Immunology
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Lecture No -35
T Cell Mediated Immunity (Contd.)

Hi everybody so now we are going to continue the T cell mediated immunity which we are discussing in the last class. So I am going to start with the last slide again.

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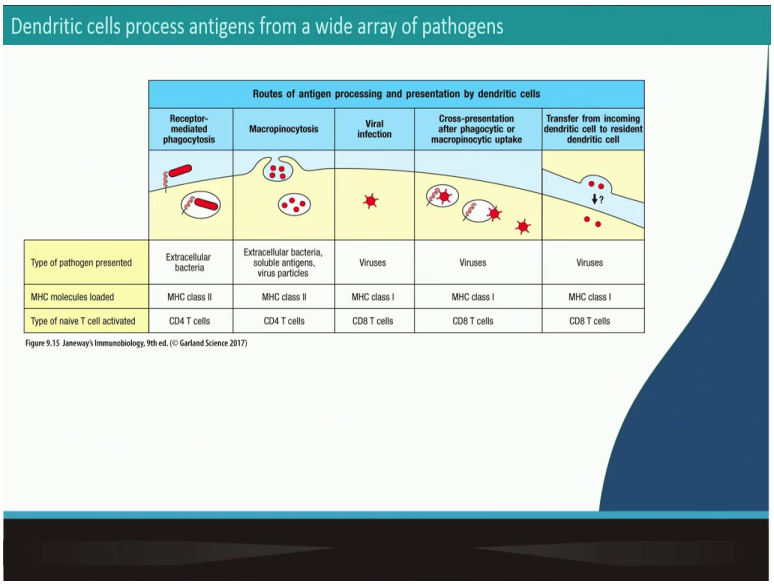

So this slide we just have discussed in the last lecture and we have seen like what kind of different kind of pathogens are presented by our process by dendritic cells and activate the T so some are activating CD 4 some are activating CD 8 what happened this also wall slide I have shown you.

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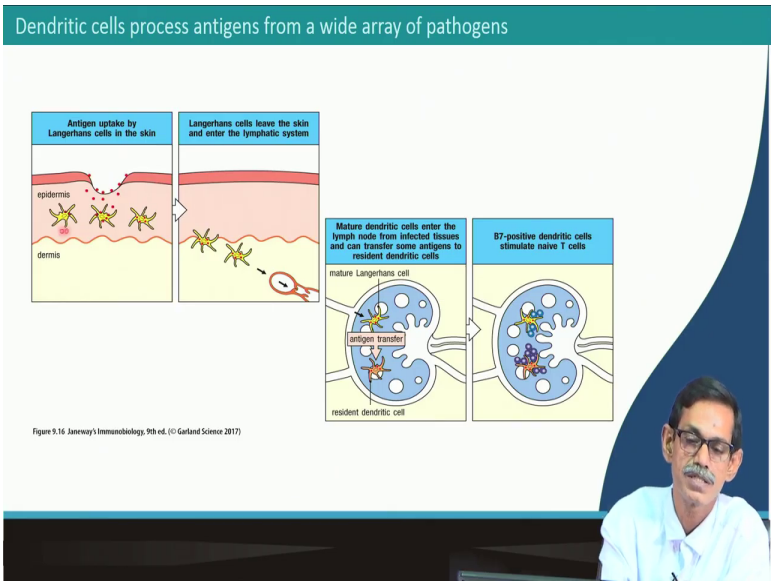

Before I came from the peripheral repeater miss tissue there are some Langerhans cells. But I think what they collect the pathogens or antigen uptake from in the epidermis on the skin and from there they migrate to the lymph node. And in lymph node they transport the antigen that which was discussing in the last lecture. The mechanism is not known so they transferred the antigen or the receipt I resident dendritic cells which in turn activate the T cells and you know what happened after that they proliferate and leave the lymph node and coming to the peripheral blood.

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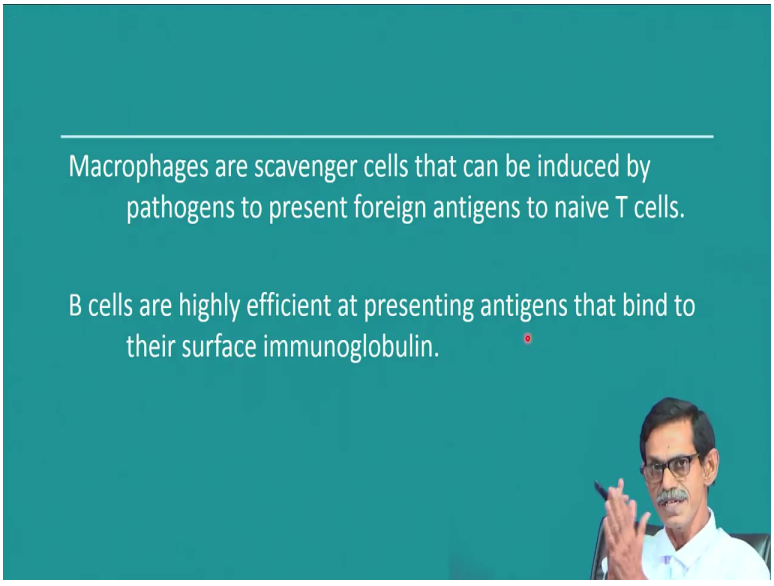

So this is again the bigger version of that so not only dendritic cells just we are discussing macrophage and B cell are also professional antigen presenting cells macrophages most of the

time they are eating bacteria and they are the scavenger. So they are cleaning up the mess. so while filling up the mess the all virus killed cell or the cell killed by apoptosis induced by T cell or any kind of death cell macrophages eating.

So they are also processed the antigen which is coming from outside present that we already know how they are doing. B cell are also highly efficient in presenting antigen right that binds to surface.

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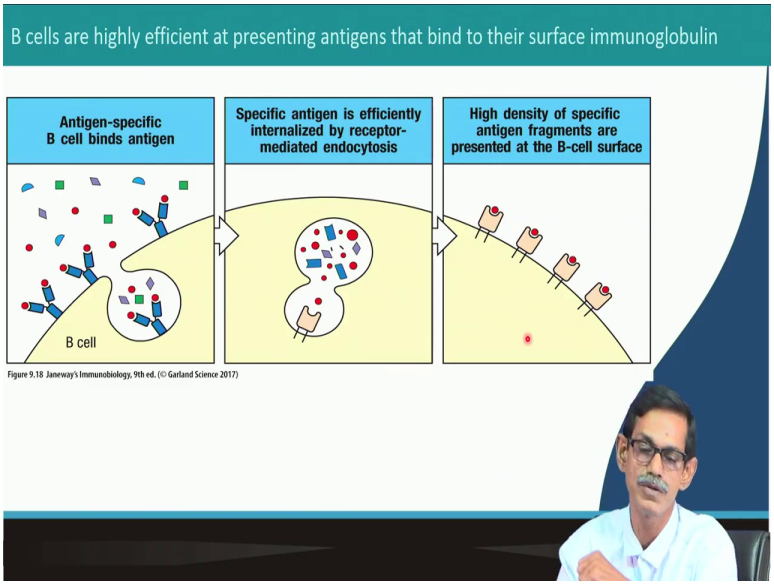

That you know that the T cell receptor a B cell receptor interact with the antigen internalized by endocytosis receptor mediated endocytosis and then mix with this and wear them MHC 2 is sitting in that vesicle and which presented by MHC 2. So this is also done by B cell.

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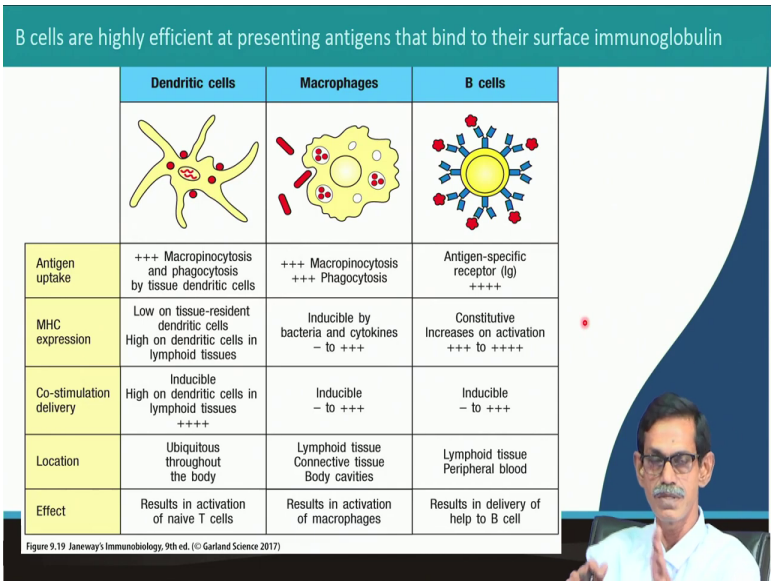

So this is in summary actually whatever I was just told before not only in few minutes back we have told many times before also dendritic cell macrophage and B cell all C and D gen presenting cells are efficient enough. So they are macropinocytosis and phagocytosis when they are in tissue. This macropods is can do macropinocytosis and phagocytosis both are efficiently they can do. And B cells are mostly by receptor mediated endocytosis.

