Host-Pathogen Interaction (Immunology)
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Lecture - 61
Adaptive Immune Responses Against Viruses

So, in previous session we have discussed about the innate immune responses against viruses and how the viruses evade the innate immunity. Now let us move to the adaptive immunity. So, in this session we will discuss about what are the adaptive immune responses are there against virus infection and you understand that this response is very important not only infection and it is also very much important during vaccination.

So, the whole principle of vaccination is a basically based on activation of adaptive immunity. So, if we elucidate appropriate adaptive immune response against any virus or viral component then that response is capable to clear the real virus infection. So, let us begin with adaptive immunity.

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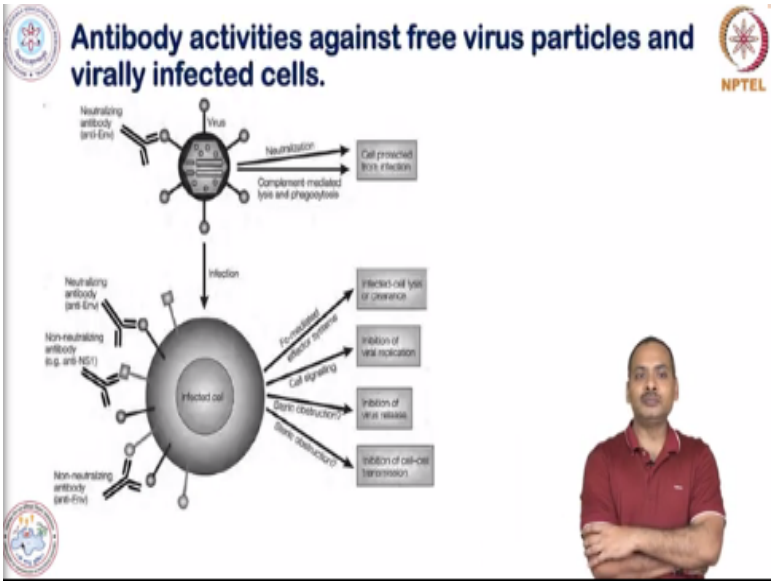

So, you know that there are two major component of adaptive immunity one is antibody production and another is T cell activation. So, let us begin with antibody component. So, as you know that when there is a virus infection there is a production of virus specific or activation of

viruses specific B cells and these B cells it is not only one ~~basal~~ cells there are repertoire of B cells there is a huge array of B cells which is getting activated during the virus infection.

So, these were these B cells differentiate into two major component one is the effector cell which is mainly the plasma cell which secretes the antibody and another is memory cell. So, this memory cells are playing very important role when there is a re-infection of same viruses and these memory cells are also playing very much important role during vaccination. So, when the individual receives the vaccine basically, we are trying to induce this memory B cells.

So, that when there will be a real infection so these memory cells will differentiate into again effector cell and then that will produce a lot of antibodies and these antibodies will clear the real viral infection. So, now let us look at how these antibodies are playing role against viruses. So, viruses are when they infect the host generally, they are present in two forms mainly present in two forms one is that these viruses is present in free form outside the cell.

So, when it is present in free form then what will happen? If there is a antibody against these viruses so these antibodies basically mask the surface protein on the viruses and there will be a two major benefits of this. One is that you know that viruses uses some surface protein in order to attach with the host cell. So, if that surface is masked by the antibody, then these viruses cannot attach to the target cell and these antibodies, we call it as a neutralizing antibody.

There are some protein which is not playing very important role in attachment with the target cell. So, there is a also generation of antibody against those surfaces we call those surfaces or the antibody which is generated against those surfaces as a non-neutralizing antibody. So, both this neutralizing antibody is playing very important role in preventing the infection. Whereas this non-neutralizing antibody they play a very important role in various processes various immune processes.

The first is this virus is coated with the antibody then what will happen? This will be readily phagocytized by the phagocytic cells. Another is if the virus is coated with antibody, then there is a activation of complement mediated pathway. You know you remember that classical

complement pathway, this classical complement pathway is basically triggered by antigen antibody interaction and you remember that there is a CH two domain in FC part of the IGGg.

