Host-Pathogen Interaction (Immunology)
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Lecture - 58
Innate Immunity During Virus Infection

Hi, so we have also finished major chunk of this syllabus and I think we are just left with one third part of this course. And today we will begin with this host-pathogen interaction in real sense. So, today we are going to discuss the interaction between viruses with host and you can understand that when virus infects the individual then this the innate immunity plays a very important role.

So, in today's session we will discuss about the innate immunity during virus infection. Most of things you are aware but all those points which you are aware I will quickly move through so that you will have a better understanding that during virus infection what is happening you can put it in correct perspective. So, let us begin this session

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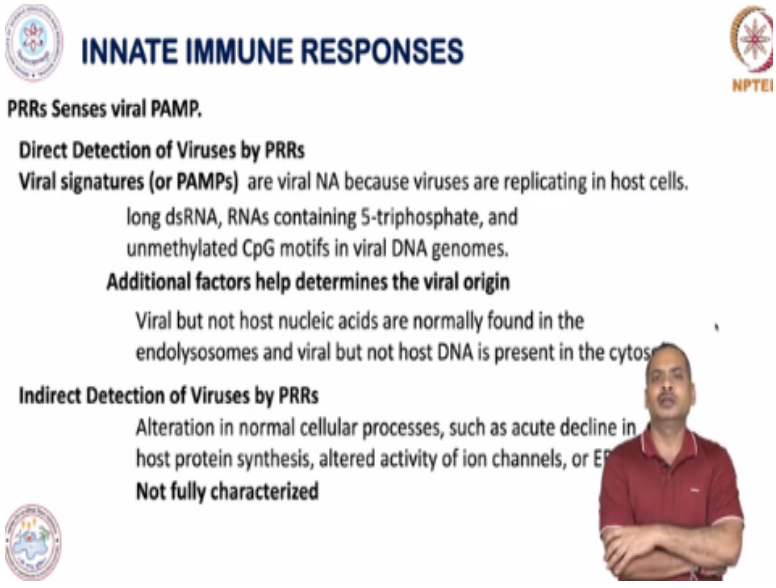

So, you know that there are varieties of innate immune component, you probably remember the previous session when I have discussed innate immunity. And there are several component of innate immunity as I can tell you again. So, first is the physical barrier another is chemical

barrier or biochemical barrier there is a microbiological barrier. There are cellular component and humoeral component.

So, here I will mainly focus on the cellular component and I will focus on how the virus is recognized. So, when we talk about the recognition of microbial pathogen in that scenario, we discuss about this pattern recognition receptor. And since this the biochemical barrier which is consists of variety of enzymes and all those things. This is mainly common for most of microbial infection. So, I am not going to talk about that.

And in humoeral component there are you know that there are complements and there are some antimicrobial peptides. So, complements do play an important role against virus infection. They basically the complement get activated against enveloped virus and they can disrupt those viruses. So, I am also not going to talk about the complement and I will straight away move to the cellular component.

Even I will not discuss about the microbiological barriers that is not so unique in case of virus infection. However, there is a pattern recognition receptor and the sensing of this virus in various compartment of the cell that is a very important. And the kind of responses they are inducing during virus infection that is also very important. So, here we will see some of the viruses which are sensed by various PRR.

So, here we will try to understand what component of which virus is sensed by a particular PRRs. So, first I will take you in general innate immune responses and then we will as we move on the pattern recognition receptor along with viruses you will understand that. These viruses are sensed by these PRRs. So, PRRs senses the viral PAMPs and these viral PAMPs are various it could be a nucleic acid, it could be a protein of the virus.

And this sensing and the detection of the virus are could be the direct sensing of the virus. And another way is that it could be sensed indirectly. So, now let us first discuss about the direct sensing of viruses by pattern recognition receptor. So, what are the signatures are you know that

the viral nucleic acid is a key signature of viruses. Because virus replicate in the host cells and since it is replicating in the host cells.

So, these nucleic acids are present inside the cell in general condition in healthy living cell, thise nucleic acid is not present in the cytoplasm or some unique location. For example, endosomes or endolysosomes. But during virus infection these are basically present in these positions. And this nucleic acid is quite different compared to the host nucleic acid that I have discussed earlier in previous session.

So, the long double standard RNA, RNAs containing 5-triphosphate and unmethylated CpG DNA from DNA viruses which is mainly present in the DNA virus and in case of DNA viruses the genomes is DNA which is quite obvious. In addition, so these are the signatures long double standard RNA which is not usually present in the healthy living cells. The triphosphate containing RNA that is also not present the hypomethylated DNA is also not present.

So, these are the unusual distinguishing feature and that is why we call it as a clampsPAMPs. Additional factors also help in determining the nucleic acid is from viral origin. As I told you viral but not host nucleic acid are normally found in endolysosomes. So, generally in endolysosomes the viral origin nucleic acid are present. So, this location is also is a trigger for the activation of antiviral responses after recognition of this nucleic acid in particular location.

