating it because we discussed long back.

You might have forgot that or even if you remember I just reminding you again. So if only one signal 1 is there and 2 and 3 is not there, that means no co-stimulatory signal. That T cell will not be activated, okay. So in that case what happen, it become anergic. Anergic means they will be non-responsive forever. So this is how it is happening.

So peripheral anergy is also happening in the secondary lymphoid organ because interaction between B cell and T cell and antigens are going to happen in the secondary lymphoid organ. There are regulatory T cells. That already you know different subsets of T cells, like T 17, Treg. And Treg is controlling the activity of other T cells. Because it is that is why it is regulatory. So most of the time it is a negative regulator.

It is repressing or suppressing the T cell activity and that how it is all you know that signaling is true cytokines. So they gave the intracellular signals and the secondary lymphoid tissue on site of inflammation, wherever the other T cell act the T

regulatory cells stop them to be activated. So that this is whatever I am telling here now is a normal case when immune system working perfectly, okay. Functional deviation.

So differentiation of regulatory T cell that limit inflammatory cytokine secretion, okay. And secondary lymphoid tissue and the site of inflammation. So that again they stop the inflammation also. Not only that interaction and killing, inflammation is also stopped by the regulatory cell, okay. And activation of induced cell death. So that we are going to discuss again. So these are the points I am telling.

So that means, if any cell interact or any cell means, any B lymphocyte or T lymphocyte interact in the lymph node with our self antigen strongly that also gets the signal to die or death okay, by apoptosis. So that means and how suddenly it will happen, because initially they are supposed to be deleted within bone marrow or thymus when they are developing or maturation is happening.

But two possibility, one is they can miss that. Somehow the interaction was not that strong. So they miss that screening, came out to the peripheral system. But there is another chance, in the lymph node also they have a possibility to interact. Even after that if it is very strong, then they will die. So apoptosis induced cell death or what kind of cell death, the B cell or T cell and it happen by apoptosis and it is also in the secondary lymphoid organ.

So this is the normal mechanisms by which our immune system works properly, clear. So any of this mechanism, whatever I just discussed, any of this mechanism if it is not working properly, that means autoimmune disease. So anything, anywhere is missed or not working properly is autoimmune disease.

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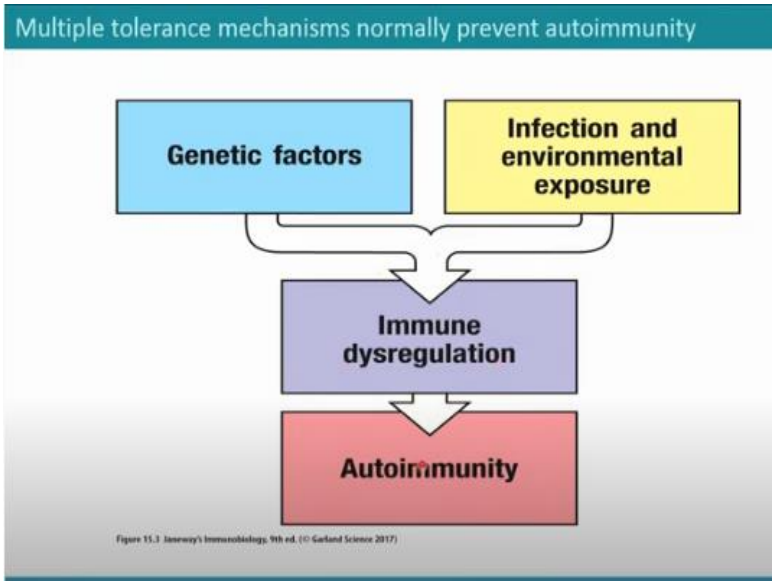

So autoimmune disease whatever the reason I just discussed what I mean how the cell tolerance can break, any of the previous points that can happen for two reasons. One this genetic factors, it may be genetically regulated or there is some genetic defects are there. Or maybe some infection or environmental exposure induce that autoimmunity, okay.

Either genetic factor or infection and environmental exposure, both are or both or independently I mean individually also can induce the immune dysregulation or dysfunction which can lead to autoimmunity, okay.