This interacts with C1q Q and then that will activate the cascade of complement pathway and that eventually result to the formation of membrane attack complex. So, these complement pathways are very important against enveloped virus. There are non-enveloped virus but these antibodies or these complement pathway or complement pathway which is basically triggered by antibody that is classical pathway plays a very important role against envelope virus.

So, there will be a formation of pore and then there will be a loss of osmolarity and all those things and then eventually this virus will be disintegrated. Another situation is virus is present in free state another could be these viruses are infected the cell already infected the cell. So, over there some viral signatures will be present over the infected cells and these if these viral signatures are present on infected cell, then you know that there is a several phenomena's are playing very important role.

If you remember there is a ADCC antibody dependent cell mediated cytotoxicity so that will happen. So, the infected there will be a lysis of a infected cell through ADCC there could be a inhibition of a viral replication. So, this is basically taking place through various cell signalling. So, when antibody will bind to these virally infected cells then that will change some cell signalling and then that will result to the inhibition of a viral replicationapplication.

And if you remember that there is a one very important family of cytokine that is type 1 and type 3 interform they are also doing same job. Inhibition of a viral release. So, there is a possibility that if the antibody is generated against the virus and it will be displayed over the surface of cell then there is a possibility that this will inhibit the virus release from infected cells. And if there is an inhibition of a release of virus from infected cell then there will be a decrease in transmission of virus through cell-cell transmission.

So, when the virus is released from one cell it will infect another healthy cell. So, this if the virus release is inhibited then transmission will be also inhibited. So, in that way these antibodies plays a very important role against virus infection.

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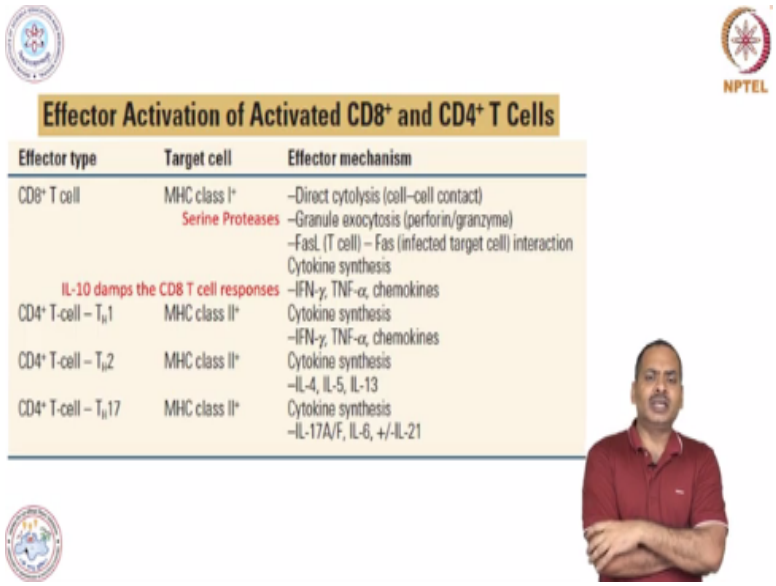

Now let us look at the T cells. So, you know there are variety of T cells and these T cells are playing very important role during any infection. In particular in during virus infection let us look at what are the function and how they play a antiviral state how they develop the antiviral state during virus infection. So, here you can see that there is a CD8~~A~~ T cells. The CD8~~A~~ T cells also we call it as a cytotoxic T cells.

So, these cytotoxic T cells basically recognizes and viral antigen along with MHC class 1 molecule. After recognition, please note that there is a need of co-stimulation which is provided by the infected cell and this core stimulatory signal is received by cytotoxic T cells then there will be a fruitful activation of cytotoxic T cells. So, once it is recognized then what will happen? There will be a direct cytolysis of infected cell.

You know that this will release some granules and the granules will be exocytosed and which is mainly consists of a perforin and granzyme and perforin and granzyme is a basically serine proteases. And these this these granules will reach in the target cell and that will cause the lysis of a target cell. There will be also the CD-8 or cytotoxic T cells will also have a fast ligand and

this fast ligand and there will be a fast over the target cell and this interaction will cause the release of some cytokine and it may also cause the apoptosis of target cell.

