Host-Pathogen Interaction (Immunology)
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Lecture - 62
Adaptive Immune Evasion by Viruses

Hi, so in previous session we have learned about that what kind of adaptive immune responses are elucidated during virus infection and how the host defended virus through antibody production cytotoxic T cells and T helper cell how these cells helps in elimination of viruses and what kind of memories are developed by different adaptive immune cells. In this session this we will discuss about how viruses evade the adaptive immunity.

So, there are several ways by which virus can evade the adaptive immunity and establish the infection. So, let us begin with these things.

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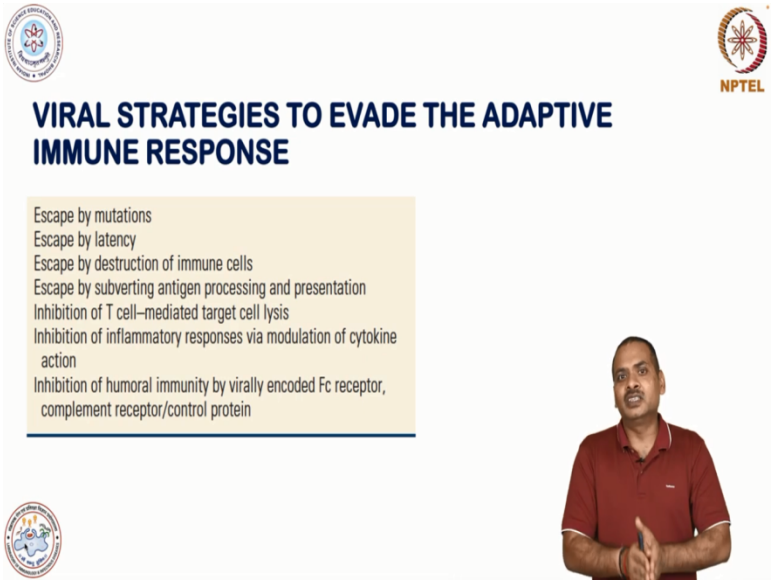

So, there are several strategies by viruses, here you can see that there are viral strategies to evade the adaptive immune responses and these are following. The first and foremost important is escape by mutation. So, you know that most of these viruses they have a polymerase and in case of RNA viruses, there is RNA dependent polymerase which is prone to incorporate mutations in the genome while replication.

So, this mutation if the virus will incorporate a lot of mutation, then they can easily evade the immunity. Immunity means I am talking about particularly adaptive immunity, the antibody which is produced against particular strain or particular virus will be not so effective. Another way is escape by latency. So, some virus play very smartly this these are generally DNA viruses. So, they incorporate the genome and then this genome is sitting in the cell just silently or what will happen.

This genome may integrate into the host genome, as you know in case of HIV. So, there will be a RNA this RNA will become a RNA DNA hetero complex and then there will be a synthesis of double standard DNA and this double standard DNA is integrated into the host genome and in that way they can set the silently and they will not do anything. And when there will be a change in homeostasis decline of immunity.

And then there will be a kind of burst of production of these viruses and they will eventually hijack the host defense mechanism. Another way is escape by destruction of immunes ~~or~~ cells some viruses can directly kill the immune cells. Escape by subverting antigen processing and presentation. So, some viruses so there is a complex pathway through which there is a processing of antigen viral antigen and this will mainly take place in all nucleated cells.

So, what is happening that these viruses make some protein which will somehow subvert the antigen processing. So, they will somehow inhibit the antigen processing and they may inhibit the presentation over the membrane. So, this is a very smart strategy in order to evade the cytotoxic T cell mediated immune response. Inhibition of ~~Elevation of~~ T cell mediated target cell lysis. So, they may make some protein or some factor which will basically inhibit the T cytotoxic T cell mediated cytolysis of infected cells.

Some viruses can inhibit the production of inflammatory responses via modulation of inflammatory cytokine or they may make some kind of protein which will sequester this inflammatory cytokine. So, in that way they can they cannot trigger the alarm in the host and in

that way, they can evade the host immunity. Inhibition of humoral immunity by viral encoded Fc receptor.

receptor So, here you can see that they will make some Fc receptor virus will make some Fc receptor like protein. So, what will happen? So, whatever antibody is produced against the virus this will be sequestered by this Fc receptor and in that way, they can nullify the effect of antibodies. They can make a Fc receptor they can make a complement receptor or they may make some antibody binding protein. So, in that way they can very easily evade the antibody responses.

