Immunology
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Lecture No -42
Complement System Overview (Contd.)

Hello and welcome to the immunology lectures and we were discussing on the complement pathway. So we have discussed about the complement overviews in our last class and if you remember that we told in the last class that the complement pathway can actually be initiated in three different ways. The classical pathway which is an antibody dependent pathway then you have an alternative pathway which is antibody independent nd you have a lectin pathway which is also antibody independent.

So it basically does not depend on any antibody antigen interaction and I also told that all these three pathways they finally tend to converge at a single point that is they try to produce a lot of C3 convertase which actually cleaves the C3 into C3a and C3b which are the cleaved products the cleaved complement products. So how these pathways they do these things. So as we told that initially the complement was found or discovered as a system which can complement for the humoral branch of immunity.

So it basically is the effector pathway of the humoral branch of immunity and it helps to complete the function of the antibodies. So it is not only that the antibodies binding to antigen will complete the function it also requires the complementation by some proteins and some factors and those are the complement proteins. So the complement proteins can initiate the pathways in three different ways the classical the alternative and the lectin of which only the classical pathway is antibody dependent and the rest 2 are not.

So let us quickly look into how these three pathways are initiated and the three pathways they try to break down the different complement proteins and produce the C3 convertase which finally leads to breakdown of C3 into C3a and C3b.

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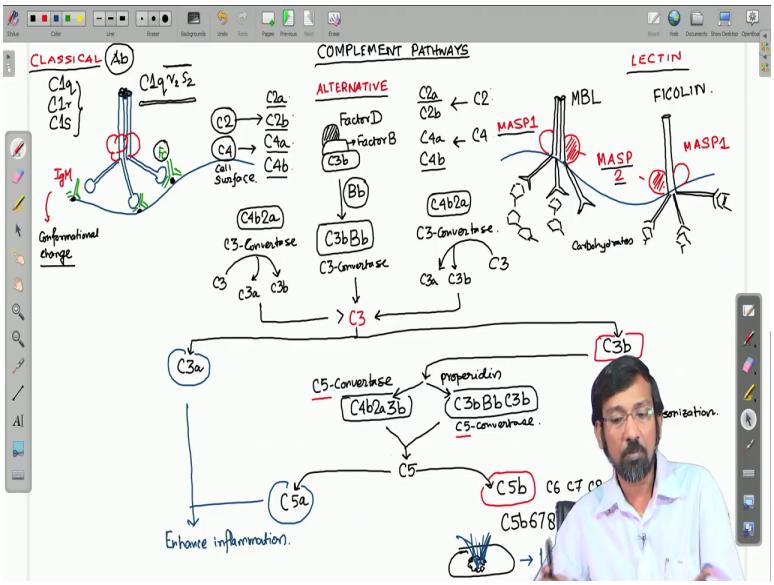

So, starting from here so if you look in this picture we have the classical pathway the alternative pathway and the lectin pathway, let us consider this portion to be the surface of the cell that is a cell surface where this antigen is bound to the antibodies primarily the IgM the immunoglobulin M. Now binding of this IgM when the IgM binds to the corresponding antigen on the surface of the pathogen or on the surface of the bacterium that leads to a conformational change conformational change.

And this conformational change exposes the regions on the FC region on the antibody so on this FC portion of the antibody which has binding sites to the complement proteins. Now to which complement protein it binds to the complement protein which the name looks very complicated if you look at the C1 q r2 s2. So basically the C1 complement protein it comprises of many polypeptide chains among which this C1 q it comprises of approximately there are 18 peptide chains we arranged in a ring like structure like this.

So into six ring-like structures and this can bind to the are and the s so he basically forms are all eggomatic structure in presence of C1q C1 r and C 1s. So basically it is written together as C 1 q r 2 s 2 it comprises of the C1 q the C1 r and the C1 s and they together forms this complex structure which is the C1 q r 2 s 2. So part unit there are 2C1 r and 2C1 s so that is why it is r 2 s 2 and this is the C1 q r 2 s 2 and this bar over here usually in a complement activation pathway this bar usually indicates an active protease or an active protein.