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Autoimmunity means development of the disease. So now we are going to again one by one to see little more detail. Central deletion or inactivation of newly formed

lymphocyte is the first checkpoint of the self-tolerance. That we already told right, that you know already. So many times so many ways we discussed that.

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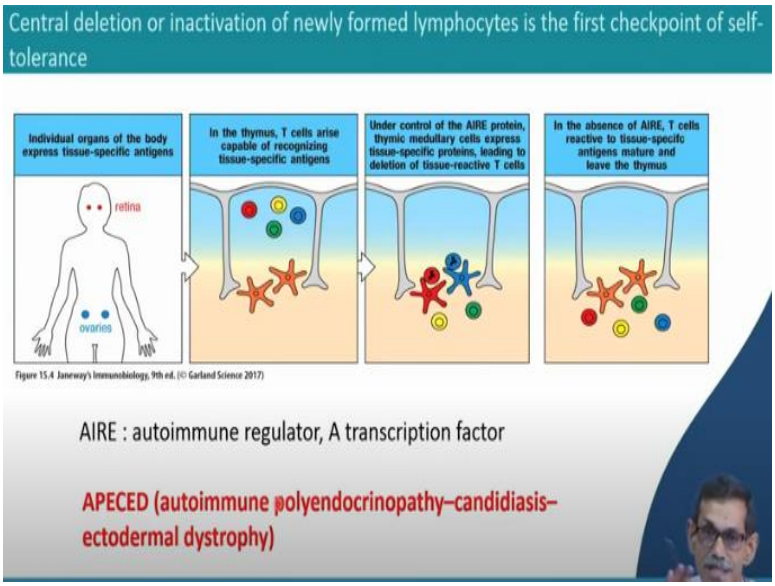

How this thing happen? Because you see when this thing happen in bone marrow and thymus. See here are only two examples are given. Say retina or ovary. Retina and ovary expressed some specific proteins. Many other organ produce specific proteins. Say pancreas produce insulin, okay is a pancreas. And not only whole pancreas there are islets of Langerhans and beta cell only produce insulin. It is so specific.

Now how a T cell this is an example of T cell you can extrapolate to B cell also. How T cell will see insulin and retina specific or the ovary specific proteins in thymus? There are many proteins which develops after puberty, right many hormones develop after puberty, many proteins may synthesize after puberty when T cell is almost done, okay. So what happens?

So there is there was a theory like all the thymus epithelial cell, okay medullary cells, where the negative selection happen, they express all the proteins. So they express all the genes transiently so that during T cell development, they can see what is going on and they expose to all the proteins and eventually what happen there is transcription factors AIRE, which is autoimmune regulator. Gene was discovered later on okay.

It was found that AIRE actually the transcription factor which regulates the expression of all the proteins in the thymic medullary cells, okay in the thymus

medulla, where the negative selection happened, it expressed all our own protein. So what happen, so during that period, that means a time of the negative selection they expose to all our own protein. So whichever is interacting strongly they die.

But normally, if they interact mild, interaction is mild or not that strong or moderate, they ignore it. Otherwise, I just told in the beginning that if they eliminate everything, then our immune system will also be very weak. So strong binding will die and only those which is not interacting strongly they survival and come into peripheral. Then the peripheral tolerance will come.

How it is discovered, because the mouse okay, what they did? They delete this AIRE okay. If the AIRE they deleted it develops autoimmune disease in human, you cannot do that. Okay, but there are disease, okay. If by any chance genetically, I mean if this gene is not acting properly or expressing properly, what can happen? It can happen you can see autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.

So this is a very big name, APECED. Now you do not have to remember all this. You can, but you think that this is how each gene or each function. So when any gene function was discovered, and we have to find for human we have to find is there any individual where this gene is not there and see what is happening, okay. So this is autoimmune disease.

And now after this AIRE, but we have a very handy model, we already discussed the mouse. We can make a knockout mice. So we make a mouse but this gene is not there and see what is happening, okay. But incidentally what happen? We have some in human which defective AIRE and this autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy kind of disease, their symptoms and many this thing we do not have to remember, okay.

Or I did not put in the slides also because again I am telling we are not you are mostly not the medical students and I am also not a doctor to explain all these things. And this is not also scope of the study.