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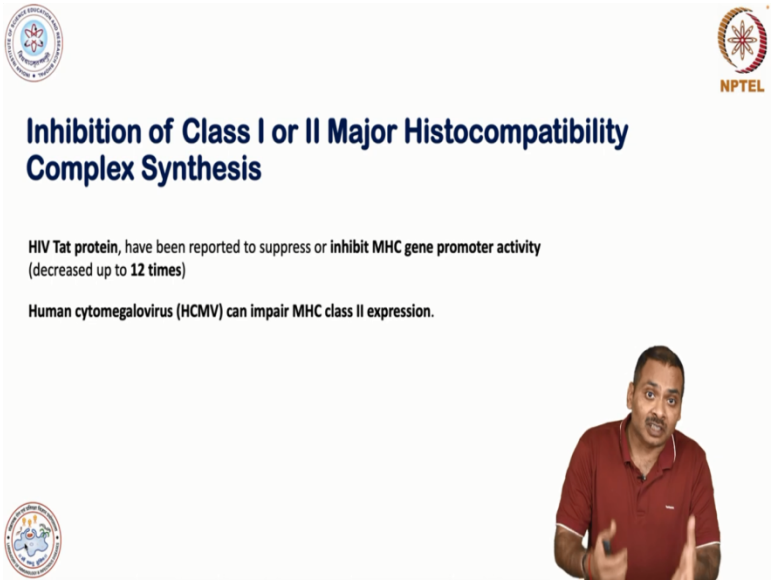

There could be an inhibition of class 1 and class 2 MHC complex synthesis, here I will show you that there is a protein in HIV which we call it as a Tat and that Tat protein basically suppresses or inhibits the MHC gene promoter activity. And since it is suppressing the MHC gene Promoter~~from motor~~ activity there will be a less expression of MHC molecule. And then if there is a less expression there will be a very bad T cell response against HIV.

So, you can see that this is a very smart strategy and this suppression could be more than 12 times or up to 12 times. There is a some HCMV so a human cytomegalovirus can impair the MHC class 2 expression. So, this virus infection there must be some factor which will basically

inhibit the expression of class 2 MHC class 2, expression. So, in that way they can smartly manage TH2 response.

And subsequently this TH2 response will inhibit or reduces the B cell responses, antibody~~iotic~~ production.

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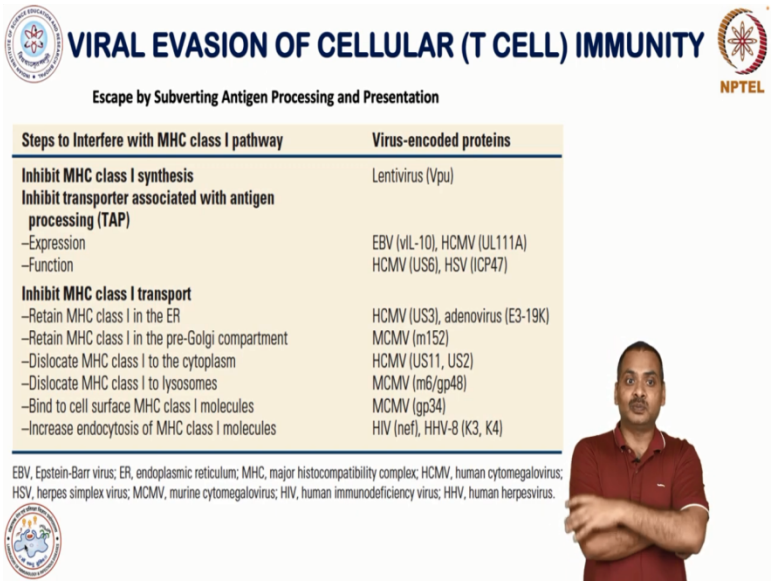

So, viral evasion of cellular particularly T cell immunity. So, basically escape by subverting antigen processing and presentation. Here you can see that there are several viral factors which is playing important role in evading this T cell immunity. So, lentivirus they have some Vpu protein which basically inhibit the MHC class 2 synthesis sorry, inhibit MHC class 1 synthesis. They can also inhibit the transporter associated with antigen processing that is TAP expression and function there are so many viral protein.

