Host-Pathogen Interaction (Immunology)
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Module No # 09
Lecture No # 44
Pattern – Recognition Receptors –DNA Sensor & Diseases

Hi, so in this session we will discuss about the various diseases associated with the DNA sensor some are reported not too much information is there. But whatever it is reported I will discuss with you. And there are some molecules which is used in therapeutic.

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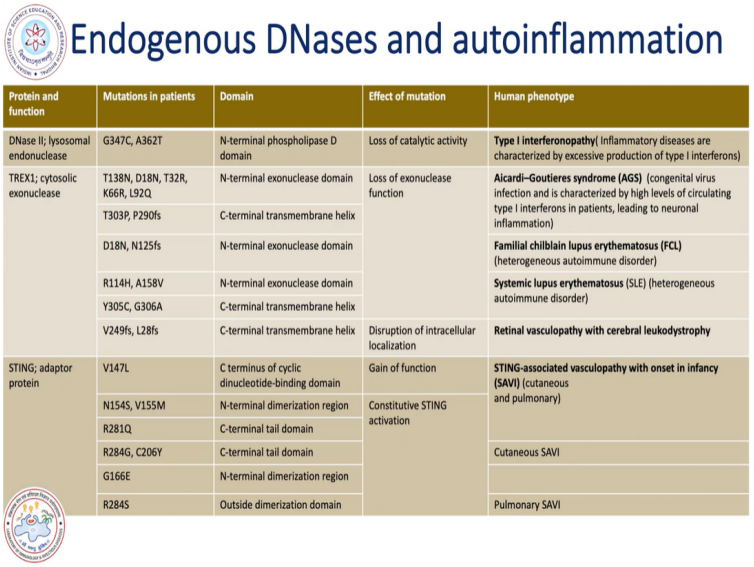

Protein and function	Mutations in patients	Domain	Effect of mutation	Human phenotype
DNase II; lysosomal endonuclease	G347C, A362T	N-terminal phospholipase D domain	Loss of catalytic activity	**Type I interferonopathy**(Inflammatory diseases are characterized by excessive production of type I interferons)
TREX1; cytosolic exonuclease	T138N, D18N, T32R, K66R, L92Q	N-terminal exonuclease domain	Loss of exonuclease function	**Aicardi–Goutieres syndrome (AGS)** (congenital virus infection and is characterized by high levels of circulating type I interferons in patients, leading to neuronal inflammation)
	T303P, P290fs	C-terminal transmembrane helix		
	D18N, N125fs	N-terminal exonuclease domain		**Familial chilblain lupus erythematosus (FCL)** (heterogeneous autoimmune disorder)
	R114H, A158V	N-terminal exonuclease domain		**Systemic lupus erythematosus** (SLE) (heterogeneous autoimmune disorder)
	Y305C, G306A	C-terminal transmembrane helix		
	V249fs, L28fs	C-terminal transmembrane helix	Disruption of intracellular localization	**Retinal vasculopathy with cerebral leukodystrophy**
STING; adaptor protein	V147L	C terminus of cyclic dinucleotide-binding domain	Gain of function	**STING-associated vasculopathy with onset in infancy (SAVI)** (cutaneous and pulmonary)
	N154S, V155M	N-terminal dimerization region	Constitutive STING activation	
	R281Q	C-terminal tail domain		
	R284G, C206Y	C-terminal tail domain		Cutaneous SAVI
	G166E	N-terminal dimerization region		
	R284S	Outside dimerization domain		Pulmonary SAVI

So let us begin with disease there are some endogenous DNAase~~'s~~ and inflammation. So as I told you the DNAase ~~is~~ 2 in previous session I discussed about the DNAase~~'s~~ 1 and DNAase~~'s~~ 2 so D is DNAase~~S~~ 2 is present in extra cellular space. So and it is also present in lysosome there you know that lysosome has a variety of hydrolysis. So DNAase 2~~'s~~ is present in lysosome and there are some mutation associated with this DNA~~'s~~ase 2 as you can see in this slide there are G is changed to the 3 and G changed to C at 347 and A changed to the are mutated to the 362.

And that basically this mutation is present in N-terminal phospholip~~h~~ase D domain and there will be a loss of catalytic activity. And the phenotype in human is there will be a type 1 interferonopathy that is a inflammatory disease characterized by excessive production of type 1 interferon. If you remember the previous session when I was discussion about the RLR at

the time also I told that if there is a persistent production of type 1 interferon then that result to the disease and that diseases there will be a generalized inflammatory condition.

So the similar thing is happening in this case also if there is a mutation in DNAase~~'s~~ 2 then that will cause the over production of type 1 interferon. TREX~~ricks~~ 1 which is basically a cytosolic exonucleases and this molecule is quite well characterized as you can see that there are so many mutations are reported. And if you see there are 2 major groups of mutations and one group of mutation is basically associated with loss of exonucleases function.

