Immunology
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Lecture No -41
Complement System Overview

So welcome to the immunology lectures and today we will start with one of the very important effector systems in the immune system we call it the complement system. So the complement system is one of the major effector systems of the humoral branch of immunity by now you have known what humoral immunity means what is how the innate system and the adaptive system they work together.

So the humoral immunity which is primarily the B cell based immunity and which is mostly mediated by the antibodies. Now what do these antibodies do we told in our classes in humoral immunity that these antibodies can do many functions like neutralization, opsonization but how were these functions mediated. So one of the very important effector system of the humoral branch of immunity is the complement system.

The complement system although it looks a bit may be a bit complicated but actually I will try to explain it very clearly and lucidly to you so that you get a idea how this complement proteins they act as part of this effector system and they actually kill the pathogen or they do many other functions they can also elicit inflammatory responses. So how was this complement system discovered and what exactly the role of the complement system is.

So although the compliment system as I told is the major effector system for the humoral branch of immunity there can be complement systems or complement activation which does not depend on the antigen-antibody reaction. So a branch of complement activation starts from the interaction between the antigen and the antibody. So when there is an antigen antibody interaction there is complement activation as well as there are antibody independent complement activation pathways.

Before we come to these pathways or describe this pathways we first try to understand or try to know what these complement proteins are and how they work and what they do actually. So the discovery of the complement proteins and as you can understand the name that it complements something that means it completes some incomplete job. Now what does it complement for so back in like 1890s there was a very interesting discovery from a very talented scientist Julian Bouquet.

So what he found was that he took the antiserum you know what the antiserum means so the antiserum contains antibodies. So he took the antiserum from frib colon infected person so took the antiserum and using that antiserum he applied that antiserum on the bacterium and when the antiserum was applied or given on the bacterium he found that the bacteria was eliminated that means it was dying. So the bacteria was killed so now definitely the antiserum contains something which is able to kill that bacterium.

And that something is probably the antibodies so of course the antiserum means it contains antibody to that pathogen but now what he did was so he heated that antiserum he heated it raised the temperature tried to denature the protein components inside. So if you heat the antiserum there will be denaturation of the protein components so it was denatured and used that antiserum against the bacterium.

He found as expected that the heated antiserum was clearly not able to clear that infection or kill the pathogen killed the bacterium. Now what he did was he took another fresh serum he took some fresh serum not the antiserum remember so it was not the antiserum the antiserum was heating activated so it was heated and supposed to be inactivated and it does not work against the bacterium. Now he took some fresh serum and added to that heat in activated and antiserum and he found that the fresh serum is expected not to contain any antibodies.

And because antibody is present only in the antiserum so the fresh serum that he took does not contain any antibodies. So it is not expected to work on the pathogen. So now he found that when he added this fresh serum it again became competent to kill the bacterium. So that was a

very interesting finding. So then there must be something in that serum which is complementing the function of the antibodies which are still present in the antiserum.

So heat inactivation actually killed or destroyed some components or some protein components which are not the antibodies the antibodies could still survive the heat treatment but those proteins were very labile to the heat treatment so they were destroyed. And upon addition of the fresh serum along with the antiserum again regained the bactericidal or the bacterial lytic activity so the cells that mixture of that inactivity antiserum and the fresh serum could actually lies the bacterial cells or kill the bacterial cells. So this was an interesting finding.

So then he thought there must be something in that fresh serum that is complementing for the inactive cell or the heat inactivated serum. So the heat inactivated serum is supplying the antibodies which were not destroyed due to the heat treatment but some other proteins which were serum components which were which are normally present in the serum they were destroyed.

Now when you give this antiserum when you give this fresh serum those components come in and they can now together with the antibodies from that heat inactivated antiserum they together can complement for this function and can lead to the Lyses and killing of the bacterium. So this experiment clearly established that the serum contains something which or some protein components or some components which are very much heat labile so they are susceptible to heat or sensitive to heat.

But their presence is important for the antibodies to work against the pathogen. Later on some years later another scientist called Paul Ehrlich. So Paul Ehrlich he actually later on worked on the same components and he coined the named for these components is the complement system or the complement proteins. Now what did this complement protein means that they can complement the function they can complement the function of the antibodies as the completes the function of the humoral branch of the immunity.

