Host-Pathogen Interaction – Immunology
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So in previous session, we have learned about the NLR. We have looked at this family of pattern recognition receptor is an evolutionary highly conserved which is a present in very phylogenetically primitive animals right like sea urchin. And it is widely present in all plants and animal. We have also learned they have a quite big family and play important role in defense particularly inside the cells.

We have learned that this can activate this family of protein can activate NF – Kappa B map kinesis and also it plays a very important role in maturation of IL1 family Cytokines. Now since this family is quite big and there are a lot of mutations are associated with this NOD like receptor family members and these mutations basically result in either gain of function or loss of function. And this gain and loss of function may result to the some disease which is heritable.

So in this session I will discuss in a great length about this there the mutations associated with these family members and those mutations which are associated with this family member or result to the development of disease.

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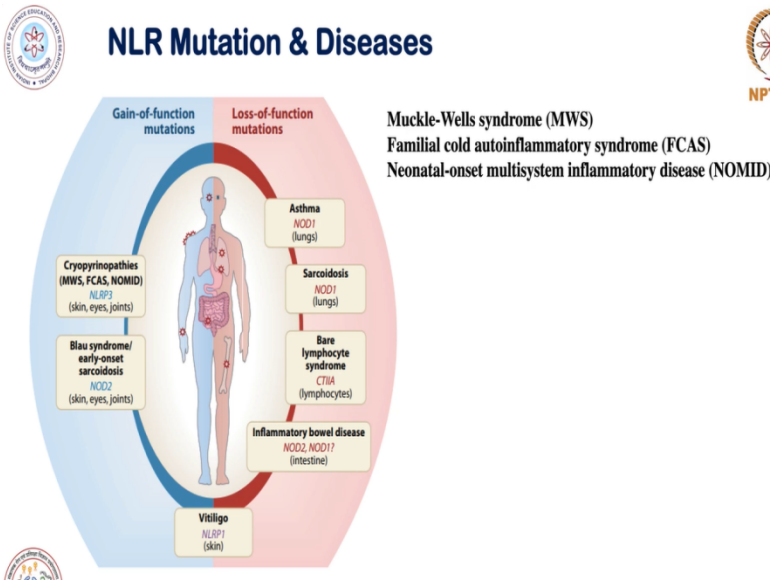

So here this is a very simple schematic here you can see there is a gain of function. And if you see this gain of function there are list of disease which is associated with one or other mutations in the NLRP3 protein and NOD 2. So here you can see there is a cryopyrinopathies. Cryopyrinopathies are basically a list of disease which is consists of Muckle-Wells syndrome, Familial cold autoinflammatory syndrome and Neonatal-onset multi-system inflammatory disease.

So Muckle-Wells Syndrome or MWS is basically in these individuals there are fever, recurrent fever, rashes and it is also associated with joint pain. Another is a familial cold Auto inflammatory syndrome, so this disease is also associated with ~~her~~ intermittent episodes of rashes, fever & joint pain. And it is also associated with a systemic inflammation and this systemic the interesting thing is that this systemic inflammation is basically induced by cold exposure of cold.

So this systemic inflammation is basically induced by exposure to the cold. So this is called interesting that is why the name is a Familial cold autoinflammatory syndrome. Another is a Neonatal-onset multi-system inflammatory disease so this disease is associated with neonate as ~~you~~ the name suggest and there is a persistent inflammation. And that persistent inflammation result to the tissue damage and this persistent inflammation also result are it affects a nervous system skin and Joint.

So this is a please note that these disease are quite rare but these disease are do present in the population. Another list of disease is basically Blau syndrome, Bare syndrome and early onset of sarcoidosis so this is associated with NOD2 and this is an again due to the over activation of NOD2 mediated signaling and it affects skin, eyes, joint. So this Blau syndrome is associated with early onset of granulomatous~~granular matters~~.

So there will be a granulomatous ~~granulus matuses~~ there and this granular matters is a basically you know when infection is not clear then this will make a granuloma. And this granuloma is or granulomatous disease is associated with arthritis or sometime there will be skin rashes. Another is sarcoidosis, sarcoidosis is basically again granulomatous ~~granular matters~~ affect any organ of the body this can affect any organ.