And this loss of exonucleases function basically result to the various congential diseases like Aicardi-Goutieres Syndrome and if you remember a Aicardi-Goutieres Syndrome or AGS it is also associated with MDA5 in previous session when I was discussing RLR I have discussed. And this is basically characterized by high level of or high amount of type 1 interferon in patient.

And basically, this leads to the neuronal inflammation and some of the mu~~no~~tation as shown in this table that result to the development of other disease that is familial~~;~~ chill~~;~~ blend~~;~~ lupus eryhtromatous this is FCL. It is a heterogeneous auto-immune disorder and mutations also result to the development of systemic lupus erythematous. And now you are aware after going through all; this course you might be, understanding that one disease can be happen by multiple things SLE can happen by various ways.

And if there is a~~m~~ mutation in ~~tricks~~TREX1 also that result to the SLE it is a auto-inflammatory or auto-immune disease which is inflammatory in nature. And there is a; various category of SLE so since I am not clinician I am not the right person to explain various categories of SLE based on the symptom. Another mutation which you can see that there is some frame shift mutation.

And this mutation result to the disruption of intracellular localization of his protein and that result to the retinal vesiculopathy with cerebral leukodystropy. So I do not know much about this disease so clinically I am incapable to explain this disease but this result to this disease. There are various mutation associated with a STING which plays a very important role in DNA sensing pathway. It acts as adopter for various molecule you have seen that it is adapter for ~~CJ~~cGMP it is adapter for IFI16.

And there are various mutation and these mutation can result to the gain of function as you can see in this table. There is a gain of function and there is a condition which is a disease condition that is STING as associated vesiculopathy with onset in infancy in short it is also SAVI. So this result to the SAVI which; is basically affecting the cutaneous and pulmonary region.

There is various conditions which is happening due to the constitutive activation of STING molecule and that can result to the various kind of SAVI that is Cutaneous as well as pulmaunary SAV. So these are some disease whichthat is associated with DNA sensing pathway the mutation which is present in those molecule which are involved in DNA sensing pathway.

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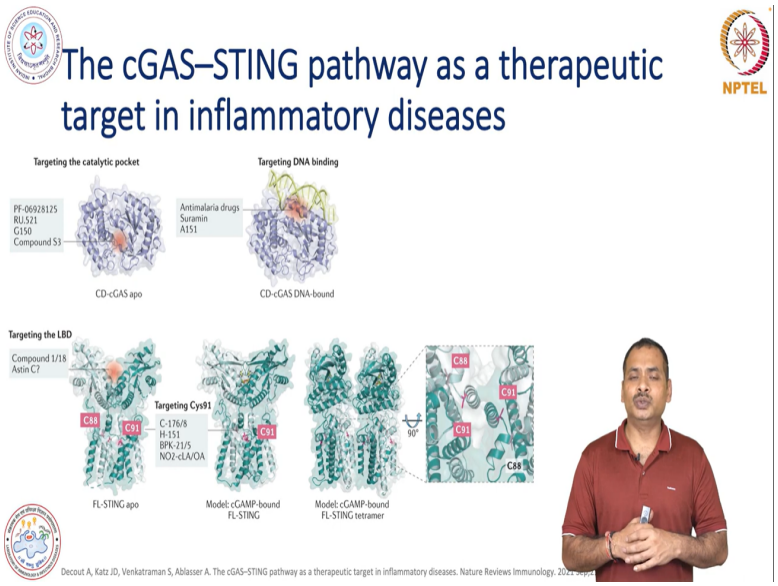

Now I will take you to the some therapautic component here you can see that the cGAS-STING pathway as a therapuatic target in inflammatory disease. Now this is a kind of crystal structure of CD-cGAS and there are some drug anti-malarial drugs or suraminpseudonym; which can kind in this to this protein it is a co-crystal basically. And here you can see that there is a compound STING-c so this can be used as a therapeutic molecule.

And this is much more detail structure so this work is still quite a new work it is published in 2021 the review article. So there are some attempts in order to use this pathway cGAS-STING pathway in order to treat some inflammatory diseases. Here with this I am completing the whole pattern recognition receptor I have discussed in great detail the concept of pattern recognition receptor.

And then we have discussed of toell like receptor TLR signaling pathway TLR and diseases and TLR ligand used as a therapeutic agent in various kind of infectious as well as non-infectious diseases. We discussed in great length about the RLR pathway and we discussed ligand signaling pathway and disease associated with mutation in RLR pathway or in molecules of RLR pathway and we have also discussed NODnot like receptor in great length the ligand signaling and the disease.

And we have discussed DNA sensor pathway and we have discussed the signaling pathway and the diseases associated with DNA sensor molecules or the molecules involved in DNA sensing pathway. And with this I am completing whole pattern recognition receptor and I am also completing the sixth week and in next session we will start with one very important component of immunity which we call it as complement.

And this complement is a soluble factor which is playing a very important role in innate immunity. And it is also linking this is a soluble factor which is linking the adaoptive immunity. We will talk various complement pathways in upcoming session thank you very much.