So that is the function of the complements. So these complement proteins later were studied very well and of course this person Julian Bouquet he received Nobel Prize in Physiology and medicine later on. And this was very thoroughly studied later on and people found that there are at least 30 different types of complement proteins that are present in our system and they are circulating proteins.

So are they are usually proteins or glycoproteins and they circulate in our system all the time in the blood. So they are always present in the blood but they do not act they only act when there is a pathogen present so they will act only in presence of a pathogen or in presence of an antigen antibody interaction. When there is an antigen antibody interaction they can start acting. So what do these complement proteins to and what they are actually.

Before we go into the complement activation pathways, so this complement proteins as I told this complement proteins there are thirty different proteins and they move around in the their moves around in the blood.

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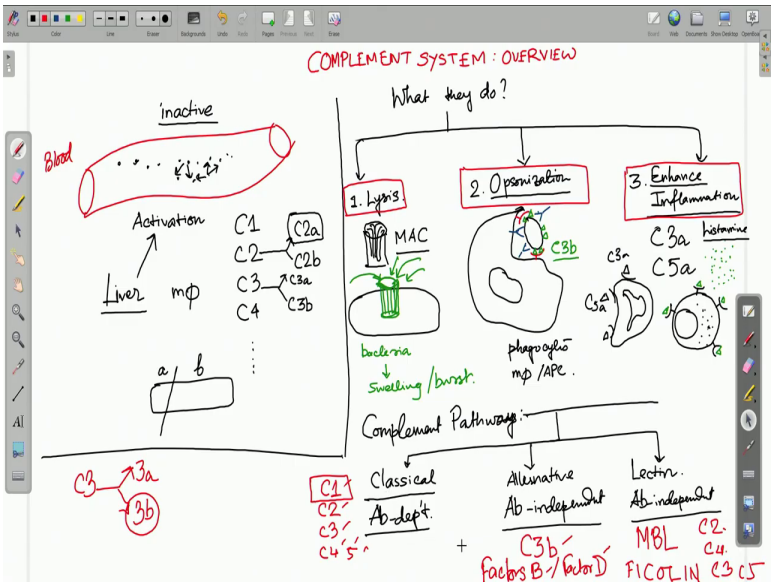

And so let us say in the bloodstream, so there are these complement proteins which move around in the in the blood but they are in inactive form. So they are in an inactive form, so they are not active what happens is whenever there is activation of the complement system whenever there is

activation these proteins they start activating each other. And this activation is primarily based on proteome protease activities.

So these are somehow these proteins they have prototypic activities of protease activity. So they can cleave each other and these proteins these complement proteins they are cleaved and they get cleaved into a small subunit and a large unit. So now these small and the large fractions that are the cleaved fractions they are actually the active complement proteins. And now they start to associate with other complement proteins right.

So their one stays they are cleaved they get activated they find another target protein and then associates with that target protein and starts to activate another complement protein. So this is a cascade the activation of the complement system is a cascade of events it goes on as a cascade as a chain reaction one after the other. And that activation leads to finally a certain killing of the bacterium. So now these proteins as I told they are moving around in the blood all the time in inactive form and then they are activated by that cleavage.

Now why do these proteins come from all these proteins they usually come from the major source of this protein is the liver and also to some extent from the tissue macrophages and to some extent from the epithelial cells of the GI tract and some these are minimum sources. So the maximum source that is where it comes from is the liver. Liver is the main source of these complements proteins. So they come here and they go into the blood they circulate in the blood and whenever there is a signal primarily from antigen antibody interactions they get activated.

And once they are activated they start cleaving each other so that is a very interesting phenomenon that they start to cleave each other. And once they start to cleave each other they generate active proteins or active proteases. Now these proteases in turn cleaves other complement proteins and this cascade of event keeps going on and until there is killing of the bacterium and how it kills the bacteria we will come to that or how it kills the pathogen we will come to that.

So these complement proteins just to understand the nomenclature this complement proteins are named like starting from they are called like named like C 1 C 2 C 3 C 4 likewise and they are cleaved products. So when they are cleaved like for example when C 2 is cleaved it can give rise to C 2a and C 2b. Similarly when C 3 is cleaved it can give rise to C 3a and C 3b. So usually when they are cleaved the smaller fragment is denoted by this term a this is a smaller fragment.