It will also induce the activation cytokine. For example, production of interferon gamma, there will be a production of TNF alpha and some another chemokine. So, these are the key anti-viral role of cytotoxic T cell. Another is a CD4 T cells and CD4 T cells you know there are several subtypes that is TH 1, TH 2, TH 17 and so on. So, there are TH 9, T RAG and all those things. So, basically this T helper cell we also call CD4 T cell as a T helper cells.

So, these T helper cells that T helper cell also we call it as a TH 1, TH 2, TH 17 or TH 9. So, this TH 1 cells plays a very important role after recognition of the MHC class 2 molecule which is present over the cell along with the antigen. So, this will be recognized by CD4 T cells and then that will induce the production of cytokine like interferon gamma, IL 12 and they will also induce some chemokines.

So, basically TH 1 cells play important role during intracellular pathogen infection or microbial infection however the TH 2 cells they play a very important role during virus infection. They basically stimulate the antibody production through the production of IL 4, IL 5 and IL 13. There is a TH 17 cells this TH 17 cells are playing very important role in inducing some kind of inflammation.

So, its role in virus infection is not very well clear but they do play important role in direct or indirect way. Basically, they induce the inflammation. So, maybe it is playing very important role in triggering the alarm when there is a virus infection in the host. So, that the immune cells will come at the site of infection and they will take care of that infection. So, here you just I would like to say that there is a some cytokine which is anti-inflammatory in nature.

And this cytokine basically damp the cytotoxic T cell activity and here you can see that there is a IL10 and these are IL 10 damps the CD8~~A~~ T cell responses.

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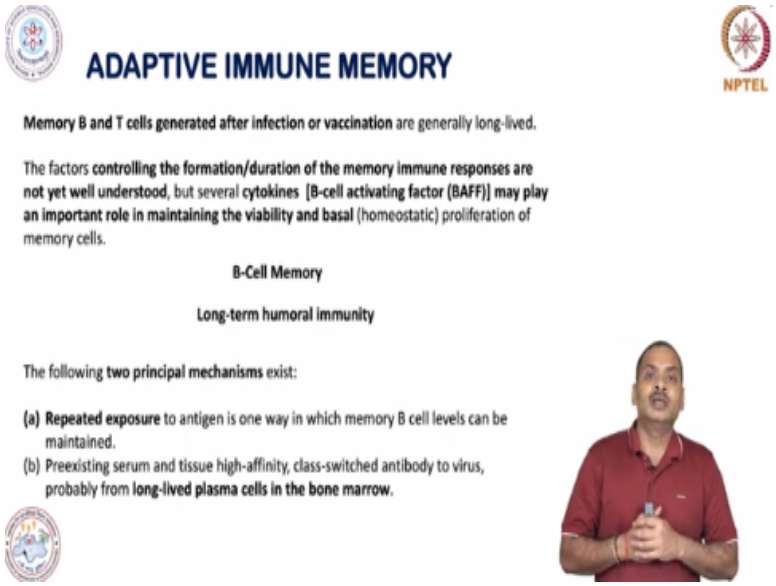

So, there are the hallmark of adaptive immunity is the memory. So, our adaptive immune system remember the infection and when there is a re-infection this will trigger the all those molecules the synthesis are all those molecules very quickly and clear the second infection. So, memory B and T cells are generated after infection or vaccination are generally long lived. It is a you may know that you may receive some vaccines when you are kid.

So, this vaccine is still working because there is a memory inside our body. If there is infection then this will clear the infection and you will not know that thing. So, there are several factors which maintains this memory and there is a one cytokine which we call it as a BAFF, B cell activating factor. So, this cytokine may play a very important role in maintaining the B cell memory which basically helps in formation of memory as well as duration of keeping this memory.

However, what is the precise molecular mechanism of maintaining this memory is not so well understood. However, there are some or there are some theory that there will be a slowe proliferation of these memory cell and that memory cell will just present throughout the duration. So, the B cell memory is there are we call it as a based on duration we call it as a long term memory or this long term memory is basically there are two major principle which people suggested that.

One is that the repeated exposure to the antigen. So, if the individual will receive the antigen keep on receiving the antigen a small amount of antigen, then that will maintain the memory. And if you remember that you have received the vaccine you received first dose and second dose and then preventive dose so this receiving of these the second dose and the preventive dose the aim is to maintain the memory.