But it is quite often seen that this is affecting lungs and lymph Nodes and patients basically feel fatigue and they will also have a joint pain and sometimes shortt~~t~~ness of breath. So these are some disease which is due to the gain of function ~~not~~NOD1 ~~one~~ mutation may result to the asthma and this will affect the lung and Sarcoidosis which is also caused by mutation in NOD1. There is a loss of function and this is a as I explained you earlier in case of NOD2 the symptoms are similar.

Another is a bar lymphocytic syndrome which is associated with a Class 2 activation Factor there is a mutation in this protein and this is basically this disease is a kind of a kind of dangerous, reason is that there will be a severe reduction in CD4 T cells. And you can imagine a situation if there is a severe reduction of CD4 T cells then what will happen? And this is happening in case of HIV patient or AIDS patient.

The patient they have a severe reduction of CD4 T cells and these CD4 T cells are kind of pivotal for adaptive immunity. So this disease is basically associated with reduction of CD4 T cells. There is a another disease which is associated with NOD1 or NOD2 it is not very well clear this is inflammatory bowel disease. So inflammatory bowel disease is also several kinds and 1 of the diseases Crohn's disease I will discuss in upcoming slide.

So this Crohn's disease is also associated with NOD1 there is a question about the NOD1 but it is quite formally established that NOD2 is associated with Crohn's disease. Vitiligo this is also a

disease it is associated with dysregulation of NLRP 1. So an NLRP1 either it is not very clear there is again a function or loss of function but it is associated with dysregulation of NLRP.

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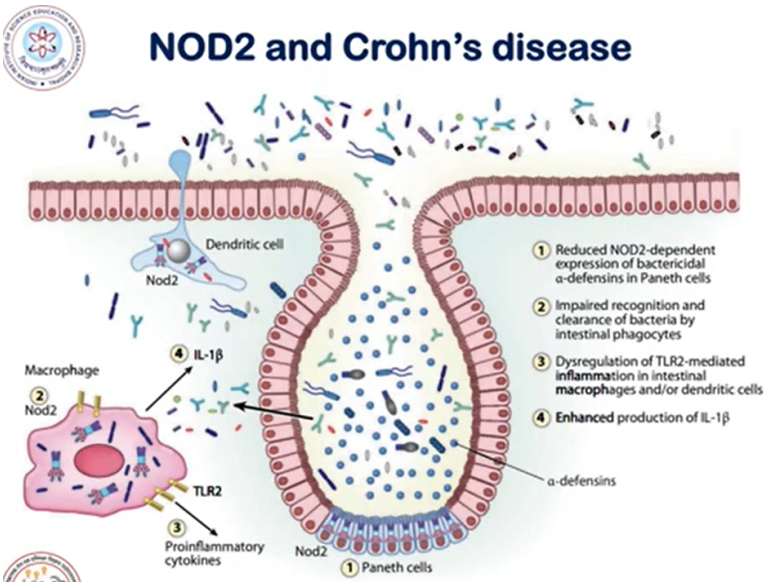

Now I will discuss about the Crohn's disease and there are several theories about the Crohn's disease but it is a quite firmly established that this Crohn's disease is associated with NOD2 and there are several Schools of thoughts. First is that if you see this slide there is a reduced NOD2 dependent synthesis of alpha defense in protein. If you remember I have discussed about the alpha defense in when I was discussing the antimicrobial peptide and this is synthesized by Panarthe cells.

So 1 theory is that there is a reduction in expression of this alpha defense in which; is dependent on NOD2. Another school of thought is that impaired recognition and clearance of bacteria by intestinal phagocytes. So here you can see that there is a compromised function of phagocytes and this may also result to the Crohn's disease the third school of thought is that a dysregulation of TLR 2 mediated inflammation in intestinal macrophages and or dendritic cells.

And the last school of thought is that enhanced production of Il 1 beta. So maybe all these things result to the development of this Crohn's disease but still it is quite unclear although this disease was quite well established or well studiedwell-studied I mean to say that. And there is another school of thought which; is not shown in this slide and I have discussed in previous session probably.

