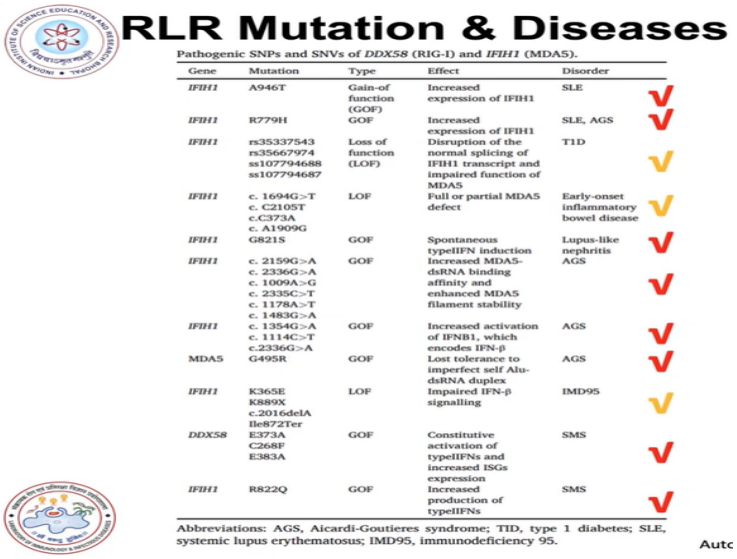
Host-Pathogen Interaction (Immunology)
Prof. Himanshu Kumar
Department of Biological Sciences
Indian Institute of Science Education and Research, Bhopal

Module No # 08
Lecture No # 39
Pattern – Recognition Receptors –RLR Associated – Diseases and Therapeutics

Hi, so in previous session we have learnt about the RLR and if you remember then you may remember that we discussed the discovery of RIG-I which is a very important discovery. And we have also learnt the basis of this RIG-I discovery and then we have discussed various members of RLR family protein or sensor that is RIG-I MDFA5 and LGP2. We have discussed lot about the various ligand and these ligands are both we have discussed some viruses.

We have discussed some artificial ligand and then we have discussed about RLR signaling pathway and I also showed you the complexity of this pathway. So this pathway is RLR pathway the RIG-I or MDAF5 mediated signaling is quite complex. So in this session we will discuss this RLR associated diseases and there are some application of this RLR ligand in therapy. And we will also discuss expression of RLR or expression of RIG-I and it is association with some disease so you will see everything in subsequent slides.

(Refer Slide Time: 02:08)



So here there is the list of mutation if you see this slide there are so many mutation and if you see carefully then you will find out some mutation result to the gain of function means some mutation result to the much more activation of these sensors. So it means much more

activation of this sensor means more signaling and more effector responses. So that is also pathogenic if you remember the previous session if this homeostasis somehow skewed to more this thing more responses are there then that is also a pathologic condition.

And if it is there is a underproduction or there is a less activation of signaling that is also result to the disease. So these mutations are basically here whatever you are seeing they are divided into 2 major component one is the gain of function that is too much activation of signaling pathway. And that result to the disease and there is a loss of function so there are some mutation which basically reducing the RLR signaling pathway.

And subsequent effector responses and that is also cause the disease so let us first take up the gain of function. Here you can see there is a mutation that is A946 this A is converted to the T and that result to the gain of function and that will basically enhance the expression of MDAF5. And enhanced expression of MDA5 somehow result to the more production of pro-inflammatory cytokine as well as type 1 interferon which is a characteristic feature of SLE systemic lupus erythematous.

There are other there mutation that is R779H that is also increases expression of this MDA5 and if you see there is another mutation that is G821 this is amino acid. This G Glycine is basically converted into the serine and that will also cause a lupus like ~~Nephtiris~~Nephritis. There is another mutation and this there are so many mutation associated this is a DNA level and here you can see that this mutation which is like this is 2159 position this G is replaced by A and so on.

And basically, this increases the MDA5 DNA double standard RNA binding affinity and enhances the MDA5 this stability the complex and then that will basically activate the signal more and then that result to the various diseases. In morning session or in previous session I have discussed a disease known as Aicardi-Goutieres syndrome. So basically that result to this disease these list of mutations.

There is another mutation which is again so this a Aicardi syndrome basically associated with so many mutation in MDA5 this is quite well documented and I have gone through this literature and then I found out that there are so many mutations which is associated with this disease. There is another gain of function which again result to the AGS and there is an another disease which is associated with RIG-I here you can see DDX 58.

So DDX 58 is basically a RIG-I and this if you remember the previous session I have told there is a mutation in RIG-I and MDA5 and that result to a disease. This is singleton syndrome if you remember previous session and over there is a constitutive activation of this type 1 interferon and ISG expression. So ISG is basically depending on the interferon if there is more interferon then there is a more expression of interferon stimulated gene.

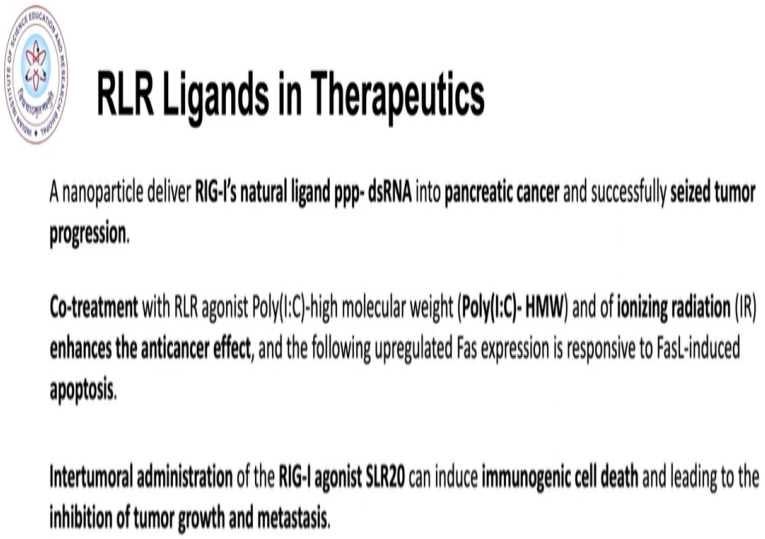
So this interferon stimulated gene and this basically cause a disease condition and please note one thing that if there is a persistent increase in type 1 interferon then that will basically result to the a pro-inflammatory condition in the host and that will be a disease condition. So another mutation which is associated with MDA5 and that result to the singleton syndrome is again it is having some mutation and this mutation is result in increased production of type 1 interferon.