So after these cleavage products they again try to associate with each other with the target proteins then they form these active proteins which can cleave further more complement proteins. So they are indicated by this kind of a bar on the top. So these are nomenclatures. So once this C1 q r 2 s 2 can bind to an IgM or the FC region of the IgM then it is kind of activated and since I told that these are all proteases.

So they can lead to the cleavage of other complement proteins that is the target complement proteins which are present in the vicinity for example they can break C 2 and C 4 so C 2 is broken down to C 2a and C 2b and C 4 is broken down to C 4a and C 4b. Now these are the cleavage products the C 2a 2b 4a and 4b. So now it forms they immediately associates in the form another compliment protein which is known as C 4b 2a it is a C 4b 2a. Now this C 4b 2a is nothing but a C3 convertase which means it can convert or break down C3 into C3a and C3b.

So what happens C1 q r2 s2 that is a C1 complement protein the C1 q r2 s2 when it binds to the FC region of the antibody after there is an antigen antibody interaction these FC region binds to the C1 q that leads to activation of the C1 leading to cleavage of C 2 and C 4. And C 2 breaks down into 2a 2b C 4 breaks down into 4a and 4b. And this 4b and the 2a they associate together to form the complement protein or the C 3 convertase which is also known as the C 4b 2a.

Now this C 4b 2a is a C3 convertase that means it can cleave C3 into 3a and 3b so it can cleave C3 into 3a C3a and C3b. So now let us look into for the time being we just stop here on the on the classical pathway. We go to the lectin pathway we see how the lectin pathway is initiated and how it is initiated. So in the lectin pathway as I told there are specific lectins like mannose binding lectin for example MBL.

And also our lectin proteins like cycling. Now these can bind to carbohydrates or mannose molecules that are present on the surface of the pathogen and when they bind to the surface of the pathogen they can also bind to a class of serine proteases which are the membrane associated serine proteases like the MASP1 and the MASP2 these are also parts or components of this lectin

pathway. So they can bind to this MASP1 and MASP2 and it forms an algometric structure similar to this and once this binding occurs.

They can also convert C2 and C4 into the broken products like C 2a C 2b and the C 4 into C 4a and C 4b similar to what we have seen in case of the classical pathway. Now here again this leads to the formation of C 4b 2a. So again the C 4b and the C 2a they combine. So 4b and 2a they combine and they form another intermediate in the complement system which is known as the C 4b 2a and it is also aa C3 convertase okay.

So now this C3 convertase can also convert C3 into C3a and C3b. So you see that in both the pathways you have formation of an intermediate which is the C 4b to a which can lead to conversion or breakdown of the C3 into C3b and C3. Now C3b is one of the very important complement components. Now let us see as I told initially that the alternative pathway is initiated only when there is C3b present and you also need the presence of another factor called the factor D.

So you have let us say it is the broken product of C 3b that is the C 3b the broken product of C 3 along with that you have another factor which we call as the factor B and with the help of a third complement protein also known as factor D. It cleaves the factor B into DB. So B again is Clifton since it is also a compliment protein it is cleaved and forms a large fragment which is called the BB. So now this Bb after breaking of this factor B so this B is a broken product of this B factor B and this is possible only in presence of factor D and the C 3b.

So now this forms another C3 convertase which is known as C3b Bb. So now this is another C3 convertase okay. So all these three C3 convertase has are formed at the end of this three pathways the classical pathway the alternative pathway or the lectin pathway. Among these three pathways if you see only the classical pathway is an antibody dependent pathway the rest of the three or antibody independent pathways. Now if we try to see how these three pathways they converge they converge at a single point now they all try to break down the C3.

So they all try to break down the their central rule is to break down this C3 and they break it down to C3a and C3b again C3a and C3b. Now this C38 the C3b can have it can work in two ways one it can further associate it can further associate with this for B to a intermediate in form C 4b 2a 3b. So it is just simple addition. So if you see it forms another convertase which is also known as C5 convertase.

So now their role is to break down the complement protein C5 some somehow they have to break down the complement protein C5 a second way is they form another C5 convertase by the action of a protein pro paradeen. So this proper reading it can also associate with the C3b and it can form the C3b Bb C3b. So this is also another C5 convertase, so this is also a C5 convertase. So at least you have to C5 convertase is here 1 and here 1.