So, here you can see that there is an endo-lysosomes and there are some PRRs that will sense and then that will induce. And viral but not host DNA is present in the cytoplasm so this is also unusual location of nucleic acid. There is a indirect detection of virus by pattern recognition receptors and this indirect recognition of virus in is basically you know that viruses hijack the host cellular machinery.

And when they hijack and when they make their own copies then the cell are under stress. And then there will be a stress responses so that what I want to highlight. So, this is also sensed by the PRRs and when this is sensed in general the cell trigger their own death that we call it as a

program cell death. So, here again I would like to say that alteration in normal cellular processes of course because they viruses hijack the host cellular machinery.

Such as acute decline in host protein synthesis suddenly when there is a virus infection there will be an almost no synthesis of host protein that is a stress. Altered activity of ion channels and ERS stress so that will also result to the ERS stress because you know that protein is a synthesized over ERS endoplasmic reticulum. So, there will be a massive synthesis of viral origin protein and that also cause the ERS stress.

Alteration in ion channels you can understand so basically the virus skews the cell machinery for its own benefit and since it is taking too much benefit. So, cell also senses those things. So, these are the indirect sensing of virus by PRRs. However, it is not very well characterized still it is a very active research area. So, people are trying to understand how this is what is the molecular mechanism of all this thing.

Although we know the phenotype and end effect. When virus is infecting there will be a cellular stress and that stress cell, undergo the cell death. So, this is known but the precise molecular mechanism is not very well understood.

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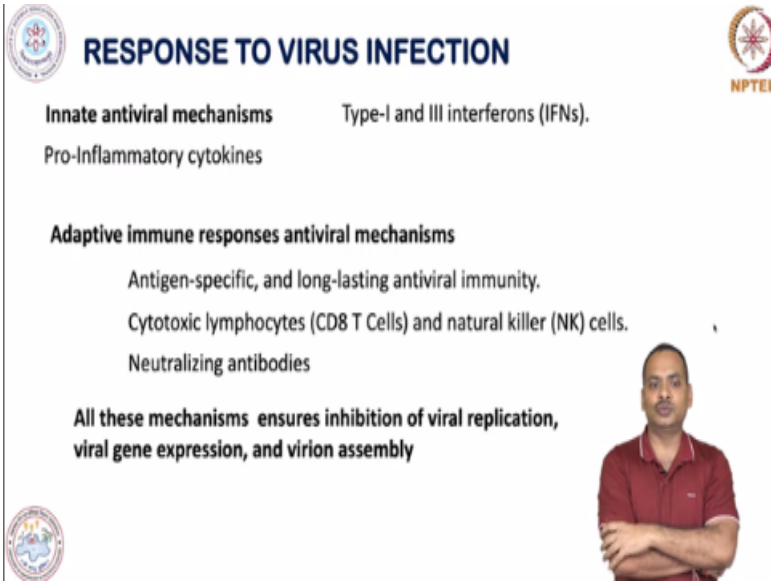

So, responses to the virus infection I have discussed earlier but I will quickly go through so that you will put it in this perspective during virus infection this is happening. So, there is a innate antiviral mechanism and you know that there is a production of type 1 and type 3 IFNs which is one of key thing. Another is production of pro-inflammatory cytokines and in addition there is a one more innate immune response is there that is cell death, apoptosis, proptosis.

So, these are the key innate immune response against virus infection production of this type 1 and type 3 IFNs, pro-inflammatory cytokines and cell death. That is also productive response I have explained you earlier. Of course, when the virus is not cleared by innate immunity that will trigger the adaptive immunity, we have discussed earlier. And this is basically the generation of antigen-specific long lasting antiviral immunity which is mainly mediated by Cytotoxic T cells which is CD8 T cells.

Here there is a involvement of natural killer cells which we consider it as a innate immune cell. So, natural killer cell and cytotoxic T cell basically they kill the virally infected cells. So, now you can understand the one of the outcome of protective responses is production of these interferons and pro-inflammatory cytokine and the cell death that is also protective response. There will be a generation of neutralizing antibodies.

There are the lot of antibody will be generated which will basically mask the viruses. They so antibody can coat these viral particles and then this will be phagocytose this is a one way they can coat those molecules which is basically needed for attaching with the target cells. If the antibody will be there on that molecule which is basically needed for the attachment to the target cell that will so once the antibody will bind over there then they are not able to combined with the target cells.

So, this is the way by which neutralizing antibody works. So, all these mechanisms basically all this is state ensures the inhibition of viral replication, viral gene expression and virion assembly. So, these are basically checking points.

