Host-Pathogen Interaction (Immunology)
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Lecture: 35
Pattern-Recognition Receptors-TLRs and Diseases

So, in previous session we have learned about the concept of PRR we have learned various families of PRR like TLR, RLR, NLR. We have learned in Greater detail about the toll-like receptor we have learned about their ligand and we have learned about the signalling pathways activated by TLRs. If you remember there are two major signalling pathway one is that My-D88 dependent pathway and another is TRIF dependent pathway.

So, after the signalling pathway it is very important to look for the TLR and diseases because after the discovery of this pattern recognition receptor which is about approximately three decades back happened in 1989 or 1996, 97, 98 it was quite well established. Thereafter this field was expanded like anything and this field still it is expanding and this field is quite promising in terms of understanding disease.

So, therefore in this session I would like to discuss about this TLR and diseases otherwise this is kind of incomplete. And most likely in another session I will also discuss about the TLR and Therapeutics. So, let us begin with this TLR and disease.

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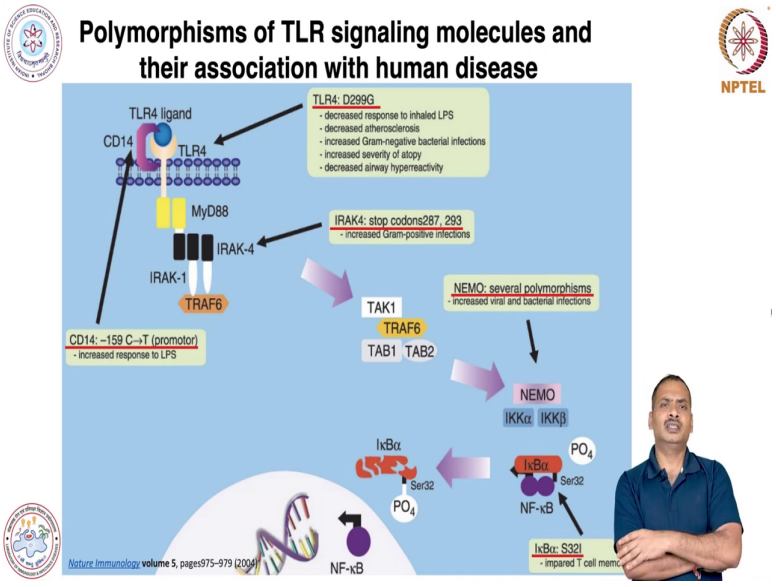

So, here you can see and it is a TDLR4 for mediatedmitigated signalling and if you remember for TLR4 signalling the ligand is lipopolysaccharide right. And this lipopolysaccharide is basically a very potent immunostimulator if you remember I have discussed in previous several sessions and this LPS sensing is not. So, simple it is little complicated you need a LPS binding protein and which is present in soluble form in body fluid particularly in serum or plasma.

And there is a CD14 and this CD14 is also a soluble Factor and there is a one molecule MD2. So, this complex basically sensed by the TLR4 and then this TLR4 induces the shock if you remember my previous session. So, this shock is quite complicated condition. So, if there is a some changes in this Gene. So, that may result to the that is not necessarily result to the development of disease it may be a protective for some situation.

So, all those things I am going to discuss in this session. So, let us look at there is a polymorphism in TLR4 where this aspartic acid which is at 299 position changed to the glycine. So, if this kind of polymorphism is there then the individual has a decreased response to the inhaled LPS and there is a decreased incidence of arthrosclerosis. So, arthrosclerosis you might be aware that this is a generally we talk in context with cardiovascular diseases right and it is simply the thickening of wall of these arteries.

So, there is a arteriosclerosis in which any artery of the body can involve and this thickening is basically is a mainly caused by depositiondeposition of various thing it could be a cholesterol it could be a lipid and whatever makes the wall thickening that narrows the the Lumen of this artery and then this will this may reduce the blood flow and if it is happening in some in major artery in the heartrt then that result to the cardiovascular disease.

So, if this mutation is there then this is a kind of good news that there will be a decrease incidence of atherosclerosis. Increased and gram-negative bacterial infection so, you can understand if there is a less response from this TLR mediated signalling then that will increase the possibility of multiplication of gram-negative bacteria right it is a quiteartz compatible or of course it is obvious.

So, if this mutation is there then there will be a possibility that the individual is kind of susceptible to the gram-negative bacterial infection. There is a increased severity of atrophy,

atrophy is basically kind of the literal meaning is the thinning atrophy can be associated with various things atrophy in neurons a drop in muscles resting of muscles and all those things. So, there is a possibility that there will be increased severity of atrophy decreased Airway hyper reactivity.

So, this is also possible. So, all these conditions are associated with TLR4 ~~for~~ mutation this D299g. There is a also some polymorphism is associated that is CD14 and this mutation is basically present in promoter region where the C is replaced by T. And if this mutation is there then there will be a increased response to the LPS. Probably this mutation may increasing the expression of a CD14 I do not know precisely but most likely if you see the response because this is a increased response to the LPS means there is a more CD14 protein available in extracellular fluid.