So both of them both of these C5 convertase is be it the C4b 2a 3b or so 4b 2a which was originally a C3 convertase when it associates with another broken C3b it forms C4b 2a 3b and this is a C5 convertase can break down C5 into 5a and 5b. Similarly this C3bBb which is a product from the alternative pathway and also in presence of pro paradeen it associates with another C3b breaks down another C3 into 3a and 3b and that C3b can also associate with 3bBb and forms C3b Bb C3b.

So this is also another C5 convertase now their job is to break down C5 into C5a + C5b. So we come across at least two major components in the complement activation pathway one is this C3b which can directly this C3b can directly coat the pathogen so it can coat the pathogen surface and it can assist in the process of optimization or it can further as associate with other complement broken products and can form the C5 convertase this C5 convertase can actually break down C5 into 5a and 5b.

And this C5b can then associate with other complement proteins like C6 C7 C8 and C9 to form C5b 6 7 8 9 and what is this C5b 6 7 8 9 it is nothing but the membrane attack complex or the MAC. So now this membrane attack complex can attack the surface of the pathogen and form this kind of a hole where you have fluids in rushing fluids fluids can come in and can finally lies or lead to lysis of the cell.

And also you have two other smaller products at the end one is the C3a and the C5a so this C3a and C5a these together, so 3a and 5a they together can lead to in hence inflammatory responses. So they enhance inflammation if you remember the classes from our inflammation enhancement of inflammation you will remember that with C3a and C5a where one of the major components that could work as chemo attractants and also they can bind to many cell surface complement receptors.

And lead to degranulation of the granulocytes leading to increase in the increase in release of the histamine and that would lead to the increase in the vascular permeability and then would lead to draw more neutrophils and will increase the inflammatory responses. So basically C3a and C5a these two clip products of C3 and C5 they enhance inflammation C5b which is a cleaved product of C5 initiates the formation of the membrane attack complex we will discuss in our next class how the membrane attack complex formation actually occurs in presence of C5b and the other complement proteins like 6 7 8 9 and C3b can directly lead to the process of opsonization that is coating the pathogen or the surface of the pathogen with this C3b the cleave product and leading to phagocytosis.

So this is a very general overview of the complement activation pathways the classical the alternative and the lectin we will go through them one by one once again. And we will try to understand how this complement activation occurs. So starting again back with the classical pathway as I repeatedly told or I am still repeating that the classical pathway of the complement activation starts only as a result of antigen antibody interaction.

So when there is an antigen antibody interaction there is a conformational change in the antibody that leads to exposure of the FC regions which can in turn with the compliment protein C1 leading to or facilitating and interaction in this region leading to the FC region of the antibody to interact with the C1 complement. The C1 compliment here is assuming an automatic structure which is basically formation of this structure occurs due to association of the three subunits the C1 q the r and the s and they form this kind of an oligomer of which the co and q itself contents 18 peptides or if 18 peptides which are arranged in a ring like six ring like structure like this.

And they associate with this r2 and s2 and forms the C1 q r2 s2. Now this C1 q r2 s2 can cleave to complement proteins C 2 and C 4 C 2 can be cleaved into 2a and 2b 4 is cleaved into 4a and 4b this C4b and to a they come together that means they associate with each other and once they associate they forms another intermediate which is the C4b 2a so we just retain the C at the beginning for the compliment and the broken fractions the broken fragments 4b 2a.

And this protein or this intermediate is known as or C3 convertase the name is given as C3 convertase because it can break down C3 into 3a and 3b. Similarly you are coming to the lectin pathway. The lectin pathway I told it is an antibody independent pathway. So it primarily starts with the interaction of specialized lectin molecules like cycling or this MBL which is a mannose binding lectin they can interact with this mannose or other oligosaccharide molecules or structures that are present on the surface of the cell of the pathogen on the surface of the pathogen.

So all these interactions are going on the surface of the pathogen so when this MBL or this Ficolin can bind to the carbohydrates on the surface that would lead to activation of this kind of serine proteases which are associated with these lectins the MBL or the ficolin. So MASP1 or MASP2; MASP1 and MASP2 are the membrane-associated serine proteases remember now when this serine proteases they are activated they can also cleave to complement proteins similar to what we have seen in case of the classical pathway.