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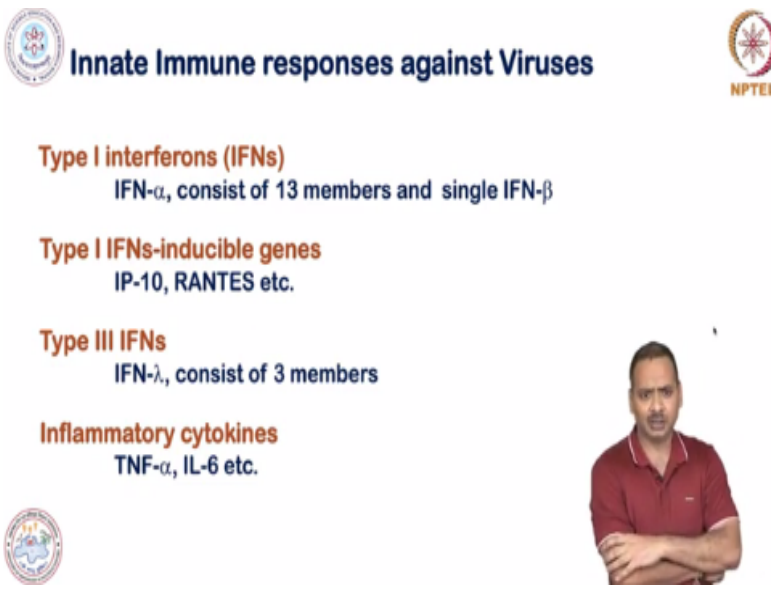

So, now I will quickly show about the innate immune response against viruses here you as I told you there is a type 1 interferons which is basically consists of interferon alpha it has 13 members and there is a one interferon beta members. There is a type 1 interferon inducible gene. So, when this type 1 interferon is produced in a reasonable amount then that will trigger the interferon inducible responses and these responses are basically triggered by interferon inducible genes.

There are just few examples but this is a hundreds of gene. One is that IP-10 and RANTES there are so many chemokines and all those things are there. There is a type 3 interferon it is basically consists of interferon lambda and there are three members. So, they are also playing very important role in checking the viral replication. Inflammatory cytokine, there are so many inflammatory cytokine like TNF- IL6, IL1 beta so and so on.

So, all those things basically you know that type 1 interferon is basically checking the viral replication and inflammatory cytokines basically they are kind of alarm system in the body. They produce and then they trigger the alarm in order to recruit the more professional killer cells at the site of infection. So, this is an all this response and there is a trigger of cell death and cell death is a triggered by various other PRRs mainly it is those PRRs are derived from NLR member.

Where AIM2 is also coming in picture. I will discuss in a subsequent slide. Here I will show you the how this type 1 interferon and inflammatory cytokine works I will quickly show which is very easy to understand.

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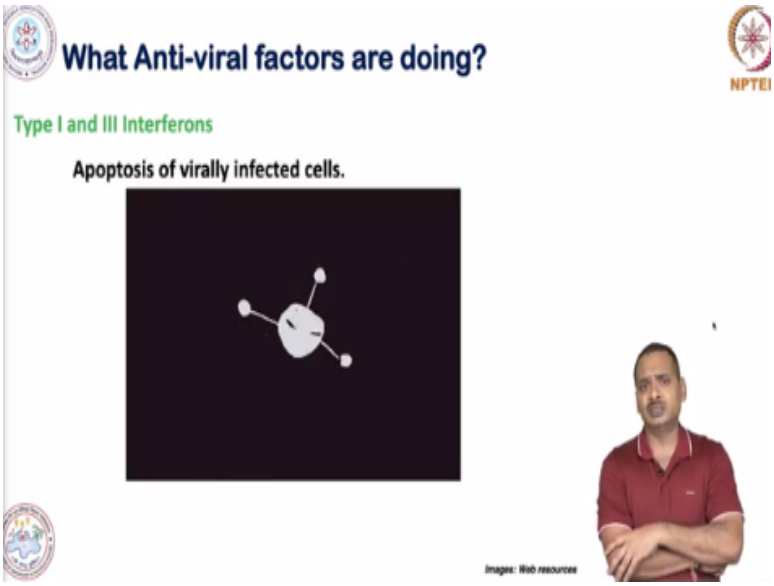

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So basically type 1 and type 3 interferon induces apoptosis~~bove tosses~~ of virally infected cells that is one of key innate immune response against viruses.

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Making healthy cells resistant from the virus infection.