So, if we do not give this this second dose or preventive dose then maybe we will lose the memory. We will lose the information how to fight with the SARS COVID-2. So, this is just one example, there is a repeated exposure. So, we are giving again and again the same antigen. So, that our body the memory will remain intact. There is another theory or another school of thought that there is a pre-existing serum and tissue high affinity class switched antibody to virus and probably from long lived plasma cell in the bone marrow.

So, there is a one theory that there is a some long lived plasma cells are present in the bone marrow and that maintains the memory. But to best of my understanding it depends on antigen, it is not only depends on the B cell or other factors. It depends on antigen you may know that for some infection for example the smallpox we have a almost lifelong memory. But for SARS COVID-2 if you take the example, we do not have a that long memory.

So, for antigen to antigen there will be a various mechanism most probably various mechanisms are existing in the host.

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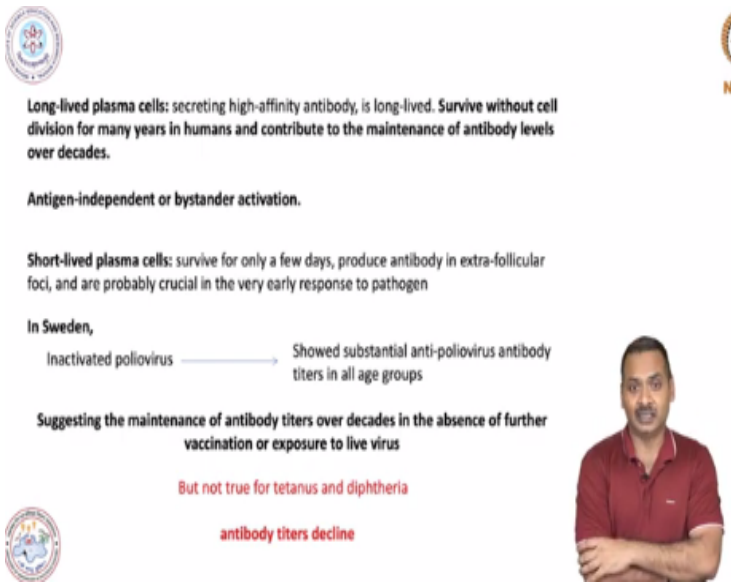

So, long lived plasma cell basically secrete very high affinity antibody is a long lived and survive without cell division. So, this plasma cell they sit in the bone marrow and then they just sit over there they do not divide. So, since they are not dividing so they will not age so fast and they will not removed from the system and in that way this will provide a memory for many years and the it will maintain the antibody level in the blood serum.

There is an antigen independent or by-standard activation. So, there is some theory that some memory is antigen independent. So, these are some of the theories. Here I will just talk about the short-lived plasma cells basically survive for only few days. So, in general the plasma cells survive for very short duration and produce antibody in extra follicular foci and probably crucial in the very early response to the pathogen.

So, this is about the short-lived plasma cell which will be short-lived and in this short duration they will produce tons amount of antibody in order to control the infection or viral replication. There are some studies people perform some studies in order to understand the memory. In Sweden people perform you know that people receive this inactivated polio virus vaccine, vaccine against the polio virus and they showed that there is a substantial anti polio antibody titer in all age group.

So, this shows that this memory is existing and this memory but we do not know what is the molecular mechanism. But this memory is present for very long time in all age group people. Suggesting that the maintenance of antibody titer over decades in the absence of further vaccination or exposure to the live virus. So, this is without a repeated exposure to the antigen it is unlike the SARS COVID-2.

Here the host receives only once the vaccine and then they develop the antibody and this antibody levels are maintained. But it is not true for other antigen like tetanus and diphtheria antibody titer decline very quickly. And if you take the case of SARS COVID-2 this is also true for SARS COVID-2 the antibody titers are declining.