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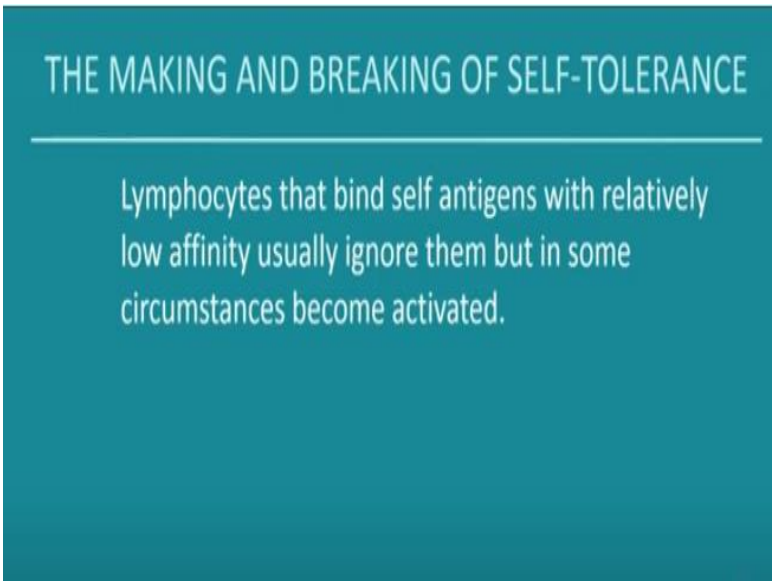

Then second point, lymphocyte that binds self antigen with relatively low affinity usually ignore them, but in some circumstances become activated. So first normally they ignore, so it is normal. But if they activated that means it is not wanted I mean in after coming to the peripheral blood, if they interact very mild interaction is happening because there are some similarities always possible.

Because anyway they are all are proteins. So maybe out of say, eight amino acids six are matching two are not matching. So interaction if eight are matching with the epitope the interaction will be very strong and nice or good. But if it is six or five are matching, it is not that zero interaction, there will be an interaction because protein protein interaction does not they do not know what is the fate.

So that moderate or low affinity interaction normally ignored but sometimes it gets activated, how?

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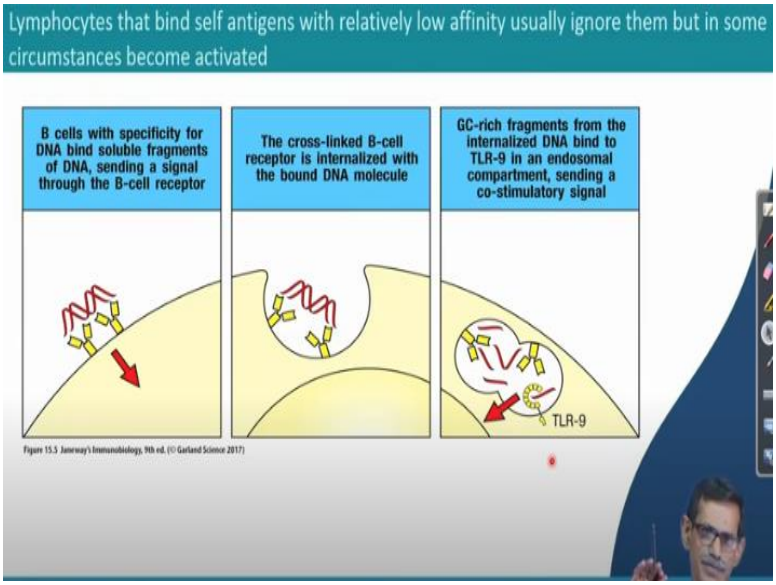

See here, this is an example. So wherever example is possible, I am going to give you the example. Here what is that? B cells with specificity of DNA. So if B cell receptor okay you also know that this receptor dimerization is very much needed. It is not single receptor interaction is not always active at the cell. So they crosslink the receptor by DNA molecule, DNA molecule is big.

So if DNA molecule internalize, what happen they are a TLR-9 which has this CPG or GC-rich actually methylated version of DNA gets activated. What happen the immune system is not made for that. Immune system is actually the methylated eukaryotic systems is eukaryotic DNAs are methylated mostly. But prokaryotic DNA that not I mean in the GC-rich region, okay.