When I have discussed about the antimicrobial peptide another school of thought is that there is you know the gut is filled with a lot of commensal bacteria. So another school of thought is that our immune system somehow destructs these commensal bacteria and that also result to the Crohn's disease. So this is quite well established that NOD2 is 1 or other way it is involved Involvement of NOD1 is not so clear.

Now I will show you the extensive list of diseases associated with NLR family members here I have just highlighted few important diseases. Now I will show you the extensive list in which you can understand that there are so many diseases associated with various NLR family members. And some of this disease is characterized in a mouse by creating a deficient mice and those mice also show some or some similar pattern of the disease.

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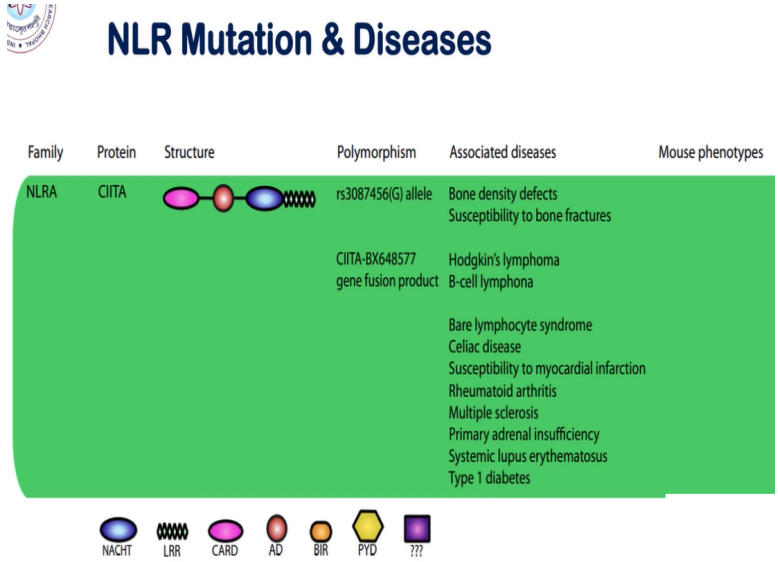

So let us take up the first this is a Class 2 Trans activator protein and this here you can see that this disease. If there is a some mutation it will be associated with bone density defect and these individual may be susceptible to the bone fracture. Another is it is also associated with Hodgkin's lymphoma B-cell lymphoma it is a barse lymphocyte syndrome. This I have already discussed where there is a decrease in number of CD4 T cells.

Another is silica diseases susceptibility to the myocardial infarction, Rheumatoid arthritis, multiple sclerosis, primary adrenal insufficiency, SLE systemic lupus erythematosus, and type

1diabetes. So, here you can see that this molecule is associated with so many diseases. And I will again put a note here that try to understand any disease is not happening only by single mutation. In general, I will not say all diseases but in general only one mutation is not sufficient or not enough to cause the full-blown disease there must be multiple factors especially these complicated disease and these diseases are quite rare.

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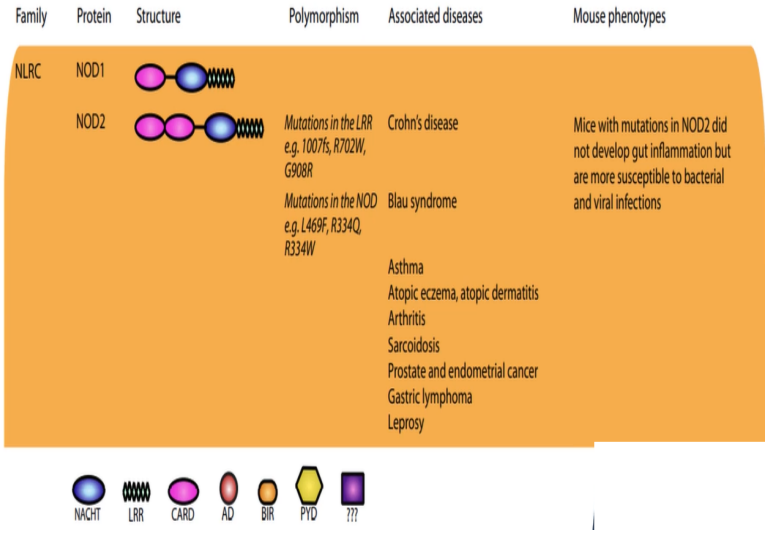

Another is a NOD1 and NOD2 here you can see that NOD2 is very well reported. There are some mutation in leucine Rich repeat domain and this is associated with crohn's disease in human and Blau syndrome, asthma, atopic eczema, atopic dermatitis, Arthritis Sarcoidosis, Prostate and endometrial cancer, Gastric lymphoma and Leprosy. So here these are the disease in human and this was a characterized in case of mice also.