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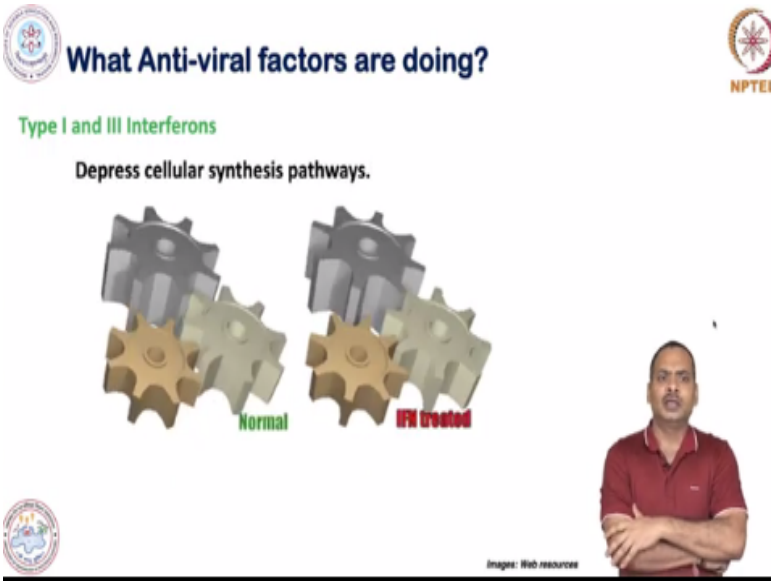

They ~~D~~depresses the cellular synthesis pathways that when if you treat the cells with a type 1 interferon there will be a decline in a metabolic pathways in the cells. That is why they are also act as an anti-proliferative and it is used in some in treatment of some cancer.

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They prepare and activate professional immune cells for development of viruses specific immunity. So, whatever common immune response if it is not able to clear then they will start generating specific immunity which is mainly taken place by B cells and T cells.

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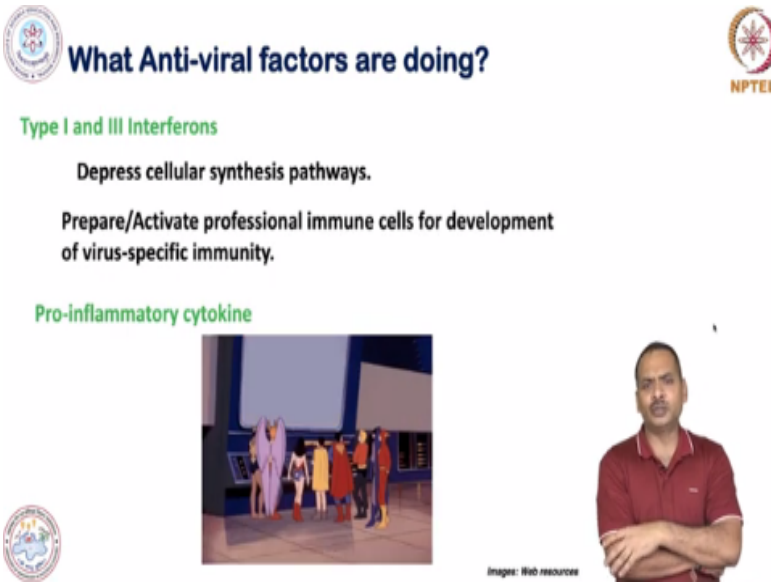

Inflammatory cytokine is kind of alert system and this when this inflammatory cytokine will be produced then there will be a recruitment of immune cell at the site of infection. It could be systemi~~sedc~~; it could be localized.

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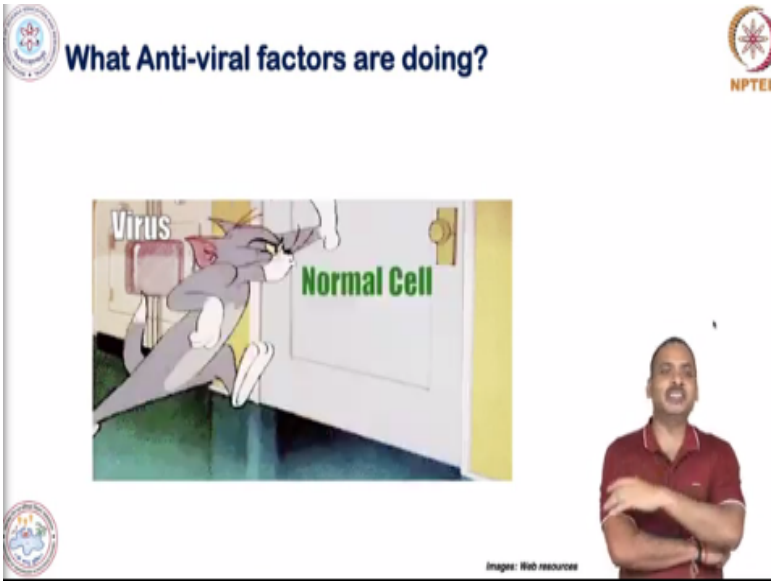

So, here I am just depicting probably you like that here you can see there is a normal situation and in normal situation there is a virus infection. So, this virus is basically dominating over the host. But once the there is a virus infection this virus basically sensed by our cells and then there will be a production of type 1 interferon. And when there is a sufficient amount of type 1 interferon the situation will be absolutely upside down.

Here you can see that there is a heightened immunity after the production of type 1 interferon and which will easily take over the virus and the individuals start becoming a healthy. So, this is for quick understanding and you will remember for your rest of your life because this cartoon kind of presentation will be much more easily rememberable.

