Host-Pathogen Interaction (Immunology)
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Lecture No # 48
Complement – Regulation & Diseases

So in previous session we have studied the classical, alternative in lectin pathway these are very important complement pathway. Now in this session we I will take you to the regulation of complement because you can see that this complement needs to be tightly regulated and there are some diseases associated with some complement. So I will take you to all these thing.

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So let us begin with a regulation of complement and as you have learned that complement, components are capable of attacking host; cell and because they can undergo spontaneous activation and inactivation. So everything need to be tightly regulated if it will undergo a spontaneous inactivation then there will be a no formation of membrane attack complex and then there will be increase in number of microbe when that result to the disease.

If they are, not stabilized with other component which is highly labile~~evel~~ then that will be also a problem. So if you see very carefully the all 3 complement pathway the C3 convertase is a major amplification step and therefore this needs to tightly regulate it. If this C3 convertase~~converter~~ is not tightly regulated or it if there is a dysregulation that may result to

the disease or that may result to, the growth of a microbial infection or whatever individual is infected there will be a increase in number of those microbes.

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Soluble factors regulating complement			
Name	**Ligand/ binding factor**	**Action**	**Pathology if defective**
C1 inhibitor (C1INH)	C1r, C1s (C1q); MASP-2 (MBL)	Displaces C1r/s and MASP-2, inhibiting activation of C1q and MBL	Hereditary angiodema
C4-binding protein (C4BP)	C4b	Displaces C2a; cofactor for C4b cleavage by factor I	
CPN1 (Carboxypeptidase N)	C3a, C5a	Inactivates C3a and C5a	
Factor H	C3b	Displaces Bb, cofactor for factor I	Age-related macular degeneration, atypical hemolytic uremic syndrome
Factor I	C3b, C4b	Serine protease, cleaves C3b and C4b	Low C3 levels, hemolytic uremic syndrome
Protein S	C5b67 complex	Inhibits MAC formation	

So this regulation we basically we will discuss in 2 major component one is soluble factor which is a regulating this complement. Here you can see there is a C1 inhibitor which is also denoted as a C1INH. And this inhibitor is basically here you can see, it is interacting with C1r, C1 s of classical pathway if you remember which is a subunit of C1 and C1q. And it is also interacting with MASP-2 of lecatin pathway so how this works basically it displaces the C-1r or s and in which is in case of classical pathway.

And in case of lectin pathway MASP-2 basically inhibiting this activation of MbBL so this is a very, important factor which; can regulate the initiation of a classical and lectinatent pathway. And if there is some defect in this C1INH or C1 inhibitor then that will result to a very complicated and very rare heredity disease and this disease is known as Heredity angiodema. So this disease is basically characterized by the individual basically frequently they develop swelling in any part of, their body.

And this swelling can be extremely fatal if this swelling is taking place and in-appropriate or in some vital places. For example if this swelling will take place in respiratory tract then that will result to the choking of respiratory tract and then the individual cannot breathe. And if it is taking place in the gut then that will be also very complicated situation, although this swelling there is an episode of swelling.

And this episode of swelling is resolving by its own but if this swelling is taking place in for example respiratory tract or gut then that may create a complication and it could be an extremely fatal. So another molecule is C4 binding protein which is also denoted as a C4bp and this C4 binding protein is interacting with C4b and, basically it displaces C2a cofactor for C4b cleavage by factor I.

So factor I is a basically a serine proteases which cleaves the protein another is CpN1 which is a carboxy peptidase N this is a simple a carboxy peptidase N. And this carboxy peptidesase and the name is very clearly suggesting that they basically cleave the C3a, and C5a and it basically make it inactivated. Another is, factor H which is binding with the C3b and basically it displaces a B, b, B, b is a larger fragment of factor B and it is also cofactor for factor I.

And its deficiency the factor H deficiency can result to the age related macular degeneration so what is age related macular degeneration. So in vision there will be the straight vision the central part will be the, bloodblurred or it will be not visible so that is known as a macular or macular related disease. And if there will be a degeneration of macular in which is present on retina then that will result to the age related macular degeneration.

Another could be the atypical hemolytic uremic syndrome so this is also very rare disease. So this in this disease there will be a formation of a small clots and this, clot can go in any places particularly in the kidneys and then that will cause the variety of problem. There is a factor I which is basically factor I is interacting with C-3-b and C-4b this is basically a serine proteases and you can understand that C 3 b which is a important constituent of C 3 convertaseconverters and C 4b also.