In mice with mutation in this NOD2 molecule so if you mutate this NOD2 Gene then these animal these knockout mice~~eyes~~ they did not develop a gut inflammation but more susceptible to the bacterial and viral infection. So please note that this is a little contrasting compared to the human. In human we say that it they develop an inflammation in gut and that result to the Crohn's disease so this is quite contrasting.

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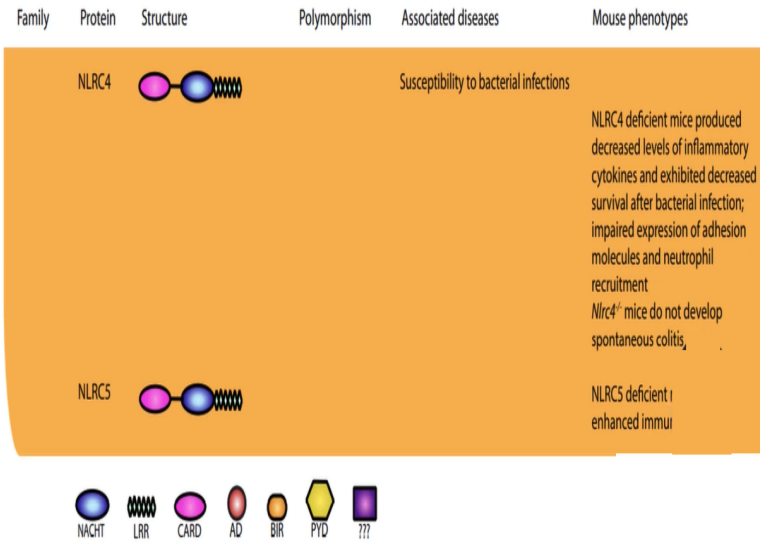

Another is NLRC 4 and this is a also associated with susceptibility to the bacterial infection. In case of ~~my~~ in case of human and NLRC 4 deficient mice produce a decreased level of inflammatory cytokine and exhibit decreased survival after bacterial infection impaired expression of adhesion molecule and neutrophil recruitment. And this mice is a ~~dismizer~~ NLRC 4 deficient mice do not develop spontaneous colitis. It is an inflammation of colon another is NLRC 5.

NLRC 5 deficient are they have a basically exhibit these mice this NLRC 5 deficient mice exhibit enhanced immunodeficiency. So these are some of the phenotype in case of mice but we do not know in case of human.

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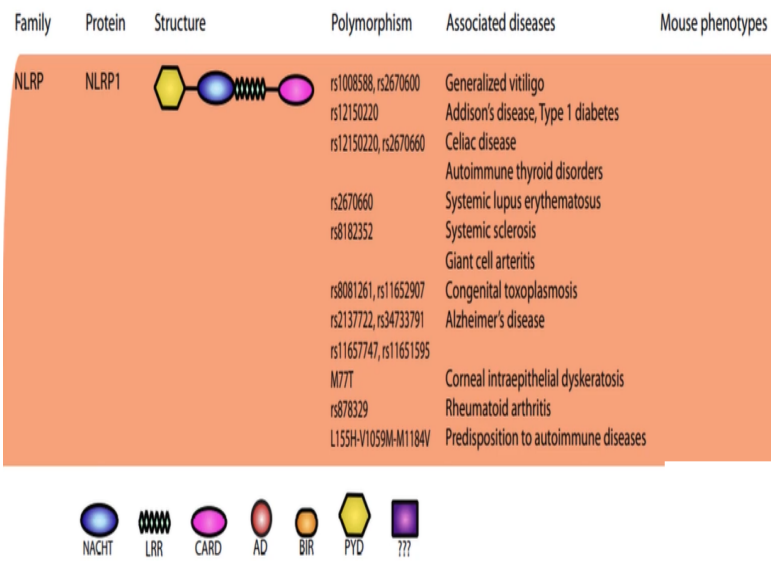

NLRP1 here you can see there are a lot of polymorphism in this Gene and all these polymorphism are reported. And these individual do show some disease like generalized vitiligo Addison's disease, type 1 diabetes, ceiliac disease, autoimmune thyroid disorder, SLE systemic lupus erythematosus, systemic sclerosis, giant cell ~~arthritis~~ arteritisy. It is an inflammation of arteries congenital toxoplasmosis, Alzheimer's disease.