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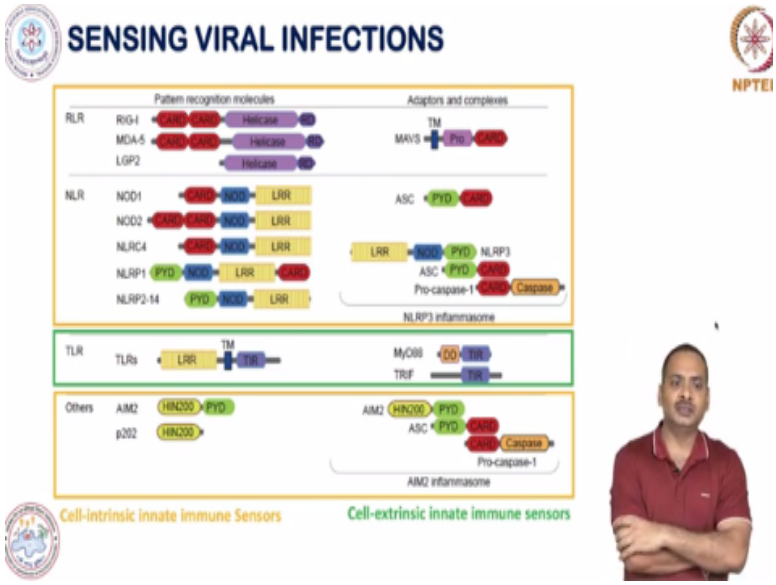

So, now I will take up you what are the various specific senses for the viruses. Here you can see that there are RLR pathways, NLR pathway, TLR pathway and there are some another. So, here you can see that there are cell-intrinsic innate immune sensors and these are the basically RLR, NLR and there are some another sensor which is consists of AIM2 and p202. And there is a some cell-extrinsic innate immune sensors basically it is consist of TLR.

Here you can see that TLR is a playing a very important role in recognition of a virus or viral signatures over the cell membrane and endosomes.

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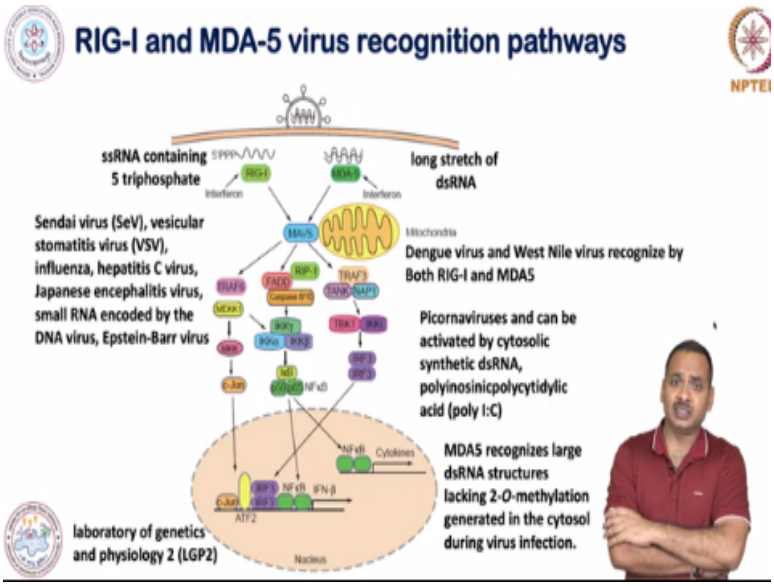

So, I will take you to each one quickly. So, first is RIG-I and MDA-5 which is playing a very important role in virus recognition. So, here you know this RLR pathway I am just showing you again so RIG-I ~~regard~~ basically senses 5 prime triphosphate you are very well aware. Here this is new information besides a Sendai and VSV they can sense the influenza virus, hepatitis C virus, Japanese encephalitis virus and this can also sense the small RNA encoded by DNA viruses such as a Epstein-Barr virus.

So, Epstein-Barr virus is a basically a DNA virus and during replication they make a small stretches of RNA and this small stretches of RNA can be sensed by the RIG-I ~~guide~~. So, you can understand that the RLR pathways are very important against not only for virus RNA virus infection but it plays a also important role in recognition of DNA viruses indirectly. You know that MDA-5 also senses the RNA molecule basically the sense is long stretches of double standard RNA.

And they can sense the dengue virus MDA-5 can sense ~~oncerns~~ the dengue virus, west Nile virus and basically these two sensors basically RIG I and MDA-5 basically senses these viruses and dengue as well as west Nile Virus. MDA-5 basically senses the picornaviruses and can activate cytosolic synthetic double standard RNA, I have told you previously if you introduce the synthetic poly~~-~~ IC ~~-see~~ inside the cell then that will mimic like a virus infection and it is mainly sensed by the MDA-5.