So immune system made for any DNA if it is non-methylated that they will bind and this TLR-9 will act. But in some case, if the methylation is not proper in any part of our DNA that can activate the B cell and give the co-stimulatory signal. Okay, they can express and activate the T cell. Am I clear? So DNA sometimes get endocytosed by this receptor mediated endocytosis which interact with the TLR-9 and can be activated to activate again by co-stimulatory signal.

Normally, it normally does not happen. But if it happens, then disease can also happen. You can see it is very unlikely that DNA is traveling around in the blood or in other tissue because DNA is so, inside the cell it is so much protected. See they are covered with histone and then nucleus, the nuclear membrane then cell membrane.

So suddenly coming naked DNA into blood or exposed to the immune system is very rare. So this is not a very common but it can happen.

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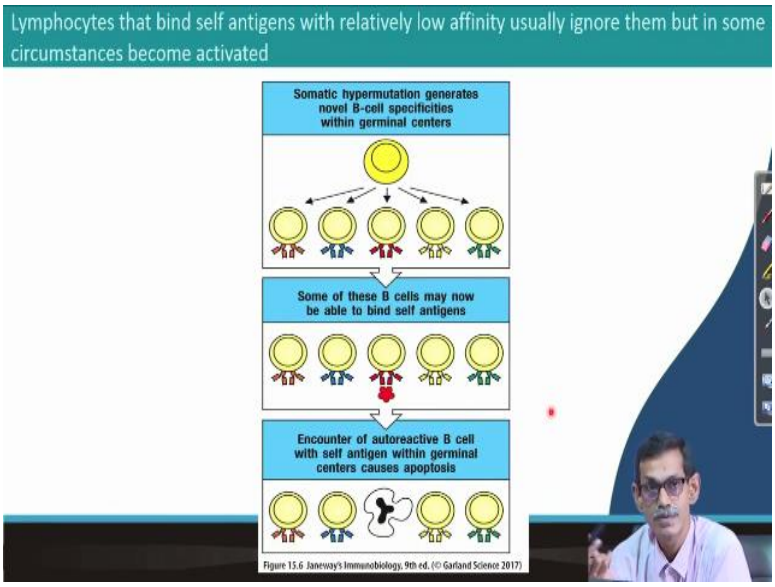

So now again what we studied in the peripheral tolerance. So this is the normal case okay. All the B cell receptor or T cell receptor, which is interacting with the self protein are eliminated. But we already discussed about hypermutation. And I discussed during diversity generation and Professor Ganguly already discussed during B cell what when it happen. You know what is hypermutation?

So B cell maturation or B cell immunity also you have heard this term. So during hypermutation what happened the CDR region change, right? So we told that hypermutation make the B cell receptor more diverse as well as more specific okay, better anybody right? So during that hypermutation, when change is happening, that change not only doing the good, opposite thing also can happen.

By mutation, they can become the auto antigen or self antigen specific. So if it becomes self antigen specific after hypermutation, it was not before, after mutation it changed the specificity towards our own protein. If this happen, this single interaction or crosslinking gives a signal to die. So that cell will also die in lymph node or the secondary lymphoid organ. So they also are not going to come or see the, we will see them again.

So this is also a very good mechanism for the cell tolerance. Okay, but by any chance if this does not happen for any particular antigen, that B cell will be activated or T cell will be activated and that will cause autoimmunity, okay.