Here you can see that ~~abstain bar virus~~ Epstein–Barr virus basically synthesize the viral IL 10 and HCMV they have a protein known as UL 11A which so this protein basically reduces the expression. HCMV HS6 and HSV ICP 47 they reduce the function. Some so there will be inhibition of MHC class 1 transporter here you can see that there are some protein, basically HCMV US3 and adenovirus E319K, these proteins basically retain the MHC class 1 molecule in endoplasmic reticulum.

MCMV m152 protein, basically they retain MHC class 1 in pre-Golgi compartment. So, here you can see that this pro this viral protein are very specific they cannot miss the target something like that it is a highly specific to particular process. Similarly, this HCMV US 11 and US 2, this protein basically dislocate MHC class 1 to the cytoplasm it is turning to the wrong direction so, that it will be not presented over the cell membrane.

MCMV m6 and gp48 protein basically dislocate MHC class 1 to the lysosome. So, it is a quite a smart way in order to evade the cytotoxic T cell mediated immunity. Another is MCMV gp34 protein that binds to the cell surface MHC class 1 molecule and in that way, they will prevent the T cell activation. HIV nef protein and HHV 8 this is a virus HHV is a basically human herpes virus, K3 and K4 protein increases the endocytosis of MHC class 1 molecule.

So, here you can see that all this viral protein they specifically target this MHC pathway, MHC there is a processing and presentation of antigen that is specifically targeted by these protein and eventually they will shut down the cytotoxic T cell mediated immunity. So, this is very smart way.

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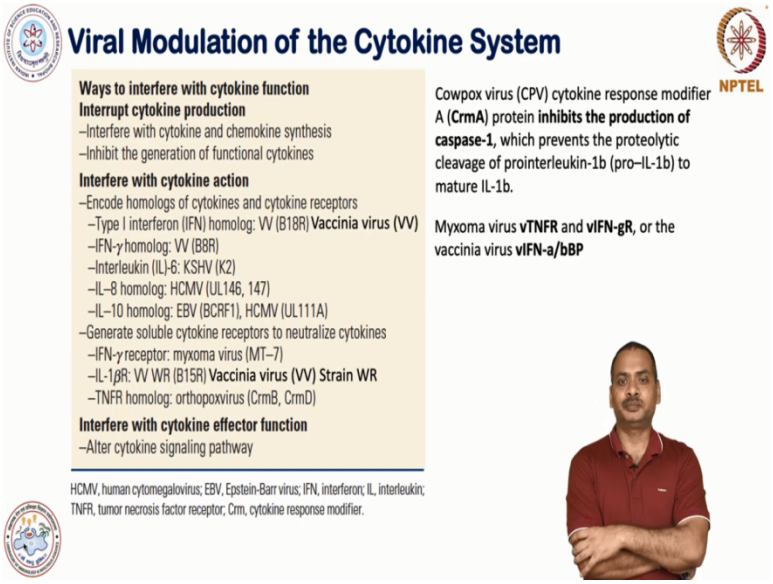

And you know that cytotoxic T cell mediated immunity is very important against the virus infection. So, viral modulation of cytokine system some of these viruses they make the homologue of our cytokine which is non-functional. So, this is again a smart way to evade the

immunity. So, where to interfere with cytokine function basically interrupt the cytokine production.

Interfere with cytokine and chemokine synthesis, they inhibit the generation of functional cytokine and interfere with cytokine action. So, here you can see that there is a some expression of a viral encoded cytokine homolog here you can see that there is a VV virus so as you can see that this vaccinia virus they produce a protein known as B18R and vaccinia virus is a you know that this is used for immunization also.

So, they this B18R protein is basically a homolog of type 1 interferon which will be non-functional. Similarly, vaccinia virus B8R protein there is another protein which is a homologue of interferon gamma you know that interferon gamma is pivotal for macrophage activation, T cell activation. So, if the wrong interferon gamma is there then the immunity will be somehow damp, KSHV makes a IL 6 like molecule a inflammatory cytokine like molecule.

HCMV there is a protein UL 146 and 147 they make a IL 8 homolog. Epstein bar virus they make some homolog of IL-10, IL-10 please remember IL10 is the anti-inflammatory cytokine. So, they make a IL10 and then that will damp the immunity. So, some of these they generate cytokine receptor to neutralize the cytokine effector effect like myxoma why does MT7 they produce interferon gamma receptor.