MDA-5 recognizes large double standard RNA structure which is basically lacking 2 O methylation. 2 O methylation is needed generated in cytosol during the virus infection. I have discussed about the LGP2 molecule basically this potentiate the RIG I and MDA-5 mediated signalling originally it was discovered as a negative regulator. But the physiological studies reveal that this is basically potentiating the RIG-I and MDA-5 recognition pathway.

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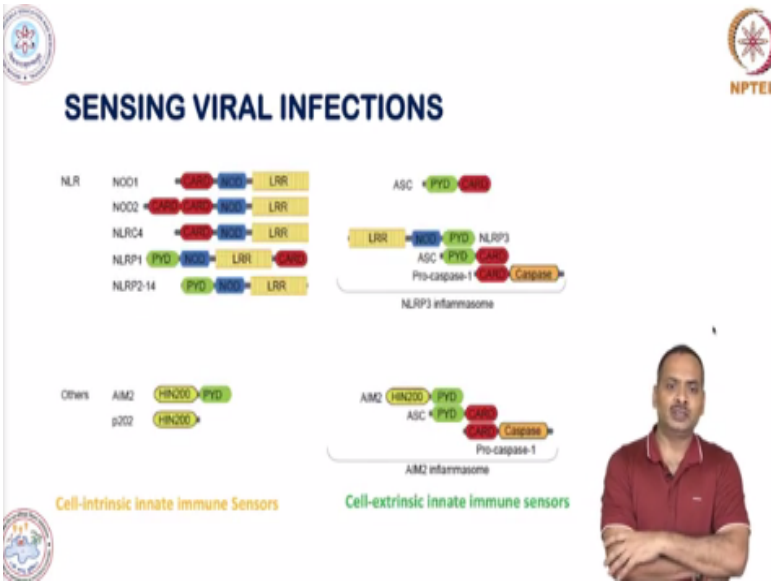

So, sensing of a viral infection now we will discuss about the NLR and others that is AIM2 and p202. So, this is basically you can see that there is in AIM2 there is a domain known as HIN200 domain and there is a pyriene domain in case of AIM2 and in p202 there is only HIN domain. Basically, this domain is binding with the DNA molecule and upon binding this makes a one multi-protein complex which we call it as an inflammasome which I will discuss in subsequent slide.

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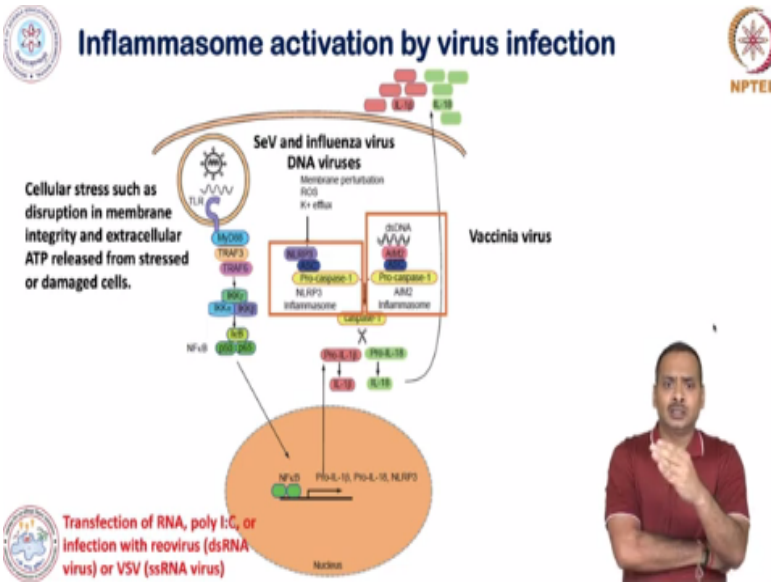

So, here you can see that there are various kind of inflammasome there is a NLRP3 inflammasome which can be activated by various PAMPspam and there is AIM2 inflammasome. Cellular stress such as disruption of membrane integrity and extracellular ATP release from stress cell so you can understand that when the other cells are under stressed which is already infected and when these cells is under stress, they will release the ATP.

And this ATP can be sensed by this NLRP3 inflammasome and then that will induce the production of IL-1 family cytokines which is consist of IL-1 beta, IL-18, IL-33, ~~(()) (25:11)~~. Sendai virus and influenza virus they can also activate the NLRP3 inflammasome besides this the DNA viruses can also activate the NLRP3 inflammasome. So, DNA virus is basically not only activating the NLRP3 inflammasome but it also activates the AIM2 inflammasome which is AIM2 can bind with the DNA molecule.

And upon this activation there will be a production of IL-1 family cytokine. You can activate this inflammasome by transfection of RNA, poly I:C which mimics like a virus infection and there is a RNA from Reio virus and VSV. So, these can activate these inflammasome. DNA sensor or aim to inflammasome can also activated by the vaccinia virus.