They can also cleave the C2 and the C4 leading to from C2 it forms C 2a 2b from C4 it forms 4a and 4b once C2 is broken down to 2a 2b + 4 to 4a 4b again similar to what we have seen in the classical pathway there is interaction between the two cleaved products leading to formation of our C3 convertase which is C4b 2a. Now from the two independent pathways like the classical pathway and the lectin pathway we get the same intermediate product that is the 4b 2a 4b 2a.

So in this case also we have 4b 2a here also we have 4b 2a and both of these are nothing but C3 convertase. So C3 convertase which can convert C3 into 3a and 3b looking into the older native pathway. Now what is the role of the alternative pathway the alternative pathway is initiated only

when C3b 3b is available how can see 3b be available in two ways one it can be available as a product of the classical or the lectin pathways or there can be spontaneous breakdown of C3 into 3a and 3b and there can be minimal very minimum amount of 3b is available.

So the alternative pathway basically is an amplification system it just amplifies the signal if the cleavage product 3b is available then only it can amplify the signal. So when there is 3b available it can associate with another complement factor or a complement protein we call it the factor B and this factor B can also be cleaved it can be cleaved into Bb. So the larger fragment of the cleavage of B is the Bb.

Similar to 3b 4b it is the Bb, now this Bb is cleaved in presence of another complement factor which is the factor D. So if you see this portion this 3b associates with a factor B and a factor D leading to the cleavage of factor B into Bb. And now this BB associates with the 3b and forms another C3 convertase which is C3 B Bb. So from the three independent pathways what we get is 3 C3 convertase and what they all do is they attack the C3 again and they try to break down as much C3 possible into 3a and 3b.

Now you see the b products I have marked them in red and the a products I have marked them in blue. So why because the 3b products that either the three or the five the b products they are effective in two pathways that is the lysis and opsonization. What this 3b can do is 3b can have two different functions one it can again form or associate we 42a to form the C4b 2a 3b this C4b 2a 3b is a C5 convertase it converts C5 into so it is a convertase means it converts the target.

So C5 is the target it converts C5 into 5a and 5b. Similarly this C3b in presence of another complement protein which is the proper reading Pro paradeen it can associate with 3b Bb and form another C5 convertase which is known as the C3b Bb C3b so there are 2 C5 convertase is that are possible and they are formed one is C4b 2a 3b and C 3b Bb C 3b. So these two what we see in this part these two are C5 convertase is like these where C3 convertases this is a C5 convertase.

They are also sometimes known as C3, C5 convertase because they also still retain the property of C3 convertase but they are mostly C5 convertase. So they these C5 convertase can then cleave this C5 into 5a and 5b, 5b is a component of the membrane attack complex or the MAC. So it associates with other complement proteins like C6 C7 C8 C9 and forms the membrane attack complex and this is this tubular structure that is formed because of association of these complement proteins 5b 6 7 8 9.

So this is nothing but the membrane attack complex or the MAC and this MAC is nothing but a tubular structure that is inserted on the cell surface leading to formation of a whole and that leads to lysis of the cell. At the same time the C5 which has been into 5a and 5b the 5b as we see is mainly forming the membrane attack complex the 5a as well as the C3 which was also a clip product of C3 the 3a and the 5a these two together they can be important factors in enhancing inflammation.

And finally 3b as we have seen here three be independently other than forming the C5 convertase it can also lead to optimization it can go in coat the surface of the pathogen and assist the phagocytic process and lead to optimization. So this is our overview of the entire come are the three different complement pathways the classical the alternative and the lectin pathways. I hope you understand this, this is a very general overview how these three pathways are being activated.

The Cascade of the events that are occurring in the three different pathways how they are being activated and how they finally converge at the formation of the C3 convertase and breaking down the C3 into 3a and 3b and finally breaking down of C5. And either mediating inflammation or cell lysis or opsonization. So we will keep continue we will keep a continued discussion about this complement system in our next lecture as well for today that is all. So thank you very much.