Again, this will sequester the interferon gamma, they will just it is like a you know~~node~~ when fighter plane one fighter plane chase another fighter plane, so the first fighter plane will make the flares because the missiles are heat seeking, so they seek the heat in order to hit the target. So, when they will release the flare so this missile will go and hit these flares and then they are protected, so something like that.

So, viruses also make these flares in like they make the interferon gamma receptor. So, that whatever interferon gamma is produced by the host cell it will not act on these viruses and it will act to these proteins and then this will be non-functional. Again, the vaccinia virus they have

some protein B15R which is like a IL 1 beta receptor. Orthopoxvirus they make a CrmB and CrmD protein which is like a TNF receptor.

So, TNF receptor you know that it is a very potent pro-inflammatory cytokine and it is needed in order to eliminate the virus. So, if this virus this cytokine will be bind with these virally encoded receptors, then the function of TNF will be not so it will not act properly. Some of this interfere with a cytokine effector function they alter the cytokine signalling pathway and, in that way, they can evade the immunity.

Here there are few more cowpox virus, cytokine response modifier, there is a protein CrmA this protein basically inhibits the production of caspase 1 and you know that caspase 1 is playing very important role in production of IL 1 beta by cleaving the pro ILR1 beta to active ~~all one bit or~~ IL1 beta or IL1 family cytokine. So, in that way they can damp the inflammation myxoma virus can also make this virally encoded TNF receptor as I have told you there is another virus.

But myxoma virus also makes this TNF receptor and they also make the virally encoded interferon gamma receptor. Vaccinia virus also makes virally encoded interferon alpha beta receptor. So, all these way by these are like a flares and that will make the cytokine which is produced by the host will be not functional against this infection.

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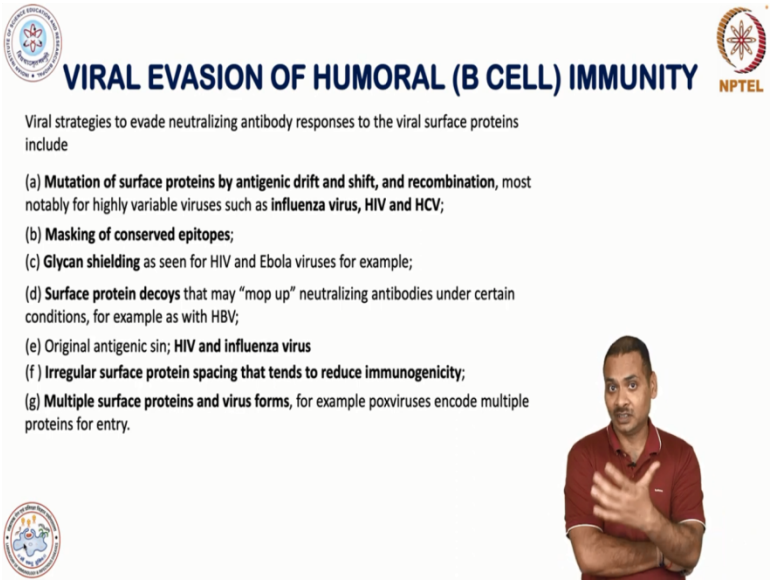

So, viral invasion of humoeral immunity, so B cell or particularly antibody responses. So, virus strategy is to evade the neutralizing antibody, so if they somehow evade the neutralizing antibody, they will win the B cells and they can establish the infection. And there are several ways by which they can do it. So, one is that mutation of surface protein surface viral protein and that we call it as the antigenic shift and antigenic drift.

I will explain you, antigenic shift and antigenic drift in subsequent session when I will discuss about the influenza virus. And there will be a genetic reassortment so in that way they can keep on changing the surface protein. So, when they will it is something like that the enemy is same but they are keeping on changing face. For example, if some different feature in person will enter in the country and if that individual will change its face, then what will happen.

They can be in the system and they can cause more fatal destruction. So, here I mean to say that so this pathogen they are keep on changing their face and they evade the immunity. And there are very good example like influenza virus HIV, HCV, hepatitis C virus. So, they are very smart in doing this thing. Masking of a conserved epitopes, so some protein on the surface they cannot afford to make a change because if they will make the change then this virus will be not functional.