And some mutation are also associated with corneal inter-epithelial ~~this~~ dyskeratosis and rheumatoid arthritis, predisposition to the autoimmune diseases. So just try to understand you need not to memorize all; this thing because this is quite complicated I am just highlighting that people reported that these some of these mutation or polymorphism, in the population are some or other way associated with these disease. But I do not know how firmly it was a proved it so but there is some evidences that's why people reported it.

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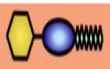
Family	Protein	Structure	Polymorphism	Associated diseases	Mouse phenotypes
	NLRP3		rs10754558, rs35829419 rs10733113G rs10754558	Type 1 diabetes, Celiac disease Psoriasis Increased susceptibility to HIV-1	
			More than 30 mutations in exon 3, e.g. R260W, A352V, L353P	Cryopyrin-associated periodic syndromes (CAPS)	Knock-in mouse models with NLRP3 mutations exhibited increase in IL-1β production and neutrophil infiltration
				Gout Inflammatory bowel diseases Alzheimer's disease	*Nlrp3*$^{-/-}$ mice more susceptible to colitis *Nlrp3*$^{-/-}$ mice protected from memory loss
				High fat diet induced obesity Type 2 diabetes Atherosclerosis	*Nlrp3*$^{-/-}$ mice on high-fat diet have improved glucose tolerance NLRP3 deficient mice protected from atherosclerosis in one study

Next is NLRP3 and as you know that NLRP3 is a quite well studied and since it is quite well Studiedate. There are so many polymorphisms associated with this and one of these polymorphism or several of these polymorphism are associated with human disease. Such as a type 1 diabetes Ssilica disease, psoriasis, increased susceptibility to the HIV that is quite interesting I do not know how this is a happening.

Another mutation is also associated with a cryopyrin-associated periodic syndrome. Gout, inflammatory bowel disease, Alzheimer's disease, high fat diet induced obesity type 2 diabetes and arthrosclerosis. So if I see this disease it is quite different kinds of disease and at least in current knowledge I cannot explain how so much variety of disease are happening. If you look at one simple thing then you can understand that most of diseases are associated with inflammation. So somehow this inflammation is deregulated and that result to the disease.

So NLRP3 knockout mice are also quite well studied and here you can see this knockout of this NLRP3 basically mutation exhibit increase in IL1 beta production and neutrophil in filtration. So this neutrophil infiltration is also a mark of inflammation. And this mice this knockout mice is susceptible to the colitis this mice is protected from memory loss I do not know how it is done but there must the researcher must be investigated quite extensively.

And these NLRP3 deficient mice on high fat diet have improved glucose tolerance and this deficient mouse protected from the atherosclerosis there is a one study. So in this way this you can see that NLRP3 is again associated with wide range of diseases.

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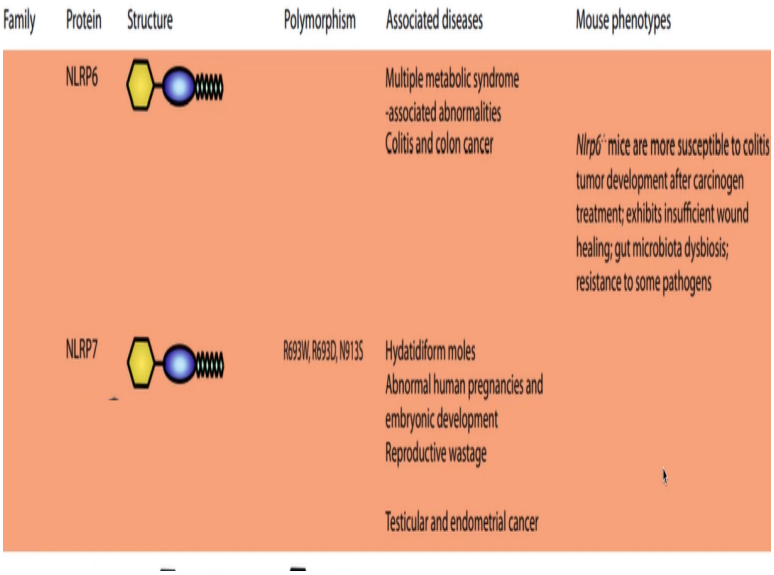