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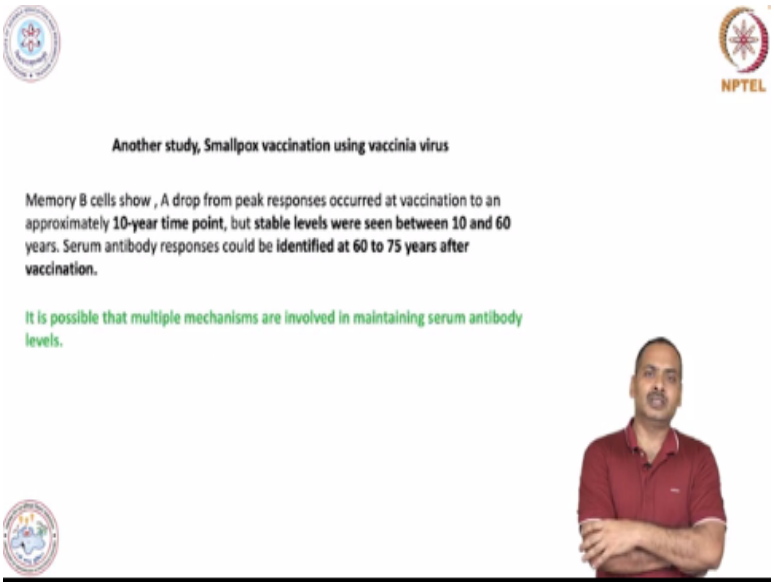

Another study this is a smallpox vaccine using vaccinia virus. So, memory B cells show a drop from peak response occur at vaccination to an approximately 10-year time point. But a stable level was seen between the 10 to 60 years and serum antibody response could be identified at 60 to 75 year after vaccination. So, this suggests that so there will be a peak of a antibody response and then it will be stable for 10 to 60 year and then there will be a some reduction in this antibody titer.

But the reduction is not so drastic it will be there but the reduction is not too much low. So, it is possible that as I told you previously there must be multiple mechanism depends on antigen

depends on host and there must be some various kind of phenomena is going on our body or in the host and there could be a possibility that these this memory is basically somehow renewed somehow, they transfer the information one when they die to the healthy cells. So, we do not know precisely what is the molecular mechanism.

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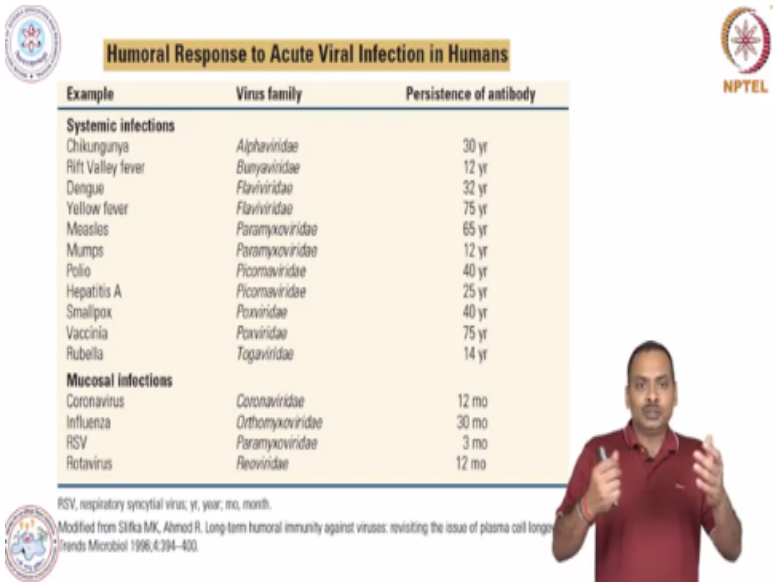

So, humoral response to the acute viral infection in human here you can see that the persistence of antibody. Again, this is the matter of memory or antibody present against particular infection. Here you can see that Chikungunya can induce memory for 30 years it is very long and here you can see that yellow fever vaccine they can induce the memory for 75 years which is a almost lifespan of human.

But for some cases like Corona virus, it is very short it is about 12 months it after that it will decline. Influenza virus is again 30 month and RSV respiratory syncytial virus it induces only three-month memory. So, this is a quite variable here I want to say that.