And you know what happened after that they induced the T cells but the result activation of T cells are there macrophage also inter mean major thing. Because sometimes macrophages are activated by T cells you know the TH1 response. Then they killed after killing they express the antigen much more efficient way and that will induce the T cell. So variety of things happen and here there are three major antigen presenting cells which differ their process of attachment or in tech but presentation in the surface of their cells by MHC 1 and MHC 2.

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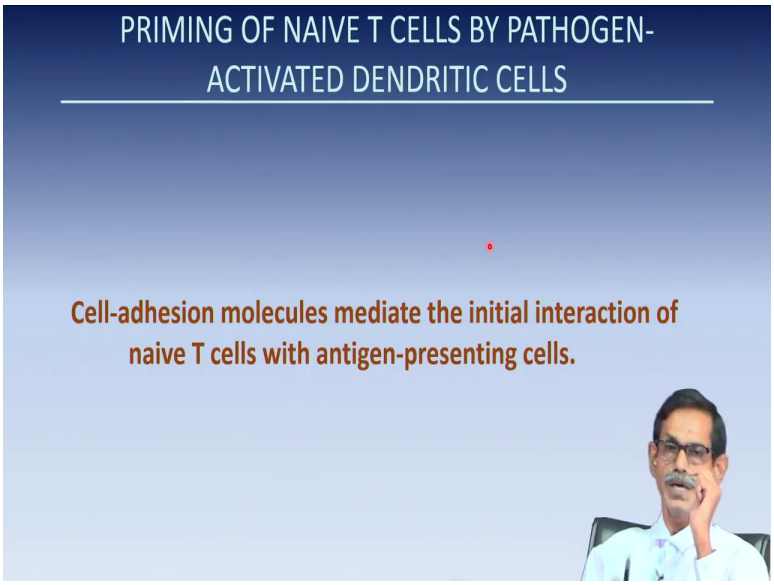

So I am coming back to again whatever discussing in the last lecture same hydration molecules mediate the initial interaction. So what happened so far we are telling how the antigen is coming where it is coming in the lymph node then it is processed and we just told that the B cell attached to the dendritic cells and proliferate. So how this attachment we told that chemokines are calling them and cell addition molecular attachment them this is also to the naive T cell and the antigen presenting cell that attachment is also through protein-protein or receptor ligand interaction.

It is not just the T cell receptor and MHC 1 what happened there is a series of rain right it these cells they are presenting variety of antigen all T cells are not going to find their own partner in every dendritic cells.

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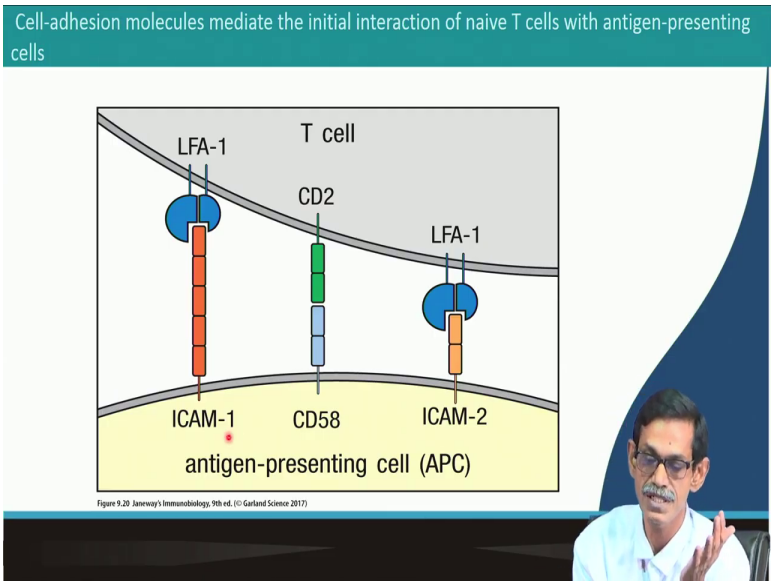

So what happened, so there are similar antigen presenting cell also presenting the ligands and night T cells they also has this integral entire molecule a little whenever they want so even there is no interaction between T cell receptor and MHC antigen complex or CD4 CD8 this interaction is happening this brings them together and DN presenting cell and T cell comes together because of such kind of interaction after that what happened.

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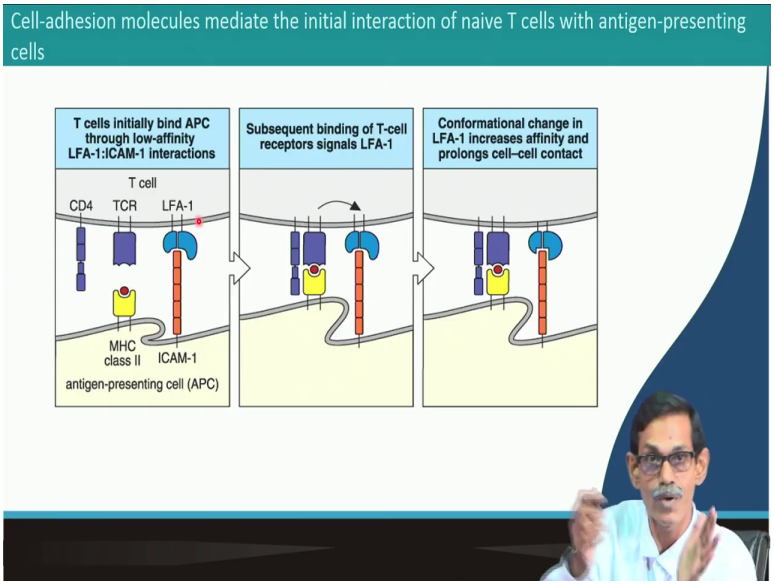

So when they come closer then they can see well this MHC 2 say for example MHC 2 have something less this here is looking for that. So this one bring them closer this interaction then this will find ok whether it is interaction is going to happen or not. If the interaction is not

happening only this interaction is not strong enough then these T cell will move to another site on the part of the same dendritic cells or another dendritic cells or macrophages.

But if these interaction after bringing this interaction if this interaction happens so T cell receptor find its partner with MHC 1 or 2 then this interaction happen means then CD4 interaction is also going to happen. So these interactions give a signal to this particular site what is happening if you see this if you see this one this region you see this is not very tight binding ok though it is a cartoon it is not tight binding in a lot of space are here.

But as soon as this signal come there is a conformational change it become more tight ok so initially what happen if this is a ligand it was like this interaction was like this but after the TCR and MS interaction happened they give the signal they become like this so it was like this it was open interaction was they are not tight but second interaction with MHC TCR CDA CD4 gives the signal to that and it become I mean it change its conformation and become more tight and specific.

So that T cell cannot leave immediately that so this is how the interaction starts. So T cell comes to come closer to the antigen-presenting cell initially lose or less interaction. But interaction is there less tight interaction but then if T cell receptor and MHC interact that gives the signal that initial interaction becomes stronger and all together they we get they become very strong interaction they all this whole interaction is very strong and then they stay together.