So, that will of course obviously occurs more response to the LPS. Another is this IRAK, IRAK 4 if you remember there is a this My D88 recruits IRAKs ~~EX~~ in previous session I have discussed and then TRAF6 ~~draft six~~ and that mimics a kind of signal or some a complex and that eventually activate the IKK complex. So, this IRAK there is a IRAK 4 IRAK one and if you remember I discussed about the IRAK M which is a kind of negative regulator.

So, this IRAK 4 has a stop codon if there is a this polymorphism will be there then there will that will introduce a stop codon this is 287, 293 and there will be a increased susceptibility to the gram-positive infection. Another is this Nemo. So, Nemo is a is a one of component of IKK complex. So, IKK complex is consists of IKK alpha, IKK beta, and IKK gamma, and IKK Gamma is also known as Nemo.

So, if there is a some polymorphism in this Nemo then there is a possibility that the individual is more susceptible to the viral and bacterial infection. Another is a I Kappa B Alpha and there is a mutation here you can see that the amino acid serine is converted into the isoleucine at 32 position and if this mutation is there then there is a possibility that that will impair the T cell memory.

So, these are some polymorphism which is associated with TLR signalling. So, I will talk more some more TLR and their polymorphism and their association with the disease as you can see in this table.

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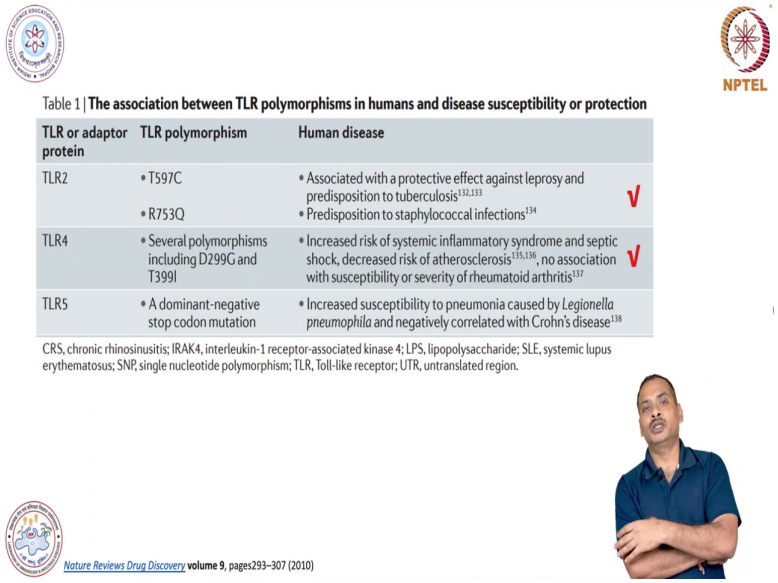

So, in TLR2 there is a there is a one polymorphism which is a basically a conversion of threonine to the side cytosine sorry and cysteine amino acid. So, this is at position 597 and when this mutation will be there this is a kind of beneficial to ~~to~~ the to the host in terms of susceptibility to the leprosy. So, these individuals are protective from the mycobacterium lepre infection some somehow and on another hand they maybe have a more chances to have a tuberculosis.

There is a one more polymorphism associated with TLR2 that is a this is ~~our~~R amino acid change which is Arginine which is converted into the to the Q amino acid and this this basically these individuals are kind of susceptible or there is a predisposition of a staphylococcal infection. So, this is associated with TLR2, TLR4 I have already discussed and I will talk about one more in this polymorphism which is basically the thre~~i~~onine is converted into the isoleucine~~ation~~ at 399 position.

And these individuals may have a uh some as I told you they there will be a reduced risk of arthrosclerosis there is increased risk of systemic inflammatory syndrome and septic shock. However, it is a not associated with rheumatoid arthritis. So, these are some mutation which is a playing very important role in protection or development of disease.

There is a TLR5 a dominant negative stop codon mutation that will basically increase the susceptibility to the pneumonia caused by Legionella pneumophila~~Regional pneumonia filler~~ and negatively correlated with Crohn's disease. Crohn's disease if you remember this is a

inflammatory bowel disease. So, there are please remember any disease or most of disease I will say particularly the complex diseases such as a cardiovascular disease or some metabolic disease, cancer generally all these diseases are multifactorial it is it is caused by multiple factor.

So, you cannot pinpoint that only this factor is responsible in general these diseases are happened by there are so, many factors. So, so here I have just discussed the role of TLR in susceptibility or protection in disease.