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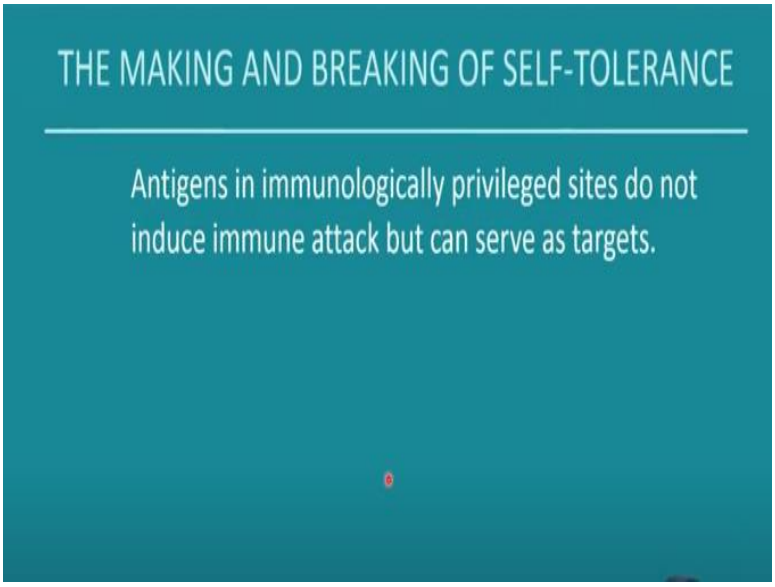

Antigen in immunologically privileged site do not induce immune attack, but can serve as target. What does it mean?

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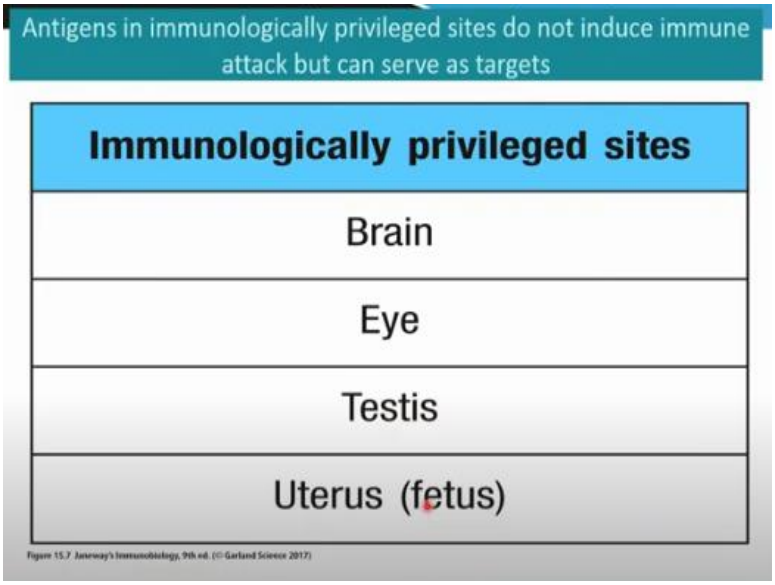

There are few places in our body like brain, eye, testis, uterus or fetus, they are immunologically privileged. It does not really mean that no immune system is there. So T cell can go there, B cell can go there, but they are at certain mechanism, okay. So brain has a blood brain barrier not everything can cross, okay. So in uterus, you have a placenta membrane or trophoblast.

So it is normally when babies born our T cell, B cell cannot travel that easily, okay. So they are they have barrier, they have certain T regulatory cell, which control the immune system. So somehow these places are not very active site for immune reaction. That is why they are called immunologically privileged site.

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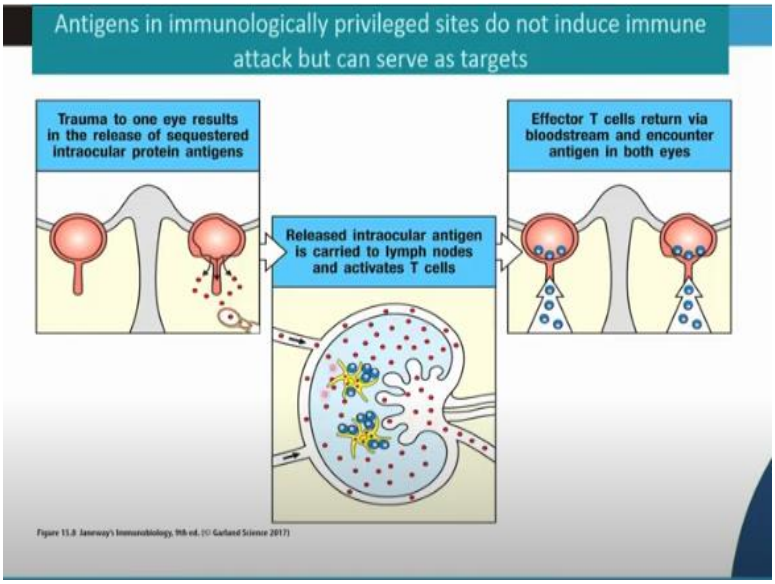

But what happen by any chance suppose there are two eyes, one eye by some trauma or blow or some accident it is damaged. What happen? Then the antigen will release. And you know the dendritic cells or Langerhans cells are there. So that broken cells or the antigen will brought to the nearest lymph node, where the reaction will happen. That we already know, I am not going to discuss.