Please note that in SLE also there is a lot of production of this inflammatory cytokine and type 1 interferon's. And here again I would like to mention one very important point so these disease condition eventually when we said that this is a disease try to understand it is not based on single change in general there are multifactorial. There are several factors and that result to the disease otherwise it will be a not full blown disease.

So here you can see this AGS and SMS this singleton syndrome this is caused by multiple mutations. There is a some disease which is associated with loss of function here you can see in MDA5 mutation some of these mutation basically result to the destruction of normal splicing of MDA5 transcript and impaired the function of MDA5. And that result to the type 1 diabetes and there is another mutation which is associated with MDA5 that will cause early onset inflammatory bowel disease.

And there are few more mutations some deletions are also there and that will cause a impaired interferon beta signaling and that will be also a disease condition which is basically immune-deficiency 95. So these are the some mutation which is associated with the disease and these mutations are basically in RIG-I and MDA5.

(Refer Slide Time: 10:08)



Now I would like to discuss about the some of ligand which activates Rig-I and MDA5 they are also used as a therapeutic. So here you can see that there is a RLR agonists and this RLR agonist basically in previous session I have told you that there is a poly IC it is a polymer of inocsine and Cytoidine. And if we introduce inside the cell then it will mimic like a virus infection and it will activate the RIG-I or MDA5 depends on the molecular weight of the poly IC.

This is a basically polymer so this poly IC and 5 prime triphosphate double standard RNA. If you remember this is a RIG-I ligand and the stem loop RNA 14 and there is a one more ligand M8 which I will tell you what is M8 in subsequent point. This basically induces cancers cell apoptosis and basically it enhances the antitumor immune response. So this; ligand if you see they basically potentiate our host immunity in order to clear or eliminate the transformed cell or cancerous cell.

So M8 is basically a RIG-I agonist it is a uridine rich hairpin 5 prime triphosphate RNA and basically it is composed of 99 nucleotide and it induces immunogenic cell death. So immunogenic cell death is a new concept it is not very new but this is a reasonably new concept. Immunogenic cell death is basically it is a kind of cell death or apoptosis which releases that DAMPS and what is DAMP?

DAMP is a damage associated and molecular pattern so this damage associated molecular pattern when it is released then this is again activate the immune system. And this; activated immune system basically clear or basically eliminate those transformed cells. So M8 is you can understand this is a ligand for RIG-I and it induces the immunogenic cell death. And in

that way the tumor can be cleared there is another ligand which is again RIG-I agonist this is SLR 14.

And this is a powerful immuno-adjuvant and it induces robust anti-tumor activity so this anti-tumor activity is when it is enhanced a lot then this will obviously this will clear the transformed cells. Another is so people made some nanoparticle and these nanoparticles are loaded with RIG-I ligand that is triphosphate double standard RNA and it is shown that this nanoparticle which is loaded with RIG-I ligand.

They put it in the cancer cell and they can cancer of pancreas or pancreatic cancer they put it in those patient and they found out that this seizedees the tumor progression basically they stop or significant stop the tumor progression. In addition you know that cancer is treated by several ways one is chemotheraphy where they use the cytotoxic drugs which kills the fast dividing cells.

People also or doctor also uses the ionizzing radiation so it has been shown that the co treatment of this RLR agonist that is a poly IC along with this ionizing radiation. So this poly IC is basically high molecular weight so most likely this binds with MDA5 or activate MDA5 mediated signaling. They found out that when they give this poly IC along with ionizing radiation then this enhances the anti-cancer effect.

And this anti-cancer effect is basically this triggers the apoptosis of these cancerous cell and this is basically this is happened due to the up regulated fast expression you probably aware about the fast and fast ligand. And that this fast and fast ligand pathway result to the apoptosis people also showed that there is a inter-tumoral administration of RIG-I ligand if you introduced this RIG-I ligand in solid tumor.

Then this will also cause the immune-genic cell death and leading to the inhibition of tumor growth and metastasis. So intertumoral administration if you remember there is a colliey toxin and he also introduced the cocktail of bacteria and he could successfully treat many people using this cocktail of bacteria. And eventually their name that toxin becomes a colaey toxin.

(Refer Slide Time: 16:27)

So these are some of RLR ligand in therapeutic now I will also tell that there is a some changes in RLR or some molecules which is involved in RLR signaling pathway result to the development disease and we call it as immune-pathogenesis. So if the individual is as I told you previously the individual is prolonged exposed with RLR ligand that results to the production of type 1 interferon. So that can lead to the anti-inflammatory response and inappropriate use of this RLR agonist may result to the out of control inflammatory disease.

So this is quite important so whatever ligands are used they should be used appropriately and monitored appropriately. So another is that there is a high Rig-I expression is associated with ovarian cancer. So it is has been reported that the ovarian cancer is having the high expression of RIG-I I do not know that more details whether it is well proved it or not. But I have found out in the literature so with this I will stop thank you.