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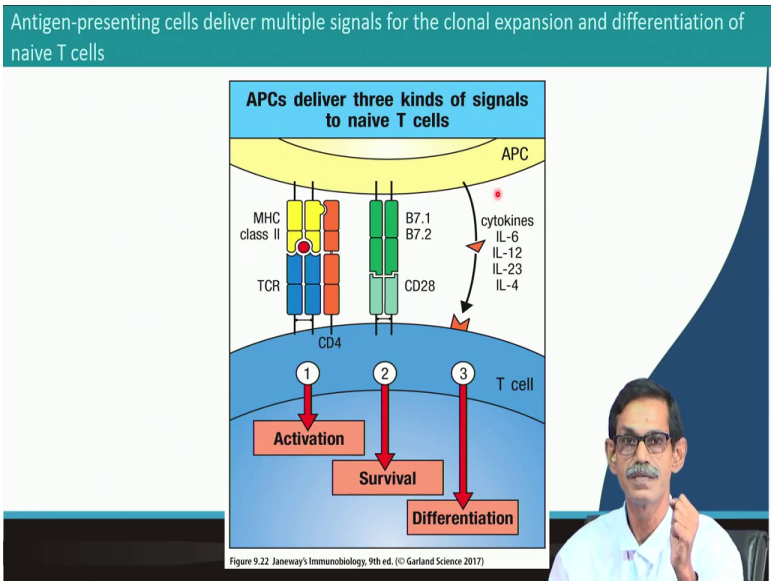

And what happened after that after that this one this interaction MHC TCR interaction gives a signal to T cell this one is T. So now T cell for activation another teaser multiple signal is required because only one signal you can activate the T cell mistake can happen. So multiple signal is important second in very important signal I told once or a couple of times like both activation of both B cell and T cell needs minimum two signal that is very, very important.

Any single interaction will not activate neither B cell or not T cell here also same so only TCR MHC complex is not this interaction is going to give a signal for activation definitely but it needs another signal which is this one. This is come between be 7.1, 7.2 together it is called B 7 molecule. So B 7 which is a heterodimer be 7.1 and B 7.2 very similar this is in the antigen presenting cell and there is another receptor in T cell is there is called CD28.

So CD28 B 7 interaction is also very, very important what it is doing? It gives the signal for the survivor so the cells which survive. So survival signal activation signal and the antigen presenting cells will release some cytokines like this is all possible I will say (())(09:05) 1234 every cytokines are not really there all at a time but these are the cytokines released by antigen presenting cells which will again there are receptor in the T cell which will bind and get third signal for the differentiation.

All three signals are required to final get the effector T cells to be active in immune system. So this is so it starts from where it was their dendritic cells come the regular integrate another surface molecule attachment brings them together then this MHC TCR then B7 CD28 these will give the signal survival and activation and the third signal by the cytokines which is released by the antigen presenting cells.

And tell the T cells to differentiate and do I will go further probably for a differentiation both should be and we could have to have the effector function for to protect us.

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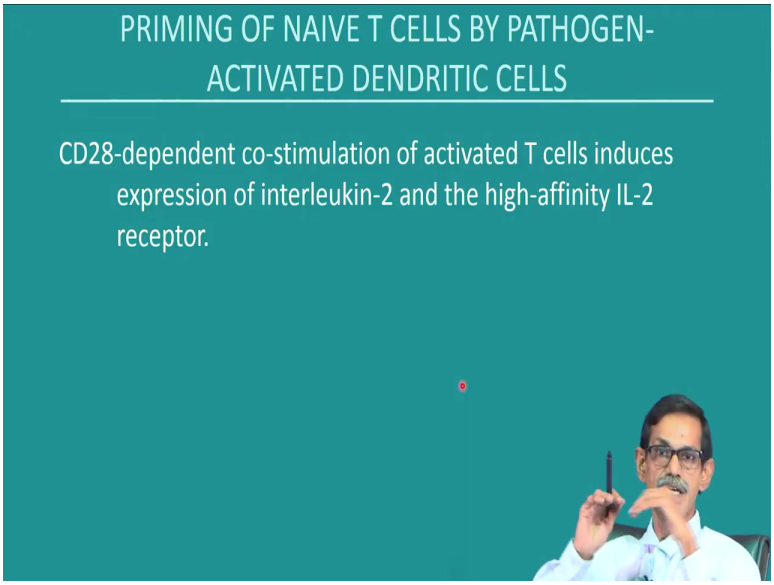

And CD28 post stimulation of activated T cells what it is doing because what it is saying it is survival so you have to survive you have to replicate you have to survive. Well it is very interesting what it is telling actually it is activating the interleukin-2 receptor more specific interleukin or more affinity interleukin-2 receptor.

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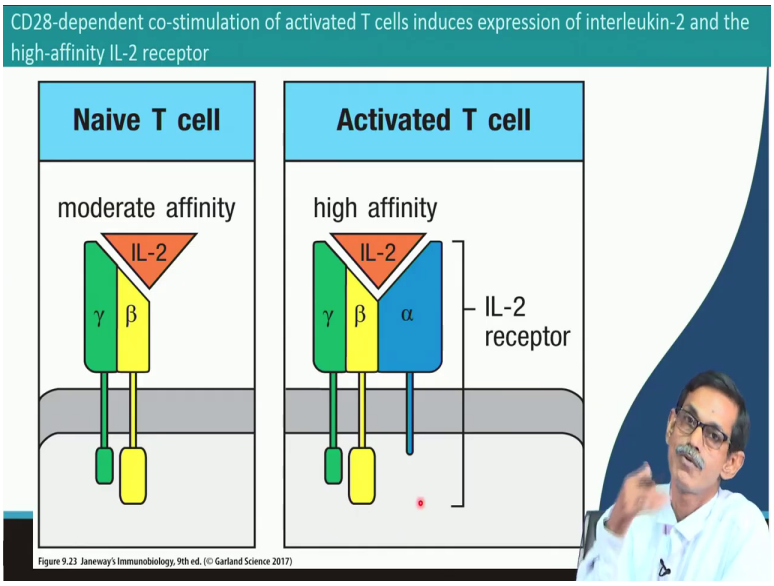

What is happening on what is there actually interleukin 2 has I mean until you can to convene to type of receptor one only alpha and beta chain at complete IL-2 receptor has three chain hetero trimer alpha alpha beta and gamma it is a heterodimer this is a IL-2 receptor part. But only beta and gamma chain also can act as aisle to receptor part interaction is also but the affinity is not as good as this. Because it will fit much better here though it is a cartoon but it is fitting much better here.

So trimer version of the IL-2 receptor is more efficient and high affinity and dimer version is moderate affinity.

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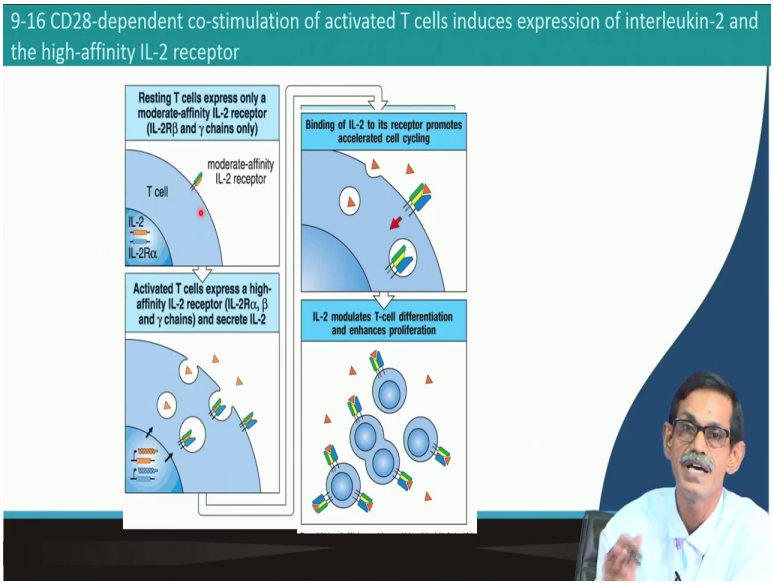

What happened actually in T cell normal T cell they express the moderate affinity IL-2 receptor. So when activation happened by B7 and CD28 molecule B7 and CD28 molecule then this interaction or that B7 CD28 signal go there and they express the IL2 molecule. IL2 I mean here if you go back if you go back in this interaction they give the signal of expressing the gamma subunit of the alpha subunit sorry alpha subunit of the IL-2 receptor.

Because beta and gamma is already there so that we CD28 B7 in interaction or signal Express the alpha subunit what happened so from moderate affinity IL-2 receptor converted to high affinity IL-2 receptor. Not only that the cell also produced its IL-2 itself. So what is happening they produce IL-2 so they get the signal so that which produce IL-2 as well as the alpha subunit of the IL-2 receptor what is happening it is producing IL-2 bind to its own receptor which is more affinity and give the signal for proliferation and survival which is differentiation and proliferation both.