So much antigen full of antigen of that originated from this retina or the eye or the ocular region come and the T cell will be activate and that T cell activity cell can go and damage both the eye. But this is not a normal case. But it can happen and autoimmunity may be responsible for that.

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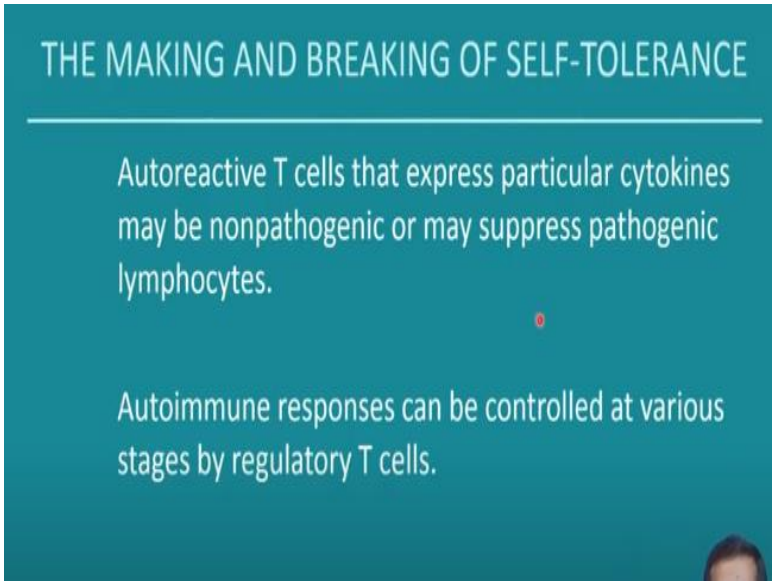

Autoreactive T cells that express particular cytokines may be nonpathogenic normally. Autoreactive means all the subset of T cell, TH 1, TH 2, TH 17 these cells are not doing any harm to us, okay. They are non-pathogenic, but sometimes they also become pathogenic lymphocyte. They suppress because just in case if some similarity are there they activated and then it will cause the problem. Autoimmune response can control at various stages of regulatory T cells, okay. How?

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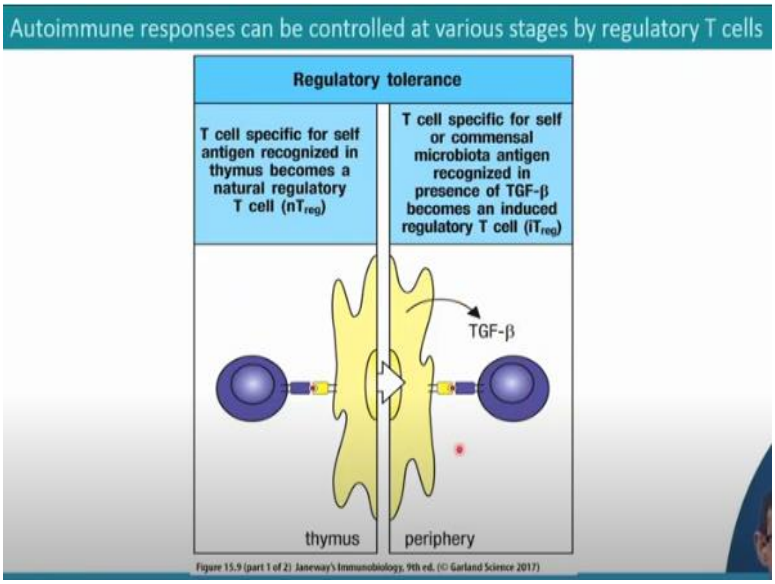

So T cell specific for self antigen recognized in thymus. So that is what we are calling. So if the thymus that we just mentioned, if thymus it react with our own antigen, the natural regulated become natural regulatory T cells. So normally T cell regulatory cells how it is developed? So when T cells interact with or moderately interact with our own protein, it become T regulatory cells, okay.