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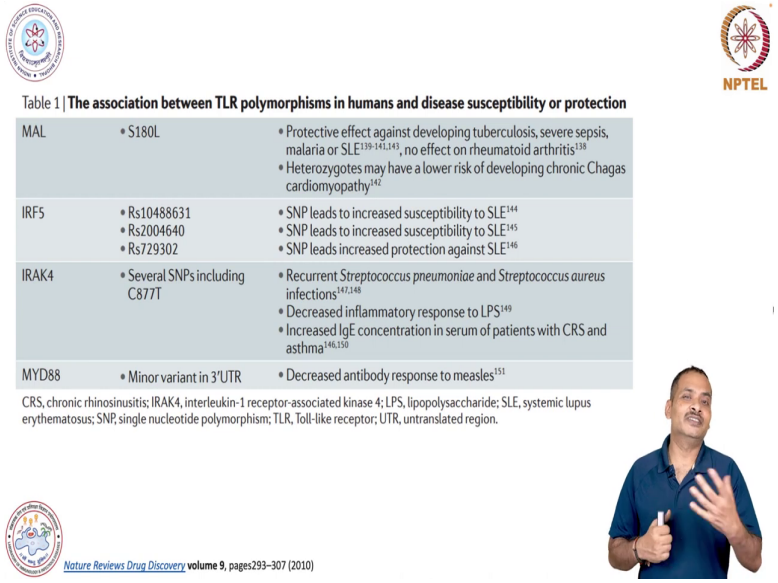

Table 1 | **The association between TLR polymorphisms in humans and disease susceptibility or protection**

MAL	• S180L	• Protective effect against developing tuberculosis, severe sepsis, malaria or SLE[139-141,143], no effect on rheumatoid arthritis[138] • Heterozygotes may have a lower risk of developing chronic Chagas cardiomyopathy[142]
IRF5	• Rs10488631 • Rs2004640 • Rs729302	• SNP leads to increased susceptibility to SLE[144] • SNP leads to increased susceptibility to SLE[145] • SNP leads increased protection against SLE[146]
IRAK4	• Several SNPs including C877T	• Recurrent *Streptococcus pneumoniae* and *Streptococcus aureus* infections[147,148] • Decreased inflammatory response to LPS[149] • Increased IgE concentration in serum of patients with CRS and asthma[146,150]
MYD88	• Minor variant in 3′UTR	• Decreased antibody response to measles[151]

CRS, chronic rhinosinusitis; IRAK4, interleukin-1 receptor-associated kinase 4; LPS, lipopolysaccharide; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; TLR, Toll-like receptor; UTR, untranslated region.

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So, I will move forward and then I will talk about there are few more molecules of TLR signalling that is Mal if you remember Mal is also known as tirap and this is a kind of linker between the TLR particularly in case of TLR 1 2 and 6 and TLR4. So, this is a kind of linker the small or TIRAP is Linker between TIR domain of these TLR with the My-D88. And there is a also some mutation are reported which is a associated with some disease.

One is that you can see that there is a serine amino acid which is replaced to the leucine at 180 position and this mutation shows the protective effect against developing tuberculosis and severe sepsis, malaria or SLE. However it is not associated with rheumatoid arthritis and heterozygote may have a lower risk of developing chronic chagas cardiopathy. So, this chronic cardiopathy is it is a parasite induced cardiopathy and this parasite is trypanosoma cruzisy.

So, this is a this is a chronic chagas it is a chronic condition it takes a long time basically that disturbs the cardio function. Another molecule is IRF5 and IRF5 plays a very important role in induction of type 1 interferon as well as inflammatory cytokines. And there are some mutations or some polymorphism is reported and it has been shown that these polymorphism is basically lead to the increased susceptibility to the SLE.

And the last polymorphism if you see the in case of IRF5 this leads to the increased protection against SLE. So, these are quite complexes understanding that the deeper biology is not so easy. So, because this polymorphism is present in human and we cannot make a genetic manipulation in human. Of course we can do it in mice and we can dissect out the basic mechanism but it is it is quite challenging.

Another molecule is IRAK 4 there are several SNPs including C877 T where the cysteine is converted into the threionine and this is associated with a recur recurrent streptococcus pneumoniae and streptococcus aAureus infection. There is a decreased inflammatory response to the LPS and there is a increased IgGE concentration in serum of patient with CRS and Asthma. So, what is CRS it is a chronic Rhino sinusitis.

So, this is cross this chronic Rhino sinusitis is a you know there is a rhinovirus infection or which is also because chronic Rhino sinusitisrhinocytositis this chronic word means if this situation is persisting for more than 12 weeks then we call it as a chronic chronic Rhino sinusitisrhinocinositis and this is a you know that there is a more release of mucus from the nose stuffy nose and all those all those things and it is not getting clear. So, then we call it as a chronic condition.

And this is also associated with the IRAK 4. The My-D88 which is a very key adapter molecule in TLR signalling there are some minor variant in three prime UTR and these individual has a decreased antibody response to the mesalsssiles. So, do you know this mesalsmissiles is a again a viral disease which is a you might be knowing that it is caused by single standard RNA enveloped virus and there is a spots all over the body particularly in trunk in hand and so on.

So, and this is associated with quite high fever about 105 Fahrenheit. So, in this session I will stop here and I have discussed there are some genetics are playing very important role in

susceptibility or protection against a particular disease in case of this TLRs. In next session I will talk about the TLR and therapeutic which is a you will see that how this discovery of TLR and now we have some molecules which we are using for treatment of various diseases.

And those molecules are basically activating or damping the TLR signalling. So, thank you, thank you very much.