So this is a very good example of auto crate and not only auto crate it also regulates the affinity of the receptor. So by any chance what is going to happen so if by any chance if any so suppose there is a neighboring T cell which is producing this IL-2 receptor and if it binds here it will not going to give that signal, it is not going to give this signal. It is always possible there are two T cells or 10 T cells together these get activated it is releasing IL-2 it will bind here as a T cell also has IL-2 receptor here it will can also bind here.

But that binding will not give this signal for proliferation and differentiation because the affinity is not same. So because once it is released from the cell it has no control it can go and bind any cell. So normally cell has moderate affinity so they are half prepared always. So, as soon as it need make the third one and do its own job, so neighboring cell will have only these and not going to be activated because all of them are in the same place.

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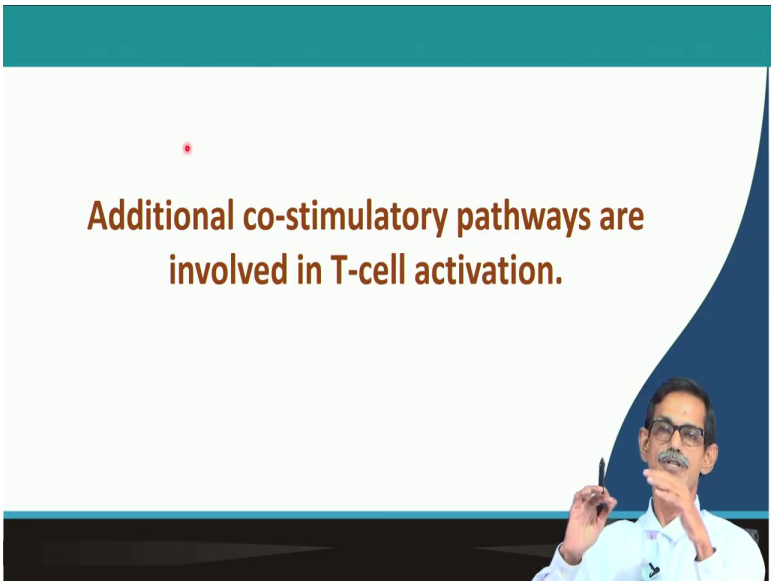

So this is how T cell get activated by MHC so three signals one signal and is IL-2 is very, very important for proliferation and differentiation. But this kind of signal the co stimulatory signal is how long it will continue. So if it is continue forever then it is a problem right.

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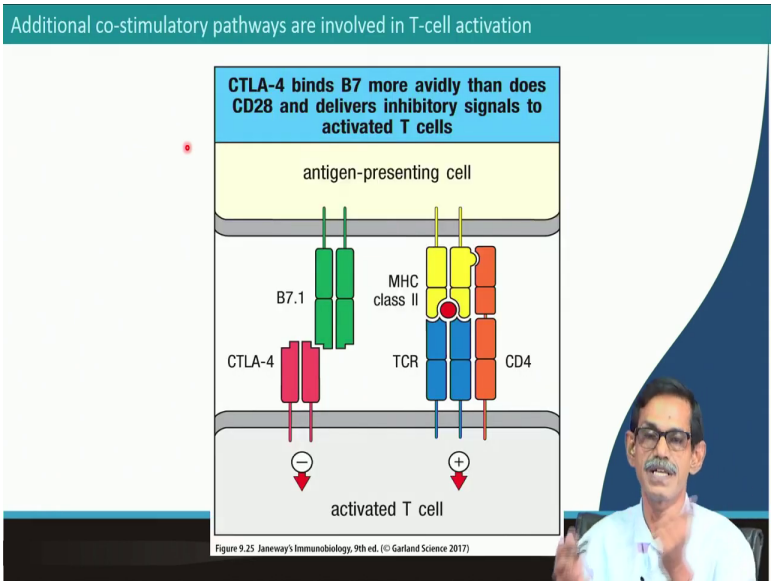

So what is happening there is another interaction because if T cell once activated and continue to do its own job and always super active then it is also not good because immune system should shut off so there is a negative control also so here this is the regular giving signal number one that is a positive that means for proliferation and activation and helping them right. This is one of one to see but there is when this thing is happening another protein is expressed by activated T cell which is called CTLA4 remember this is very common.

And many times you will find question from this place in your comparative examples so like how this co-stimulation control the T cell molecule activation because CTLF4 also has the same target B 7.1 but this interaction gives a negative feedback it is a negative sign. So once the B7 CD28 is activating the T cell but here B7 and CTL F4 is inhibiting the T cell proliferation. So that is how it is there is a competition and there is a balance also.

It is not that once it is activated it will continue to grow on ok. But this has this interaction has more every DT it can bind more and gives better signal. So once it binds it is very hard to I mean it B7 CD28 also good strong interaction but the ability is more here. So that is how the activation and inactivation is properly balanced in immune system and T cell is just doing its own job.

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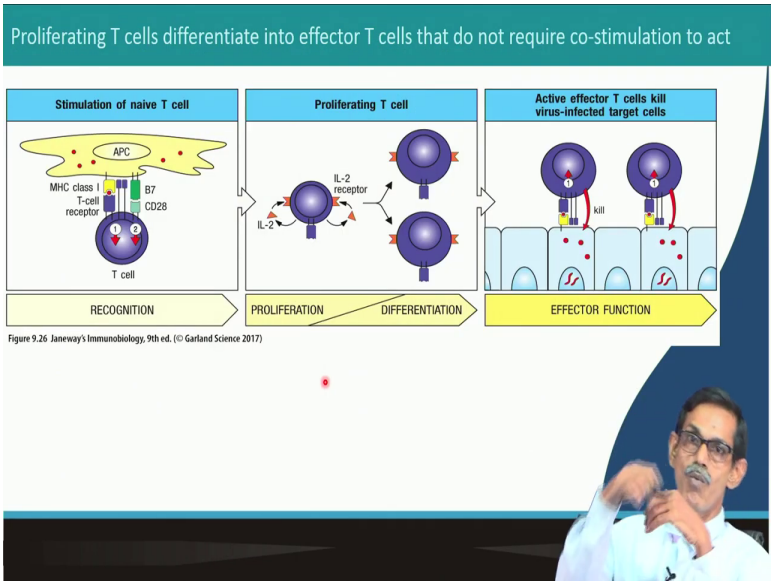

But once the T cell is activated and go and do it study so this is the activation say for example say B7 CD28 interaction MHC 1 MHC 2 1 2 and if it is number 3 by cytokines is not mentioned here, so T cell get activated. So these activities will go here and they started producing auto crate and activating itself or token regulation they divide proliferate but once it is happening they do not need anymore that once it is released get the signal.

So it will continue I mean it will do its own job as long as interaction is there. So the proliferating T cell differentiates into effector cells that do not require the continuous signal of 1

and 2. So once it is get the signal it will multiply and what it will do suppose it is a cytotoxic T cell you will go and loop the virus infect itself it will bind and kill it. So this is say one tissue where cell number this cell and this cell is virus infected.

So the two cells is produced say for the sake of this slide these two cell will go bind to cell and kill it and imagine you multiply that if there are 100 of cells on adaptive cells are producing more virus infected cells more because activation is continued. As long as antigen presenting cells are getting the supply of antigen it will remain active. As long as antigen presenting cell can present antigen it will continuously activate the T cell right.

And it will do the job the activator T cell will do its own job here particularly in this slide it is killing cytotoxic T cells. So if they can kill all the I mean killing the virus infected cell sorry you when all the virus infected cells will die gradually what will happen a PC or the antigen presenting cell will not find the antigen to present. If they do not find the antigen to present this T cell will not activate anymore so no new T cell will come and no new T cell will come means this whole process will gradually slow down.

But it is not immediately but you know that it takes 6, 7 days to get to come in this stage. So second day it will not suddenly stop gradually it will again slow down. And some of these cells will remain as a memory cell for secondary infection.