This is in thymus, this is central regulation and peripheral regulation also if T cell specific or self protein or commensal microbiota, that which is present in our alimentary canal and other parts of the body, which is helpful that if it is interacting with that protein that means, it is not supposed to do.

But by any chance if this T cell somehow released from not the regulatory regular T cell release from thymus to peripheral blood and interact with the same or similar protein here, there also the antigen presenting cell produce TGF beta, which make them T regulatory cells.

So either in the central system like thymus or in peripheral system, if it interacts with our own protein, then either by cytokines or there also cytokines definitely involved so they become T regulatory cells. And I already told T regulatory means the negative impact is there.

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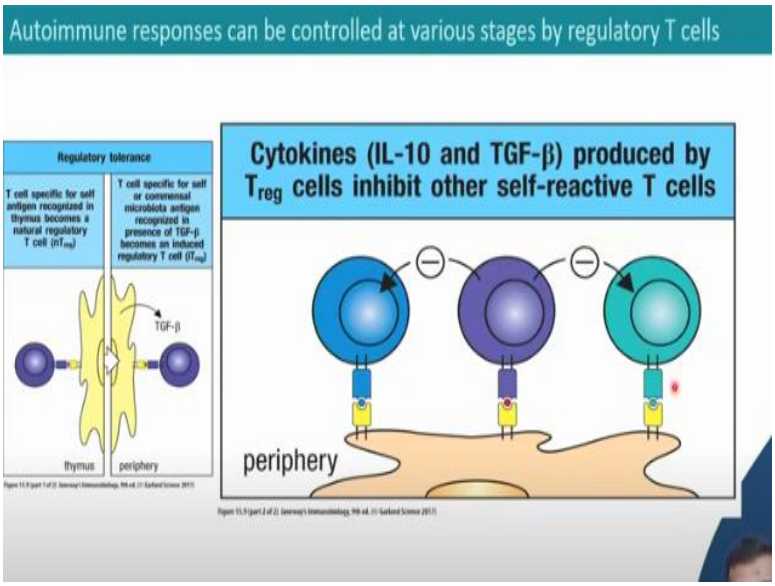

So what happen, what happen? So suppose this become T regulatory cells okay by interacting with our own protein. In this case, if non I mean some active T cells somehow they bind to this same I mean same antigen or same antigen presenting cell interacting with this. So what will happen, which is already T regulatory cell converted, it will produce TGF beta or IL-10 and inactivate them.

So what I mean so this T regulatory cells which generated in the central system or in the peripheral system can inhibit the T cells which is interacting with our own protein. This is a normal case. So that means that is how we survive. That is always happening. That is why you do not see autoimmunity so often, okay.

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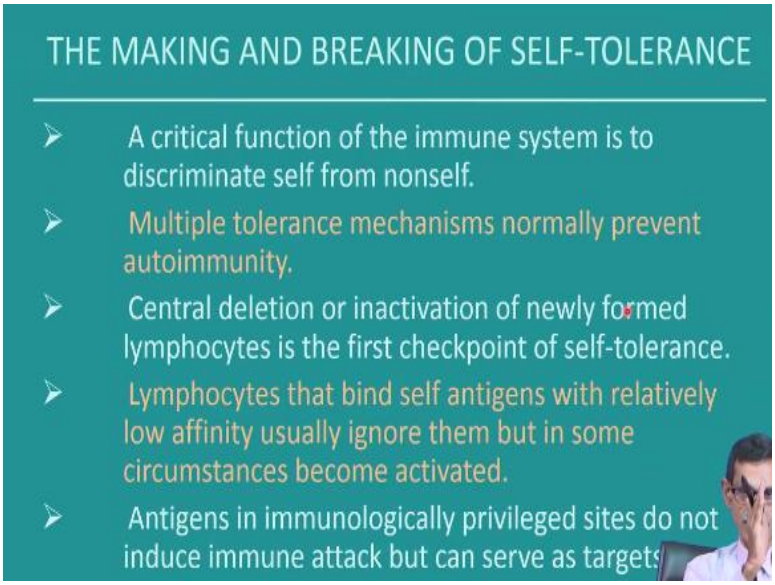

So these are the different thing like autoimmune tolerance and making and breaking. That means these are the points by which sell tolerance made. I am just summarizing what we told. If any of such thing are not function normally that means some problem will happen. And that problem means autoimmunity. What are those, I am just going through quickly.