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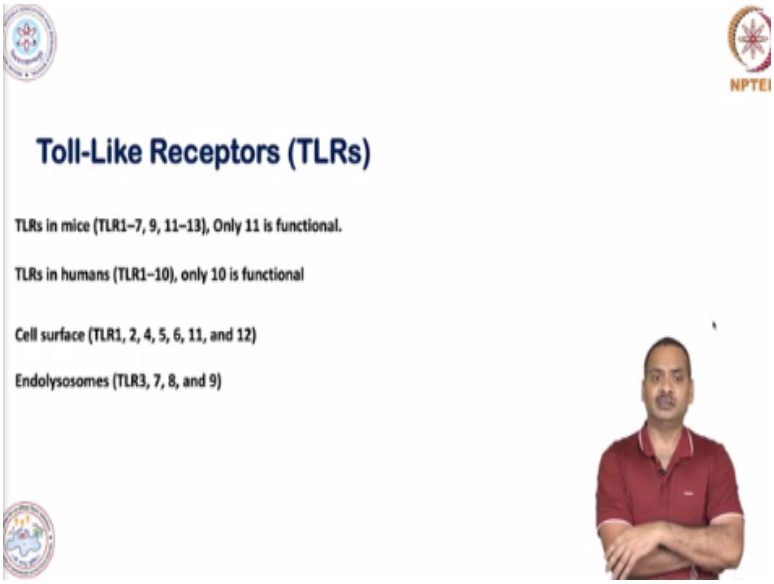

Now I will take you to the TLR which we have discussed in mice there are these TLRs are present TLR1 to 7, 9, 11 to 13. So, only 11 TLRs are functional in human there is TLR1 to TLR10 and only 10 functional TLRs are present in humans. Some of these TLRs basically expressed on the cell surface like TLR1, 2, 4, 5, 6, 11 and 12. And in endosomes there are four major ~~L~~TLRs which is present that is TLR3, 7, 8 and 9.

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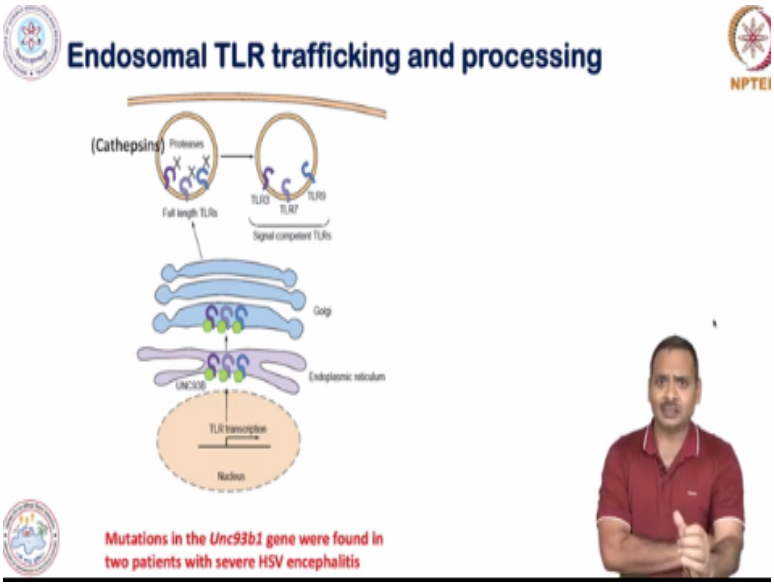

So, endosomal TLR trafficking and processing. So, there is a one very important molecule which I have not discussed during TLR in previous session. But there is a one very important molecule is there which we call it as a UNC93B. So, here there is a UNC93B so this molecule is basically

expressed over the endoplasmic reticulum. And this is very much needed in order to take this newly synthesized TLR3, 7, 9 to the endosomes.

If you delete this gene the TLR3, 7, 9 will be not translocated into the endosome or endo lysosomes and I think I have explained you these TLR do not sense the PAMPs directly before sensing they undergo proteolytic cleavage by family of proteases which we call it as a cathepsins. So, if there is a mutation in this molecule that is UNC93B1 then there will be a severe HSV encephalitis will happen.

And this severe infection is a quite complicated to control, so you can understand there is only two patient we so far, we know maybe more will be there. And if there is a mutation in this gene then this will hamper the all TLRs which is translocated into the endo-lysosomes.