So if we call this is a compliment protein and it is cleaved like this so the smaller fragments are usually the they are designated by the a and the bigger they are designated by the b or the larger fragments they are designated by the b. So that is unusual convention. So similarly they can be cleaved into different fragments and these fragments they can associate with each other and they can form new enzyme complexes which can cleave further another target complement protein and this cascade of events going on.

So likewise these complement proteins as I described they are named like C 4 complement and depending on their identification that like the C 1 C 2 C 3 C 4 they have been named like this and the cleavage products are named like C 2a 2b 3a 3b likewise we will come across these cleavage products and what do they do how do they work we will come later on slowly. So now what do these complement proteins do?

So what do the complement proteins do? They primarily do three types of functions one lysis of cells. So what is lysis of cells? So the complement proteins when after this cascade of events they can form a structure like this the a cylindrical structure like this which is also known as the membrane attack complex or the MAC and this membrane at a complex on a target cell for example let us say this is a target bacterium.

And on the surface of this target cell or on the cell membrane this MAC or the membrane at a complex is inserted like a cylinder. So it has a cylindrical structure like this and on the star on the on the cell surface or on the cell membrane they gets inserted this they insert this cylindrical structure and leading to formation of hole or pore on the membrane. Now if you suppose you are forming a hole on the membrane that means that would lead to an osmotic imbalance and that would lead to in rushing fluids.

So fluids will immediately come in and that would lead to swelling and the cells will finally burst. So once there is an osmotic imbalance if you have a structure like this and that structure goes into the cell wall of the cell or the cell membrane and creates a hole on the cell then there will be fluids coming in there in rushing fluids very simple you were just making a small hole on the cell. And this structure is fund at the end of the complement activation process.

And this structure is also known as the membrane attack complex because it attacks the membrane in that how the name comes from it is called the membrane attack complex which goes into the cell membrane of the bacterium leading to the damage and leading to in rushing fluids. And finally the cell lysis it kills the cell. So it lysis the cell and it kills the self. A second way the complement protein act is known as opsonization.

If you remember we have used this term also in case of humoral immunity that is antibody mediated immunity. So opsonization basically requires the antibodies so it is a combined effect of the complement proteins and the antibodies. So opsonization primarily that means it helps or assists the phagocytes or the phagocytic cells like the macrophages. For example another a PCS so what happens is when there is antibodies they bind to the target pathogen on the surface of the target pathogen.

And as we also studied earlier there are complements receptors. So there are complement receptors on the cell surface particularly this macrophage this kind of cells the phagocytic cells they express complement receptors on their surface. And there are complement proteins as well so the complement proteins they coat the pathogen and are recognized by the complement receptors. When the pathogen is coated by the complement protein they are recognized by this complement receptors as well as assisted by the presence of the antibodies.

So there are antibodies which quarter or come and interact with the pathogen and as well as it is complemented by the cleavage products of this complement proteins. So for example one of the very important compliment cleavage products that mediates optimization is C3b so they can coat

the pathogen they can coat the pathogen and can initiate the process of optimization along with the or in presence of the antibodies.

And a third process that these antibodies that these complements can do is enhance inflammation. So enhancing inflammation and this is primarily done by the smaller fragments of the cleavage product that is like the C 3a C 3a C 5a so these are the 2C 3a and C 5a these are the major mediators of in enhancing inflammation. For example we discussed in our classes in the initial classes of inflammation innate immunity and inflammation we have discussed about the migration of the neutrophils.

For example so the neutrophils they can bind they have on the surface they express these receptors which can bind to this C 3a or C 5a and they kind of act as chemo attractants like we have described the chemokines as the chemo attractants. Similarly these compliment cleavage products particularly the smaller cleavage products they sometimes they also act as chemo attractants and they can also enhance inflammation.

And also they can do a second function that is the degranulation. So they can also bind so these granulocytes the masked cells they can express on their surface these receptors which can bind to this cleavage product of the complement or the complement protein cleavage products like C 3a C 5a and they can lead to degranulation of the mass cells a degranulation leads to the release of histamine. If you remember we have told in one of our initial classes regarding the release of histamine which actually leads to vasodilation and increasing vascular permeability.

So these are all assisting or enhancing the process of inflammation. So what does these complement proteins they finally do after they have been cleaved? They finally do these main three things one is lysis cell lysis second is opsonization and third is enhanced inflammation or inflammatory responses. So these are the three major functions that the complement proteins can do. Now let us come to the different complement activation pathways.