A critical function of the immune cells that we already discussed okay. So that is our own system is discriminate self and non self. Multiple tolerance mechanism are there what is that? This is peripheral tolerance and central tolerance, right. They maintain like T cell. Central deletion is the major point like deletion of the auto and antigen reacting B cell and T cell so that no B cell T cell supposed to interact strongly with our own.

Now I am saying strongly. Initial part when we are studying the diversity T cell immunity, B cell immunity, their development, we were telling that deleted. But now we are telling which is acting strongly only they are deleted, not all. Because all if all the B cell receptor will be deleted, self reacting then our immune system will also be

compromised, okay. Lymphocyte that bind self antigen with relatively low affinity usually ignore them.

So normally they do not do any harm to our own protein, weak interaction or moderate interaction. Okay, only strong interaction can create problem, but do not do. But sometimes it is activated. The example I gave with the DNA. Antigens in immunologically privileged site normally they do not induce the immune attack.

What I gave an example with the eye that the normally the immune system do not react much, but if there is any breakage or injury or the damage of the tissue, that can happen also.

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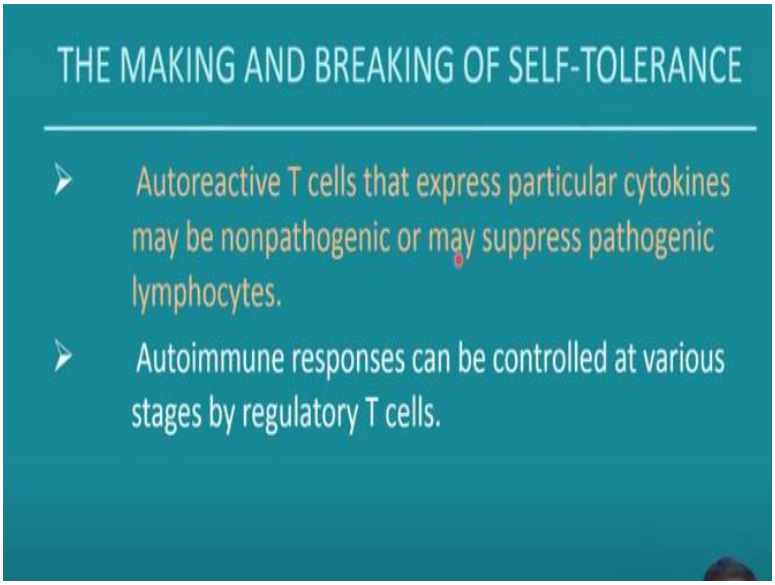

Autoreactive T cells that express particular cytokines, that is nonpathogenic, do not do. Nonpathogenic means they do not do any harm to our own, but may suppress the pathogenic lymphocyte, okay or may suppress the pathogenic lymphocytes. So that is how we survive but if there is any problem again disease. Autoimmune response can be controlled by various stages and regulatory cells, like what I said the T regulatory cell at the central, peripheral or TH 1, TH 2 all there is a balance okay? T 17.

So that balance is very important. All are there, okay. They are supposed to fight for foreigner only, but sometimes if the foreigner and our own protein, foreign protein and our own protein are very similar, we cannot figure it out, right. I mean you can

see we are so similar, I mean all suppose for example, there are some very rarely you can figure it out difference between all the Europeans, okay.

But there are certain difference, very minor difference. But for us, which who are not habituated to see the Europeans of different country for a long time, we cannot figure it out who is from which country, okay. Even that is true for India also. We cannot suddenly say who is from which state if they are look similar. So that close similarity sometime create problems okay, and that can cause autoimmunity. Okay. So for today, this is all.