So this factor I basically leaves these C3b and C 4b and if, there will be a deficiency of factor I then there will be a low level of C3 and that will also cause the hemolytic ureomic syndrome. There is another molecule which we call it as a protein S this protein S is basically interacting with C5b 6 7 complex and basically it is involved in inhibition of MACmap formation. So these are all soluble factor which is regulating the complement.

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Membrane-bound factors regulating complement			
Name	**Ligand/ binding factor**	**Action**	**Pathology if defective**
CRIg	C3b, iC3b, C3c	Inhibits activation of alternative pathway	Increased susceptibiity to blood-borne infections
Complement receptor 1 (CR1, CD35)	C3b, C4b	Cofactor for factor I; displaces Bb from C3b, and C2a from C4b	
Decay-accelerating factor (DAF, CD55)	C3 convertase	Displaces Bb and C2a from C3b and C4b, respectively	Paroxysmal nocturnal hemoglobinuria
Membrane-cofactor protein (MCP, CD46)	C3b, C4b	Cofactor for factor I	Atypical hemolytic anemia
Protectin (CD59)	C8	Inhibits MAC formation	Paroxysmal nocturnal hemoglobinuria

Another is a, the membrane bound factor which is regulating complement the first is CRI-g and this is basically binding with C3b and I C3b this is inhibitory C3b and C3c. And basically their action is that inhibit the activation of alternative pathway so CRI-g is playing very important role in alternative pathway. So if there is some problem in CRI-g then it will increase the, susceptibility to the bloodborne infection.

Another is these are the receptor these are the complement receptor one which is also known as a Cd35 which is a receptor for C3b and C4b. So basically this is a cofactor for I these molecules and it displaces the B,-b that is factor B larger fragment from C3b. So this makes a C3 convertase~~converter~~ is if you remember and C4a and from C2a, from C4b another is a decay escalating factor or DAF or CD 55 is also known as Cd55 it is the ligand will be C3 econvertase~~onverters~~.

It basically displaces the factor B larger fragment from C3 converters and C2a from C3b and C4b respect so. And if there is a deficiency in this DAF or C d55 that will result to the proximal nocturnal hemoglobinuria so what is the meaning of this term proximal means sudden nocturnal means night and hemoglobin urea means there will be a blood in the urine. So in these individual this is again a rare disease but in these individual what is happening?

When they wake up in morning then they and their urine will be having a blood it will be a dark red color it could be a brown. So they will they will produce lot of blood in the urine or dead blood which will turn to the brown in color. So this is also very complicated and rare disease and this can there is some drug which I will discuss in subsequent slide which can be used for this-p proximal nocturnal hemoglobin urea.

So there is a another membrane bound factor that is membrane cofactor protein that is MCP or CD46 which is interacting with, C3b and C4b. And action will be cofactor for factor I and if there is a deficiency of this factor then that will result to the atypical hemolytic anemia. Another molecule is protecting which is also known as CD 59 it is interacting with C-8 and basically it inhibits the mac formation and that because the proximal nocturnal hemoglobin uriea.

So these are the regulatory factor, and you can understand if there is some problem in this factor that result to the development of disease.

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Microbial pathogen invading Complement System

Pathogen	Evasion molecule	Host target	Mechanism of action
Membrane proteins			
Neisseria meningitidis	Factor H binding protein (fHbp)	Factor H	Inactivates bound C3b
Borrelia burgdorferi	Outer surface protein E (OspE)	Factor H	Inactivates bound C3b
Streptococcus pneumoniae	Pneumococcal surface protein C (PspC)	Factor H	Inactivates bound C3b
Secreted proteins			
Neisseria meningitidis	PorA	C4BP	Inactivates bound C3b
Staphylococcus aureus	Clumping factor A (ClfA)	Factor I	Inactivates bound C3b
Staphylococcus aureus	Staphylococcus protein A (Spa)	Immunoglobulin	Binds to Fc regions and interferes with C1 activation
Staphylococcus aureus	Staphylokinase (SAK)	Immunoglobulin	Cleaves immunoglobulins
Staphylococcus aureus	Complement inhibitor (SCIN)	C3 convertase (C3b2a, C3bBb)	Inhibition of convertase activity

Now I will talk about there is some microbial pathogen which evade this complement system. Here you can see that Neisseria Meningitidis this can so basically this can there will be some invasion molecule which is a factor H binding protein they make this factor H binding protein this microbe, and interact with factor H and inactivate the in inactivates bound C3-beam.