Now what how; these complements they get activated so we will be discussing about the complement now we have to know the complement pathways. So complement pathways means

the pathways that means how these complement proteins they initiate the Cascade of cleavage events. So the complement pathways can primarily be of three types one the classical pathway secondly an alternative pathway and thirdly also known as the lectin pathway.

So these are the three major pathways by which the complement activation occurs. The classical pathway as the name suggests it was one of the very first pathways that was being identified and it is the major pathway or the major effector pathway for the humoral immunity. So this is an antibody dependent pathway so it is an antibody dependent pathway. So it depends on the antigen antibody interaction it will not be initiated the classical pathway will not be initiated if there is no antibody antigen interaction.

The alternative pathway is an antibody independent pathway and the lectin pathway is also an antibody independent pathway. So this is an antibody dependent pathway this is an antibody independent pathway and this is also an antibody independent pathway. So a classical complement pathway usually is activated only when there is an antigen to antibody interaction and antigen to antibody interaction is initiated then only it starts to work.

Now before we start understanding the different pathways of the complement activation what are the components of these systems. So for example the classical pathway mainly is initiated by the C 1 the complement protein C 1 and the other components that are involved are C 2 C 3 C 4 5 likewise. So now the main component is the C1 and this component C1 is responsible for binding to the antibodies.

The alternative pathway does not require the C1 or the C2 the alternative pathway as I told is an antibody independent path so it does not depend on the antibody antigen interaction. So it starts only when there is C 3b present in the surrounding. It will start only in presence of C 3b so that means C 3 has to be broken into C 3a and C 3b. So the alternative pathway can start in two ways either there is some spontaneous breakdown of the C 3 into C 3a and C 3b so the C 3 which breaks into the C 3a and the 3b.

And if there is this 3b available then the alternative pathway will start. Alternatively it can also start as a helper pathway for the classical activation that means when the classical pathway has already been initiated then the alternative pathway can start is a signal amplification system. So it can even amplify the whole thing. And the lectin pathway is primarily activated by certain lectins that means which binds to the carbohydrates.

And they are activated when this kind of lectins like for example MBL or mannose binding lectin they can mannose binding lectin they can bind to the carbohydrates the mannose moieties the carbohydrate moieties all the surface of the pathogen. So they recognizes the carbohydrates on the surface of the pathogen by this kind of lectins like mannose binding lectin there is also Ficolin. So these are the components of the lectin path which is also an end antigen or antibody independent pathway it starts primarily by recognition of the carbohydrates or which are present on the surface of the pathogen or the bacterium.

And the components are pretty much similar to that what we see in case of the classical pathway so it also contains a C 2 the C 3 the C 3 and the C 5 and in this case in case of the alternative pathway we have two factors which are also actually compliment protein they are named like factors factor B and factor D. So these are the components of the alternative pathway so the classical pathway comprises of the complement protein C 1 C 2 C 3 C 4 C 5 mostly.

Then the alternative pathway comprises it starts from the C 3 only the C 3b and it has the factor B and the factor D and the lectin pathway it is dependent on the binding of these lectins the MBL or the Ficolin which can bind to the carbohydrates or the that are present on the surface of the pathogen and they also have these complement proteins like C 2 C 3 C 4 C 5. Now all these complement pathways we will see in our less next lecture we will see how these all these complement pathways they converge.

And the main objective of this complement pathway kind of the central part of the complement pathway is the complement protein C 3 all their efforts are towards breaking down the C 3 into C 3a and C 3b because unit C 3b one of the major components that you need for the opsonization

process or the membrane attack complex formation they are the C 3b and the C 5b. So C 3b is one of the central components you need a lot of C 3b.

So you need to break down the C 3 into 3a and 3b and that is the central part of the complement system. So all these pathways beat the classical or the alternative or the lectin pathway they converge at a point and they all try to break down the C 3 into 3a and 3b that is the main objective and for that these cleaved products of this complement system they try to associate with each other and form a complex which also is described as a C 3 convertase.

So their objective is to form a C 3 convertase and a C 3 convertase basically converts C 3 into 3a and 3b. So we will see in our next lecture how this complement pathways they try to produce this C 3 convertase and how this C 3 convertase is actually breaking down C 3 into C 3a and C 3b. So this will we will discuss more in details in our next lecture, thank you.