So, on surface or there are some enzyme key enzymes like a polymerase. So, this polymerase if they will change then they cannot make their copies. So, what they are doing? So, they mask these very key proteins with another protein. So, in that way they can evade the immunity. Some of these viruses like HIV and Ebola virus they have a phenomena of glycan sheadetting, they remove this post-translational modification.

Surface protein decoy that may mop up neutralizing antibody under certain condition for example HBV. So, they will they will just change or make a decoy so that the antibody neutralizing antibody will not work. There is a term known as original antigenic sin and this is associated with HIV and influenza. So, what is original antigenic sin? So, for example influenza infected or HIV infected the host.

So, initially they will have a one face one surface or face you can for simplicity you can understand like that. So, our immune system will recognize that face~~phase~~ and develop the immune response in order to clear that infection. But what in the same individual after some time they will change the face and whatever immune responses or information we have that will be useless against that changed HIV the changed influenza virus.

So, in that way they can successfully evade the immunity and that we call it as a original antigenic sin. There is a irregular surface protein spacing that tends to reduce the immunogenicity. Multiple surface protein and virus form for example poly and the pox viruses encoded multiple proteins for entry. So, in some cases there will be a one protein or two proteins which plays a very important role in entering to the host cell.

But some viruses they make a repertoire. So, if one will not work other will work and in that way they can establish successful infection in the host.

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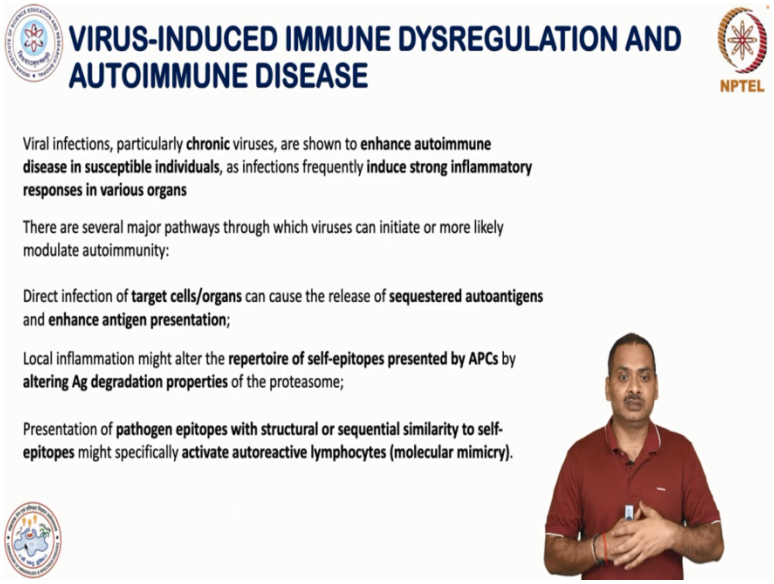

Here I am giving you some additional information you which may be surprising to you that some of these virus infections can trigger the autoimmune disease in the host. Some of this chronic particularly the chronic viral infection may trigger the autoimmune disease which is extremely bad. So, viral infection particularly the chronic virus as I told you are shown to enhance the

autoimmune diseases in susceptible individual as infection frequently induces the strong inflammatory responses in various organs.

There are several major pathway through which virus can initiate or more likely modulate the autoimmunity. There could be a direct infection of target cell or organ can cause the release of some sequestered auto antigen. So, when there is a education of our immune system after birth there are some antigen which is residing inside the cell and they never come out. But this virus infection may trigger the release of these auto antigens and that will trigger the autoimmune disease.

Local inflammation might alter the repertoire of self-epitope presented by antigen presenting cells by altering antigen degradation properties of the proteosomes. Presentation of pathogen epitope with a structural or sequential similarity. So, as you have seen that these viruses are sufficient smart to make similar protein and in some cases during infection, this similar protein can activate the immunity against those protein.

And that will cause the autoimmune disease and we call it as a molecular mimicry. So, this is all about the uh the evasion of adaptive immunity by the viruses I have discussed in a quite great length and I have also discussed how these virus infection may trigger the autoimmune disease. In next session we will talk about the influenza virus and with this I will stop here, thank you.