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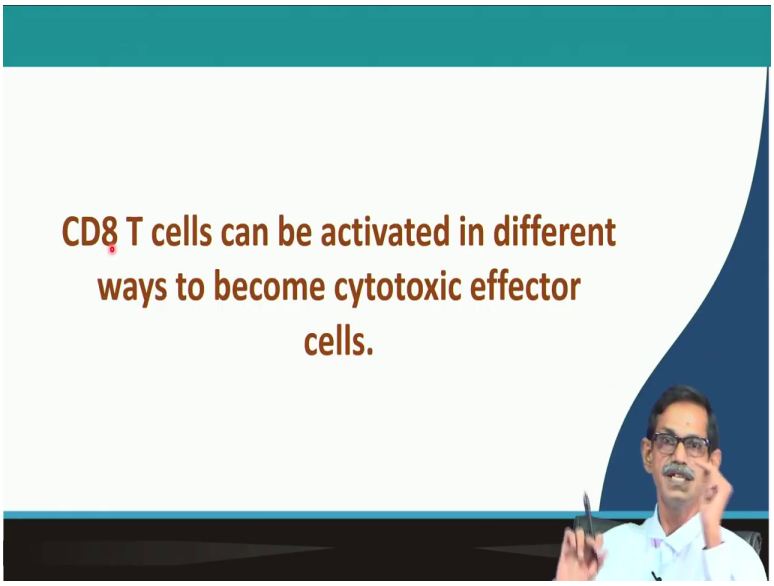

If there is any ok CD8 T cell cannot be activated in different way become cytotoxic affected that one way we said another is direct activation.

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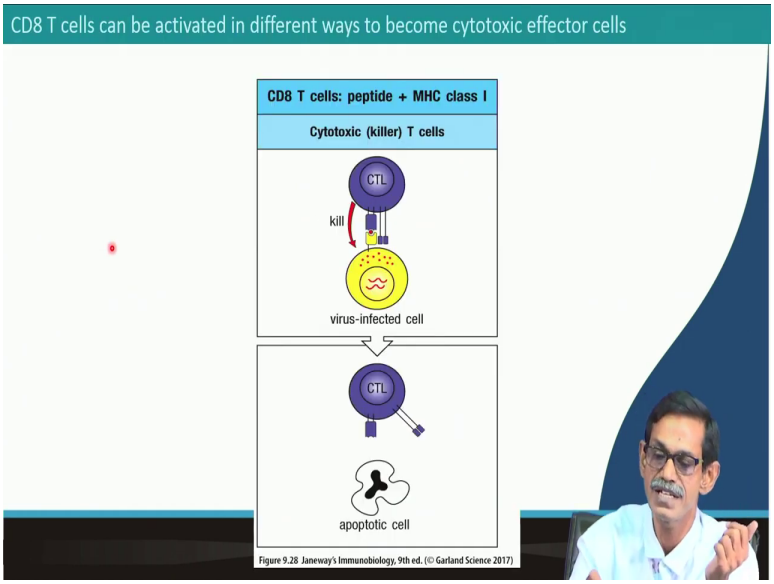

So dendritic cell itself can be virus infected and there may be interaction and the cytotoxic T cell can be directed and activated and kill it. Cytotoxic T cell if it is a genetics of the antigen presenting cell itself is virus infected it can kill virus infected self or the dendritic cells. So it is because sometimes it is happening so CD8 T cells peptide plus MHC class 1 also can bind and kill it and give the signal.

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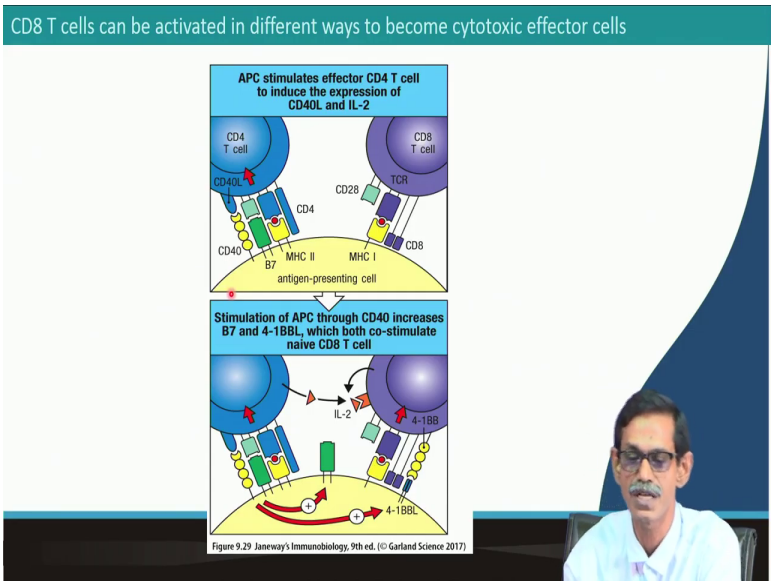

It is also can be activated by CD4 how because suppose this is the antigen presenting cell antigen presenting cell is not only expressing MHC 1 to activate CD8 it also expressing MHC 2 right a message is only expressed by the antigen presenting cells. So suppose imagine a situation where antigen presenting same antigen or same by MHC1 same antigen means same pathogenic antigen by MHC 2 as well as MHC 1.

So what will happen CD4 will be attracted like this B7 CD28 that is not only for CD8 that B7 CD28 is true for both CD4 and CD8. So these MHC 2 TCR interactions CD4 B7 and then an CD47 there are so many other interactions just main or major one we are discussing here. So this interaction will activate CD4 and these interactions suppose this interact but CD B7 is not here for some reason. So CD8 interact with this.

So what can happen activated CD4 T cell can also activate the CD8 cell which is in the same location because not only its IL-2 there are some more signal which is going to give this. So what will happen this interaction will keeps the antigen presenting cell the signal to express more B7. When more B7 will come this they will not be alone so there will be again interaction which is not shown here. So this interaction will give the signal to antigen presenting cells to express more B 7 and this B 7 will interact now and some other interaction also will help this particular cytotoxic T cell to activate.

So in this case what I can say is that cytotoxic T cell is activated not directly by the antigen presenting cells but with the helper T cells. So T helper cells also activate cytotoxic T cells in some cases, clear.

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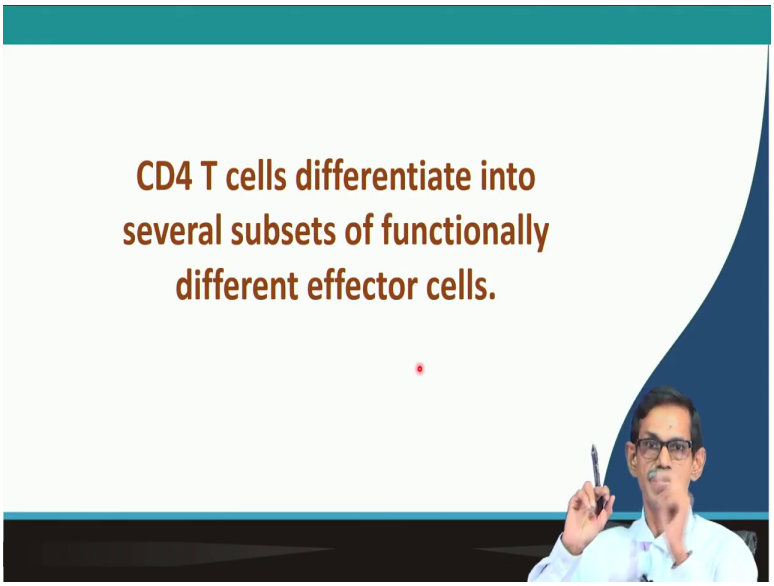

Now we are coming to CD4 T cells. Cytotoxic T cell activation is more or less what we said CD4 T cells differentiate into several subsets that will learn I will just tell the name not much function.

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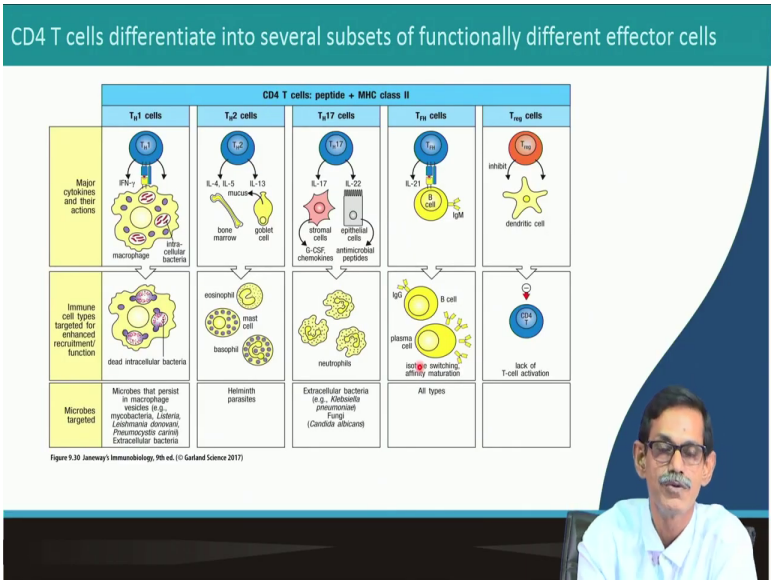

What are those you know TH 1 you know TH 2 you know T follicular, follicular means which help the B cell th17 and T regulatory cells so d they I mean CD4 T cells are of five subtypes all

of them interact with MHC class 2 these are their function one TH 1 you know already killing the internal parasite then the bigger parasite like Helminth and then T 17 cells again kiebsiella even in Candida and here this is the activation of B cells and this is T regulatory cells which is mostly regulate or inhibited cell activation it regulates T cell activation. So we will come I mean that detail it was a little more detail we do not have the scope to express much more about this but more detail will be discussed when we will study the cytokines.