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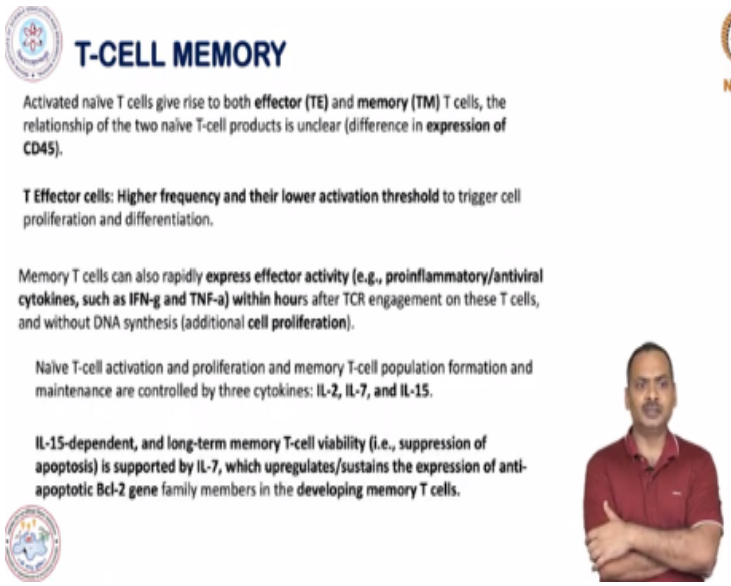

T cell memory, so activated naive T cells basically differentiate into the effector T cell and memory T cell and there is a just a difference in expression of a CD 45. This is a one surface molecule, there must be some more molecule but just for your simplicity and or for simple understanding you I am just telling one molecule it is CD 45. There is a difference in CD 45 molecule and effector T cell has a higher frequency.

And their lower activation threshold to trigger the proliferation and differentiation. So, at very less stimulation they can produce lot of effector cell and then that will control the infection. Whereas this memory T cell can also rapidly express effector activity and that is a production of pro-inflammatory cytokine, antiviral cytokine like a interferon gamma, TNF alpha within an Rhour after TCR engagement on these T cells without DNA synthesis.

And there will be additional proliferation in these cells and naive T cells activation and proliferation and memory T cell population, formation, maintenance are controlled by there are several cytokine as you can see there are IL 2, IL 7 and IL 15. So, they are playing very important role in this naive T cell activation IL 15 dependent and long-term memory T cell viability basically is supported by IL 7 which upregulate sustain the expression of anti-apoptotic Bcl 2 and anti-apoptotic gene Bcl 2 and it is developing to the memory T cells.

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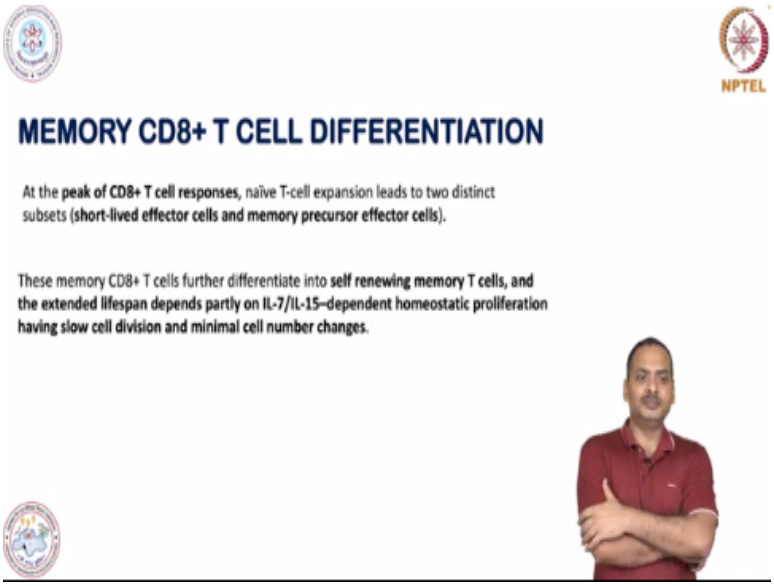

So, memory CD8 positive T cell differentiation. So, at the peak of a CD8 positive T cell response naive T cell expansion lead to two distinct subset. One is that as I told you there will be a short-lived effector cells and there will be a memory precursor effector~~refactor~~ cells. And These memories CD8 T cells further differentiate into self-renewal memory T cell and the extended life span depends on partly on IL 7, IL 15 dependent homeostatic proliferation having a slow cell division and minimal cell number changes.

So, with this I will stop about the adaptive immune responses against a virus infection. In next session I will talk about how the viruses evade this adaptive immunity and establish the infection. Thank you.