Another is ~~Borrelia Burgdoferi~~ Borrelia burgdorferi this is also pathogenic microbe and they make a protein which we call it as outer surface protein e this also interact with factor H and inactivate the bound C3b the streptococcus pneumoniae. This is also very pathogenic microbe and they make a Pneumococcal surface protein C and this is also, interacting with factor H and inactivates bound C3b. So here you can see that the microbe also have some strategy to evade the complement system.

Some of these microbes secrete some protein like Neisseria meningitis this makes a pro a which is binding which is like a C4 binding protein if you see if you remember the previous slide. So they make the C4 bo~~i~~nding protein and inactivate bound C3b, staphylococcus aureus they have a clumping factor A and this is basically binding with factor I and inactivate bound C3b. The staphylococcus aureus also has another 3 proteins staphylococcus protein a staphylococcus ~~aureus~~kinase this also they make this protein and complement inhibitor.

So basically all these protein of staphylococcus aureus can inactivate the bound form of C3b and bind, to the F~~C~~c region and interfere with C1 activation they can cleave the immunoglobulin they can inhibit the convertase activity. So in that way these pathogen can evade the complement system and establish the infection and cause disease.

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Now I will talk about the some complement deficiency although I have discussed in previous slides but I will sum up in separate session I mean in this session with, these slides. So there is some complement deficiency and that will be result to the disease. Here you can see that the deficiency of C1q, C1r, C1s, C4 and C2 basically that results to the enhanced formation of immune complex and this enhanced immune complex in the host result to the SLE like symptom and glomerulonephritis ~~Glomeronephritis~~, Vasculitis.

And individual will have this recurrent infection of a, pyogenic bacteria pyogenic means ~~first~~pus forming bacteria. Deficiency of factor D and propylene show that these individual will be more susceptible to the Neisseria meningitis but they are not susceptible to another meningococcal bacteria.

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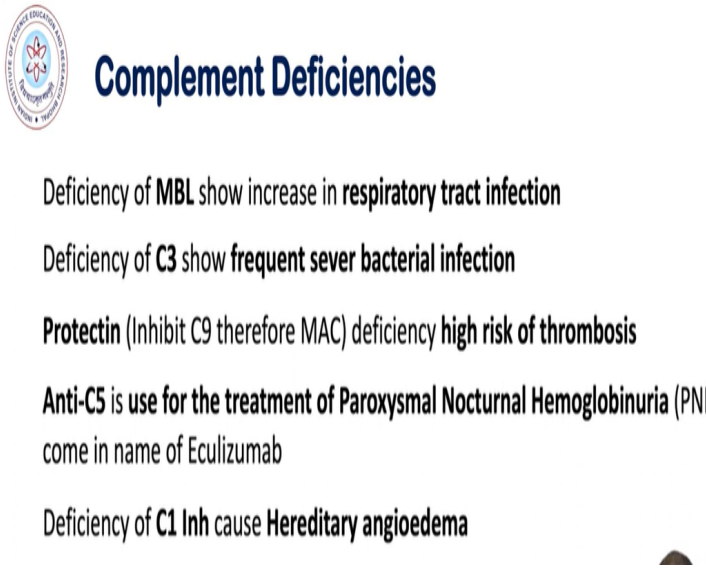

Deficiency of MBL which is mannose binding lacking a key component of lectin pathway show increase in respiratory tract infection. Deficiency of C3 show, frequent severe bacterial infection protectin which inhibits the C9 and therefore it in it inhibits the mac form formation that is membrane attack complex. So the deficiency of protectin will result to the high risk of thrombosis.

Anti C5 is used for the treatment of I have told you proximal nocturnal hemoglobin urea and so this there is a name of the drug is that Eculizumab. So most likely this is a monoclonal antibody this Eculizumab is basically a monoclonal antibody against anti against the C5 and this is used for the treatment. I have already discussed and this that there is a deficiency of C1 inhibitor and that caused the Heredity angiodema.

I have explained you in more detail that these individual will develop a swelling in their body, anywhere and this is a spontaneous and it is not known how this swelling is triggered. And sometimes these swelling can result to fatality if it is taking place in vital places such as a respiratory tract or in gut. So with this I am completing this complement and now we will discuss another topic in subsequent session thank you.