When we tell you the cytokines that time we will discuss is because it is more related with cytokines.

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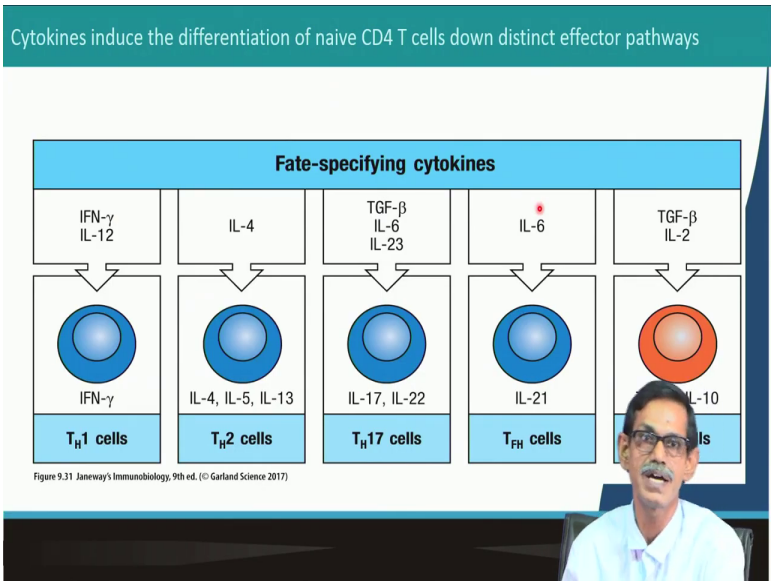

And this cytokines what just I was telling cytokines actually make their different effects. so TH 1 cells by this interferon gamma and internal in 12 TH 2 is IL 4 FHIL 6 then tumor growth factor beta will call it TGF-beta IL 6 IL 23. So these are the cells and this is the disease by which they become and after at this stage after becoming KH2 they produce IL 4 IL 5 IL 13 and it is produced IL come on IL 17 actually the origin of name of this TH17 cells.

CD4 T cell subset can cross and regulate each of the differentiation through cytokines. So, all these subsets also has some crosstalk.

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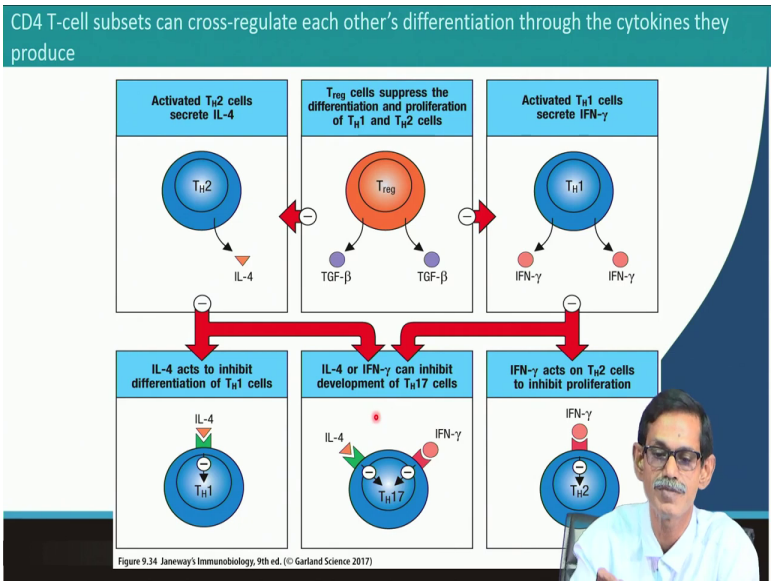

How these cross ducts means TH 2 in a way TH 1, TH 1 enovate TH 2. T regulatory new it both TH1 and TH2 so there is a balance there is a balance means all possible cells are there. But all our help ourselves but it is not that they are continuously doing helping us. So they also have a balance and that balance is again by the cytokines some cytokines release and stop some activity some cytokines activate some activity.

So this way the their function is regulated. Fortunately we do not have to know all this thing to regulate them but put study we should know that these would I mean in cytokine class you will learn in little more detail but here you should know that TH1, TH2, TH17 T rec they have a crosstalk they can control each other activity when TH 1 is important then TH 2 is suppressed when TH 2 is important is only suppressed. So that kind of control is there.

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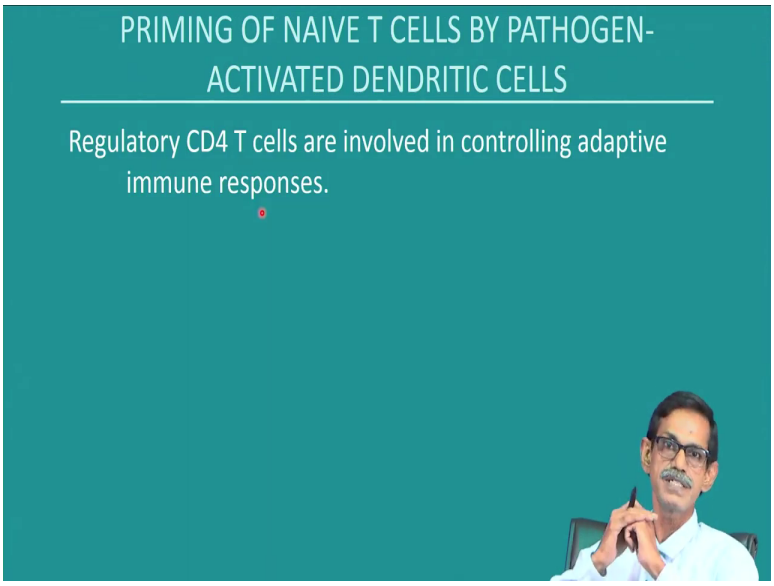

And regulated CD4 cells involved in controlling adaptive immune response today is also that you will see later ok.

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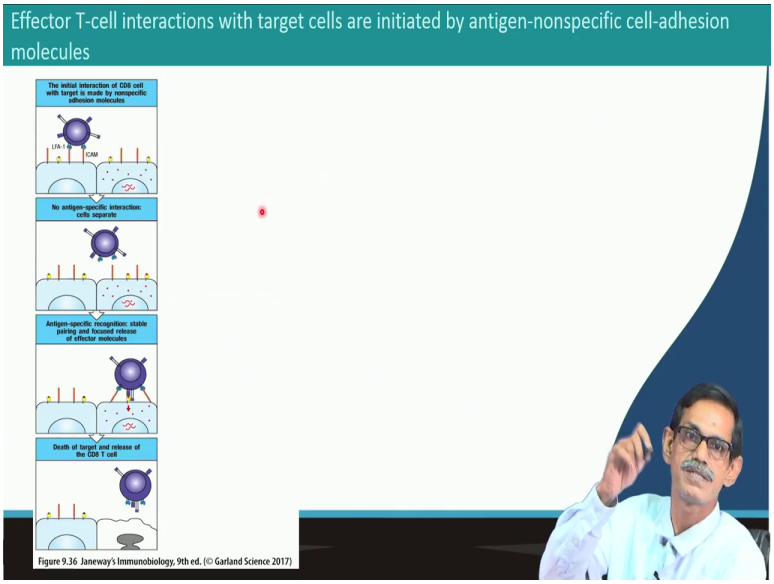

Now what we are saying the cytotoxic T cell I am I am going to come back to cytotoxic T cell again ok. Because T helper cells you will learn say helping B cell activation of production of antibody you will learn much more in B cell immunity and b cell development and then all these other cells here T cell mediated immunity we are mostly good for T cell immunity and that T cell immunity means the cell mediated immunity which is mostly is not killing by cytotoxic T cell.