NLRP6 this is also reported with human diseases like multiple metabolic syndrome,- Associated abnormalities such as a colitis, colon cancer, and the mice is also investigated this NLRP 6 knockout mice are more susceptible to the colitis tumor development after carcinogen treatment exhibit insufficient wound healing gut mi~~a~~crobiot~~a~~i~~c d bios~~ dysbiosis is resistant to some pathogen.

Another is NLRP 7 and it is a also associated with some human disease this is hydatidiform ~~igh tidy form~~ moles, ~~are there~~ abnormal human pregnancy and embryonic development reproductive wastage testicular and endometrial cancer. So NLRP7 is also associated with various human problems or human disease.

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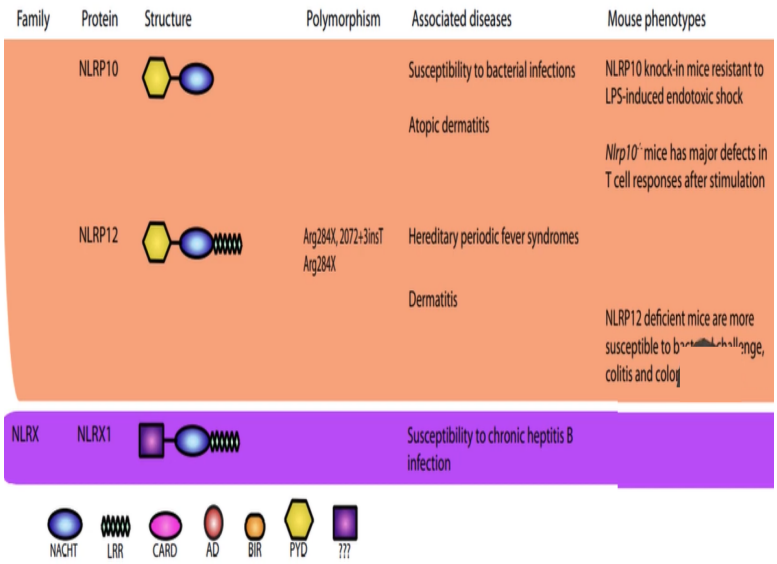

Next is NLRP 10 and this NLRP 10 is associated with susceptibility to the bacterial infection in human and atrophy and dermatitis and this knockout mice of NLRP 10 is resistant to the LPS induced endotoxic shock. So this suggests that maybe this NLRP 10 is in one or other way it is involved when in production of inflammatory cytokine upon LPS challenge. NLRP 10 mice have a major defect in T cell response after stimulation.

The second last is NLRP 12 and there are several polymorphisms is also reported and it is associated with a heredity periodic fever syndrome dermatitis and The Knockout mice are more susceptible to the bacterial challenge, colitis and colon cancer. At last there is a NLRX 1 and these some the mutation or changes in NLRX 1 is associated with the susceptibility to t~~+~~The Chronic hepatitis B infection.

The Knockout mice are not available and therefore the studies are not available. So here can see that at least I cannot say that very ~~formally~~firmly that these mutation are associated with these disease. But I can say that there some involvement in development of these Varity of diseases some Mutation in analog family protein is associated to some extent in development of disease some are very well characterized ~~correct~~such as chron’s~~s~~ disease but still lot of investigation needed.

So with this I will stop the NLR family protein or pattern recognition receptor and in next session I will discuss about the various DNA~~S~~ sensors and we will look at various ligand which

activate these DNA sensor. We will also look at the signaling pathway and the responses induced upon stimulation of cells with DNA and we will also look at the disease associated with these DNSA sensors thank you.