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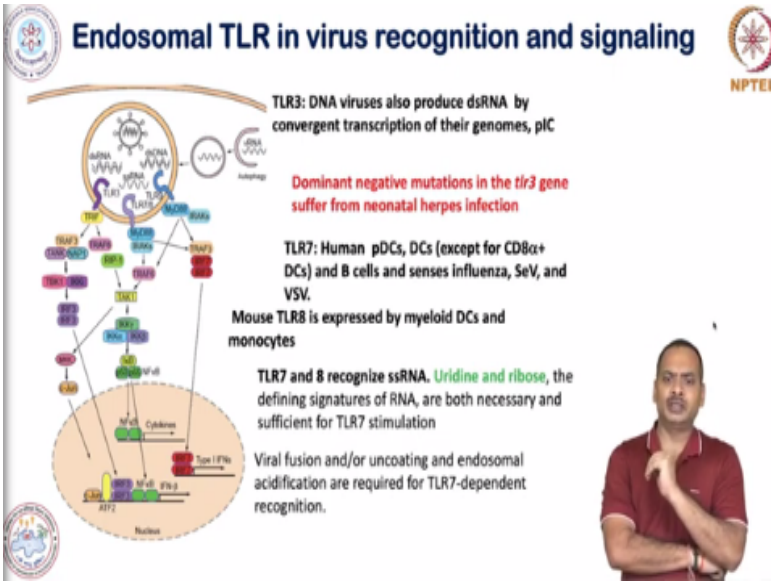

Endosomal TLR in virus recognition and signalling I will talk now this. So, there is a TLR3, 7, 8 in case of human and TLR9. So, TLR3 basically plays a very important role in sensing DNA viruses also and these DNA viruses basically produce double standard RNA by convergent transcription of their genomes. What do you mean? So, there will be a two promoters will be there and this promoter can since it is present on two different strand,

So, this can make a RNA molecule and that RNA molecule eventually become a double standard RNA molecule and this double standard RNA molecule will sensed by the TLR3. So, there is a study that the dominant negative mutation so not functional you can understand dominant negative that the TLR3 will be not functional for time beinging. Suffer from neonatal herpes infection. Herpes is a DNA virus but if there is a mutation in this TLR3 then that will result to this neonatal herpes infection.

TLR7 so Human pDCs and DCs basically express this TLR7 and B cells also and here basically TLR7 sensed since the influenza Sendai virus and VSV. Mouse TLR8 is expressed by myeloid DCs and monocytes. TLR7 and 8 recognizes single standard RNA and the recognition component is uridine and ribose is a sensed. So, both this uridine and ribose is needed for sufficient stimulation of TLR7.

Viral fusion and or uncoating and endosomal acidification is required for TLR7-dependent recognition. TLR8 deficient mice develop autoimmunity due to hyperstimulation of TLR7. These are some additional point about these TLRs which is more specific to the viruses.

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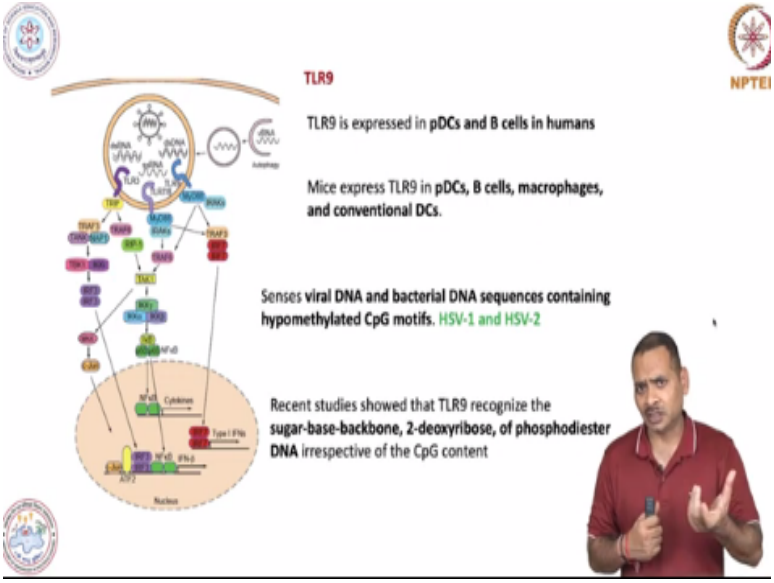

There is a TLR9. So, TLR9 is basically expressed in pDCs and B cells in humans and mice expresses TLR9 in pDCs, B cells, macrophages and conventional DCs. And senses the viral DNA and bacterial DNA TLR9 if you remember TLR9 senses CpG region in DNA which is

hypomethylated. So, senses viral DNA and bacterial DNA sequence containing hypomethylated CpG motifs there is example there is derived from HSV-1 and HSV-2.

And recent study showed that TLR9 recognize the sugar-base-backbone, 2-deoxyribose of phosphodiester DNA irrespective of CpG content. So, this is a more deeper insight for recognition of the DNA in case of TLR9. So, we were thinking that CpG motifs is sensed but this may be also true that this sugar-base-backbone and 2-deoxyribose of phosphodiester DNA is the key component which is recognized by the TLR9.

So, with this I am stopping here and in next session I will talk about the some interferon independent mechanism and in that session I will discuss about some of my work also and I hope you will like that how these interferon independent processes are also playing very important role in controlling the virus infection. Thank you.