Helper part this is also involving adaptive immunity is very prominent way but that comes mostly in the B cell activation another part that will be discussed in that time but now I am coming back to T cells cytotoxic T cell. So what is happening again here this it is the interaction starts with the nonspecific interaction again with that integral and other ligand protein. So you see here in this case I I think I brought the same slide again.

So initially they interact with this then they found the specific interaction and I these specific interaction if they found that this is a virus infected. So the virus infected cell is here this is not so it interacted the non virus infected cells then it is not that strong go to next. When it come to next it found if this particular T cell find this one a very strong interaction what I am saying here actually. And then these interaction gives the signal that the virus infected cells will die. And gives us signal for killing and it dies so that is how it work.

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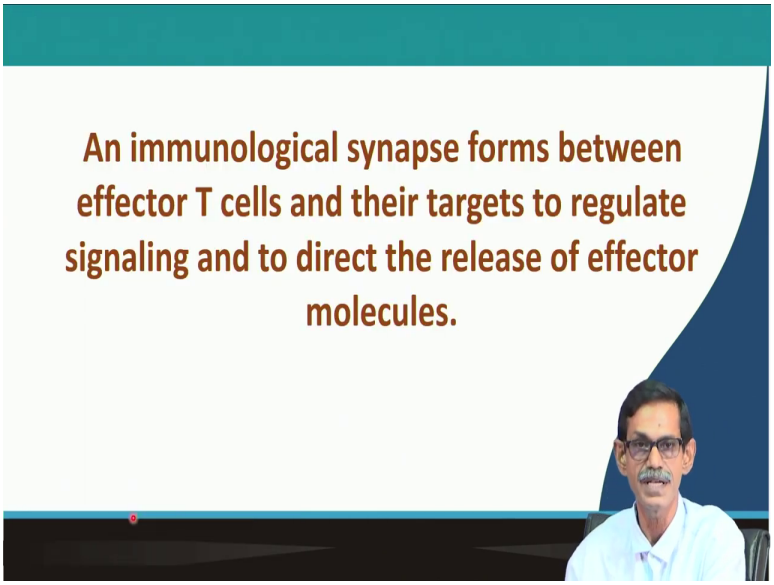

And this how it this killing is happening it is very interesting.

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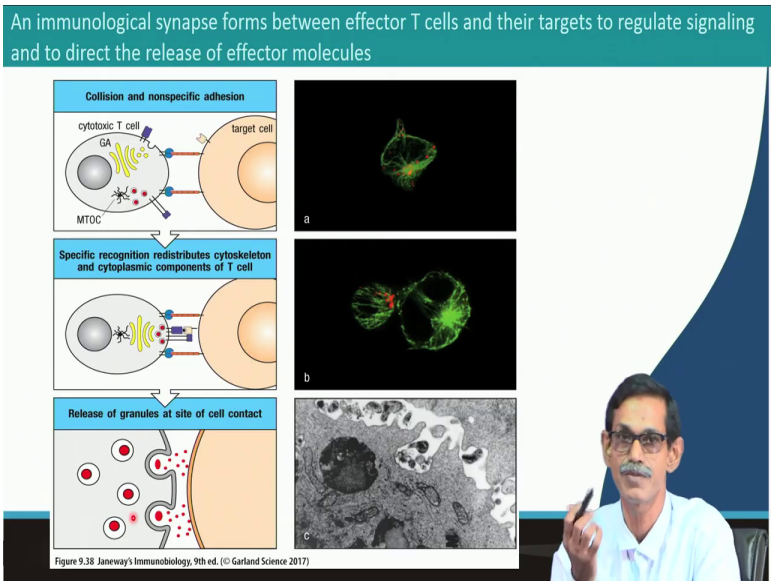

If you see this picture you have to understand because now you know immunostaining. So what happened here you see the green is the actin and red is the lysosome if you see this is the cell so actin is everywhere this actin stress fibers. And all these small red dots are lysosomal physicals there they're all over the cell this is the schematic diagram. So this is target cell that means suppose this is a virus infected cell they interact first.

At this time the Golgi apparatus this MTO sees microtubule organizing Center you may heard this in the cell biology then the lysosome they are distributed all over the cell. After this interaction if this second interaction happened that means the MHC and T cell receptor interaction happened. These interactions makes what change they change all this thing in one line you see the MTO sees here all these here then lysosome is very close to this interaction side.

This can be seen also in the fluorescence microscopy you see we cannot see all this thing but at least we can see that all the lysosome which was distributed all over the cell are here. And next cartoon is very clear that all these lysosome material they release and these red dots are very dangerous this is electron microscope you can see it is red dots are very, very dangerous what are they?

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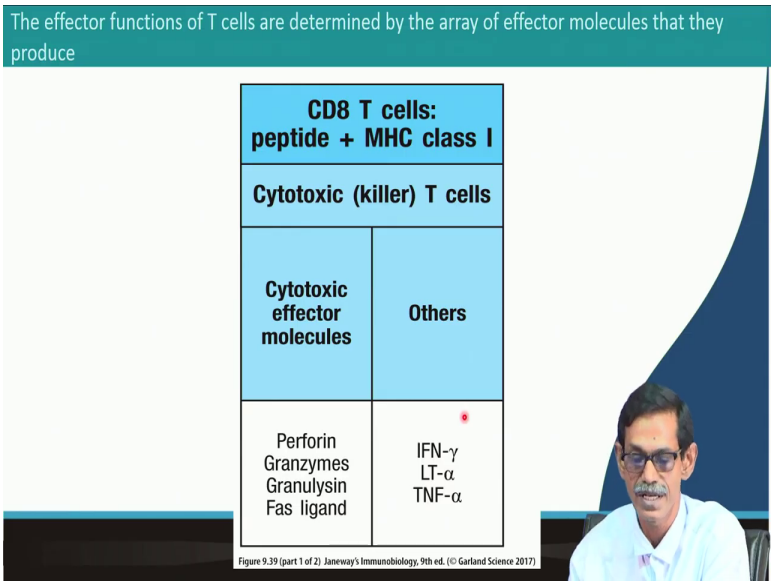

They are perforin, granzymes, granulysin, fas ligand it is actually activating their apoptosis. So what is perforin?

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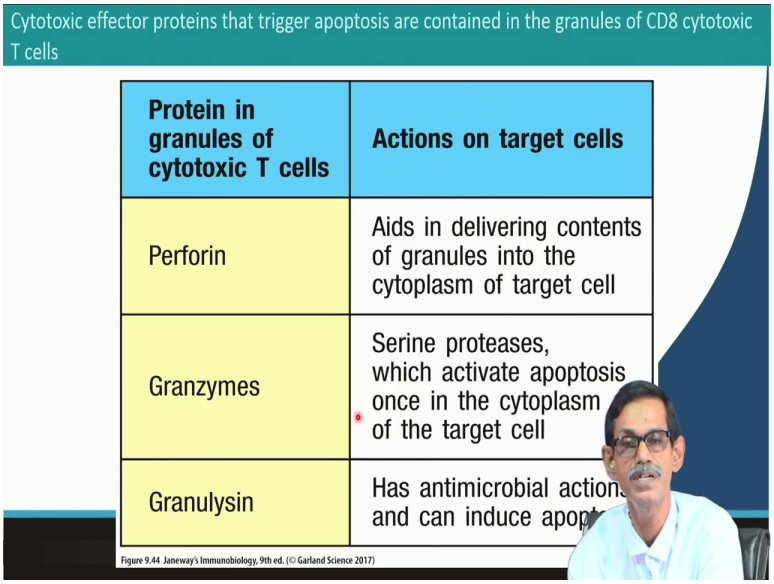

Perforin it is a small molecule pore-forming peptide you can say it makes hole inside the cell. So if I make a whole cellular material come out so that the whole cell will dies so midas cannot survive. Granzymes is a protease serine protease which activates a apoptosis ok. Granulysin is the anti microbial action and can induce apoptosis. So fas ligand, granulysin granzymes all three are good in killing or destroying the protein as well as apoptosis and powerfully make whole.

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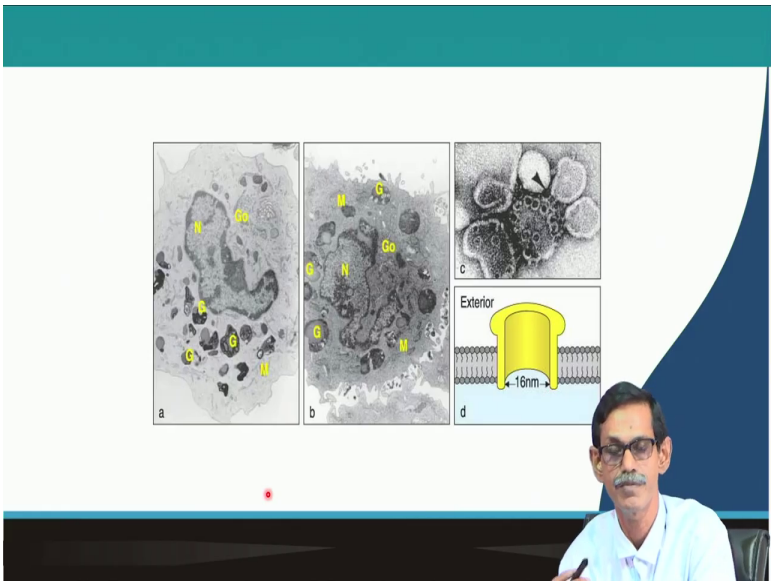

And perforin how they are making whole you can see this picture is a electron micrograph there are so many holes and this holes are like that. So the proteins are like we already discussed now with the bead the perforin making like that. So this perforin will make a whole channel everything will come out. So this is the kind of structure they form.

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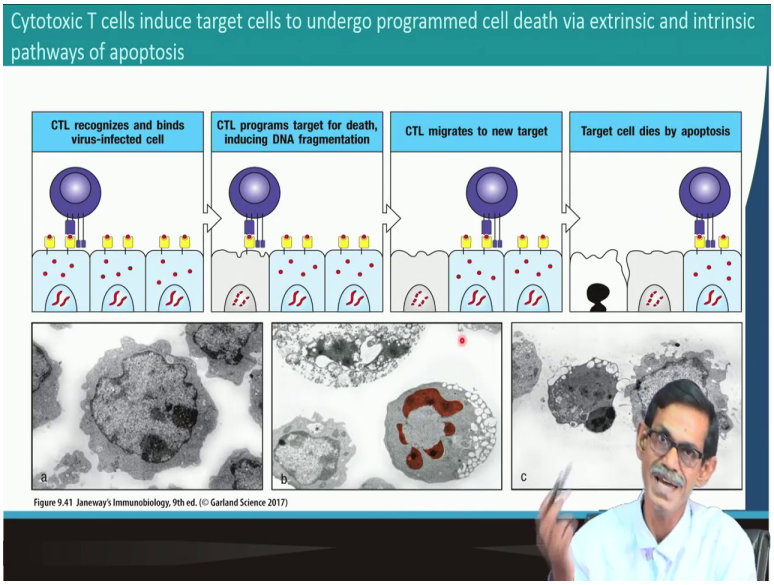

Now this is how they kill so once there says suppose all cells are virally infected what will happen cytotoxic T cell will come kill one by one or multiple cytotoxic T cell activated will come and kill.

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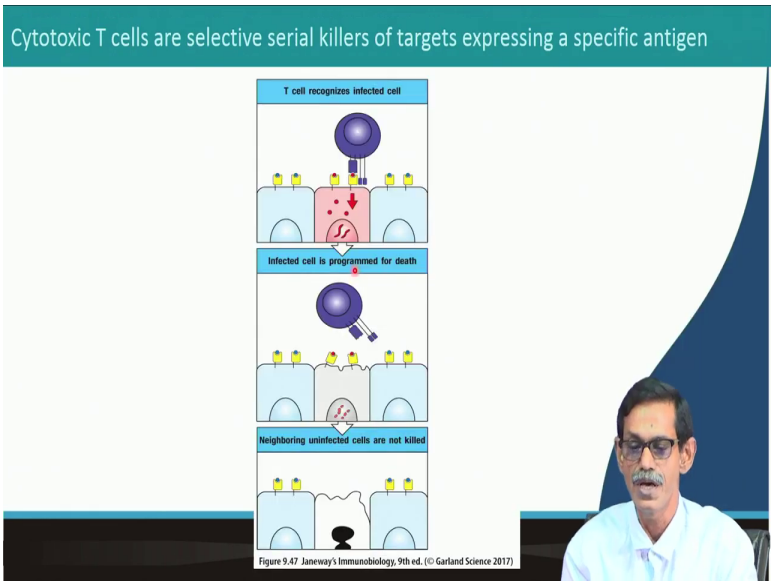

If suppose if the case that these three cells only one is virus infect itself so it is not going to hamper any of these two neighboring cells but it will get only this one. It will come here and release this granzymes and granulusin and very in the contact place only. So when it is contact in the contact place on it is not like spread everywhere so it will not disturb or kill the other cells.

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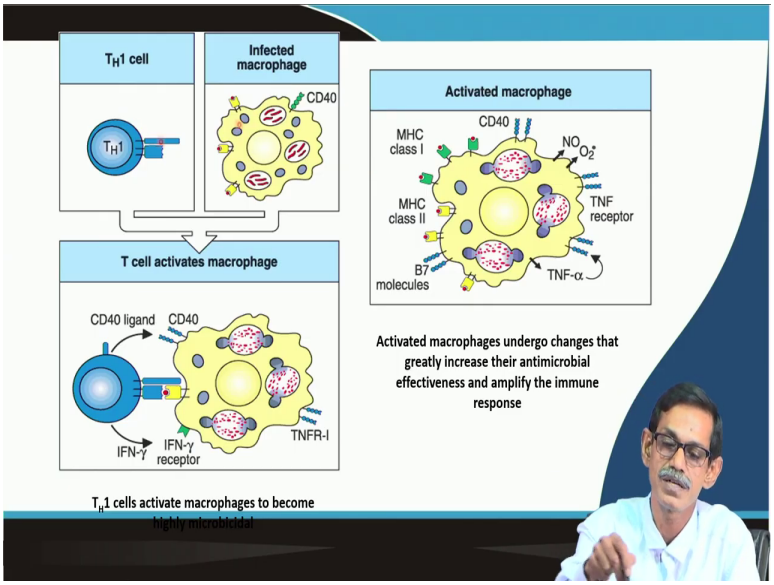

This you know that TH 1 activate the macrophage and you can see this is the regular macrophage as soon as it activated so many new molecule comes in the surface. This is activated macrophages and what happened they started killing. So initially they do not know now they know how to kill.

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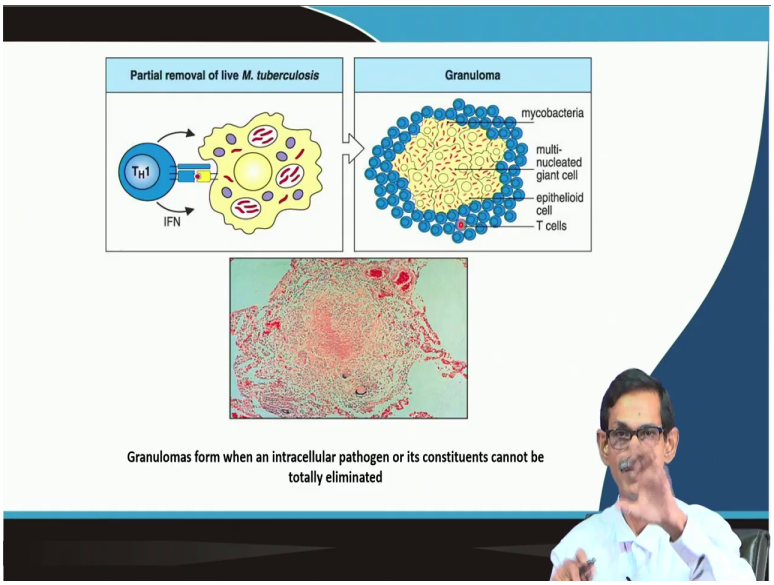

And one more information I should add that this I am skip I will skip this also one point information I will add that this structure is not alone what happened as where there is macrophage like particularly my collective infection or least many infection all the T cell just covered them. So infected macrophage are basically covered by the T cells so they cannot leave till they clean all this area and that is called granuloma.

So in TB patient lung granuloma formation bottom one you can see is there. So once this bacteria is removed then T cell will disperse granuloma formation is a positive signal for immune system and that is how doctor sometimes see the server tissue biopsy like granuloma is there or not a granuloma is there that means immune system is working fine. This is more or less cell mediated immunity or cytotoxic T cell immunity. See you in the next class.