Immunology
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Lecture No -43
Complement Biological Consequenes

So welcome back to the immunology lectures and we will start discussing so we started discussing about the complement activation pathways in our last lecture. And we will continue discussing about the complement pathway and try to understand what exactly are the biological consequences? So what does this complement system actually do or what are the functions that they perform so what we have learned what we see on the board right now is the complement activation pathway.

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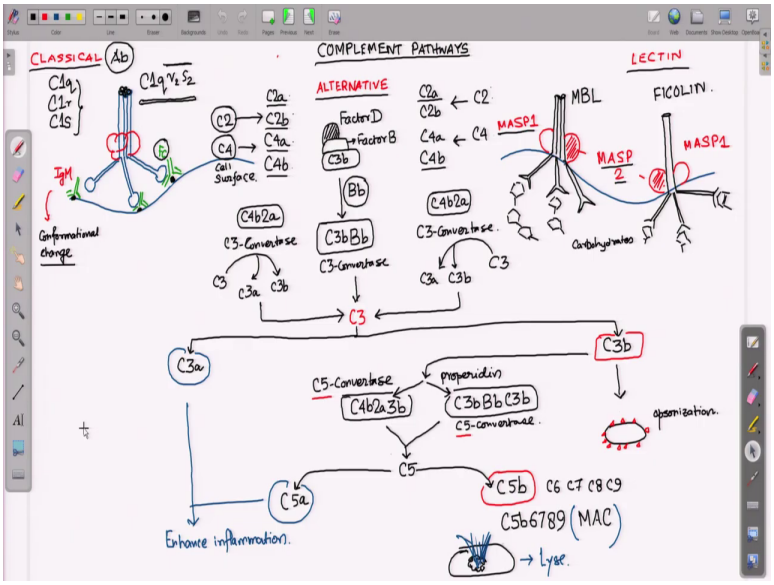

So how the whole cascade of complement starts to work all the complement proteins they starts to activate each other and the cascade starts working, so that was the whole idea. So what we found in this entire in the complement activation pathways or what I described in the last class as well that once there is antigen. So there are three major pathways there is a classical pathway the alternative pathway and the lectin pathway.

And the classical pathway starts with antibody antigen binding alternative pathway starts only when there is C3b present only in presence of C3b the broken product of the C3 and the lectin pathway is primarily it is also an antigen independent pathway it is not an antigen dependent pathway. So the lectin pathway also starts with the interaction of certain lectin molecule specialized lectins like mannose binding lectin or Ficolin with the carbohydrate moieties on the surface of the pathogen.

And all remember all these reactions most of these reactions in the or the complement activation pathways they occur on the surface of the pathogen it is all on the pathogen surface and they are all of them if you see they converge at this point of formation of C3 convertase. So at least three different sources of C3 convertase we have seen in the last class the formation of 4b 2a both from the classical and the lectin pathway.

So the classical and the lectin pathways are pretty much similar in that way or their activities are pretty much similar in that way one is just comp antibody dependent and other is antibody independent pathway and then we have the alternative pathway also where we get C3bBb so breaking down of another factor B and formation of 3b Bb so it is 4b 2a 4b 2a and 3b Bb these are the three different C3 convertases and the main idea is the central ideas is to amplify the signal and the signal amplification occurs at the level of C3 be formation.

So C3b is the main molecule that is required in all the effector paths. So C3 is broken down by the C3 convertaseis that are being formed after so much of a fourth from all these complement proteins they give so much effort to do one central job that is to break down the C3. Now they have broken down the C3 into C3a and C3b. Once C3b is available this C3b can perform its function in two ways one is directly another is again in association with other complement proteins.

And what is that that is in presence of 4b 2a it can associate with the 4b 2a that is one of the C3 convertase and produce another convertases which is known as the C4b 2a 3b and it is a C5 quantities. So which means it converts C5 to 5a and 5b. So these are the two cleavage products

of C5. Similarly this C3 be in association with another protein called proparadeen can also associate with the C3 convertase derived from the alternative pathway which is the C3b Bb.

And finally it forms another C5 convertase which is the C3b Bb and C3b. So basically this contains three different cleavage products three different broken cleavage products which together they form a bigger complex. And this most of these complexes they are membrane anchored complexes so they are anchored to the membrane of the target cell usually the pathogen. And this is the C5 convertase so these both of these are C5 convertase and they again as the name suggests they can convert C5 into 5a and 5b.

Now comes the main point so now we have come to a situation where we have a load of C3b and we have C5b. We also have C3a and we also have C5a. So now how all these broken products are the cleavage products of the complement system they finally mediate the action or what do they do so for that we need to understand the biological consequences or the functions that all these complement proteins or the cleavage products of the complement proteins they do.

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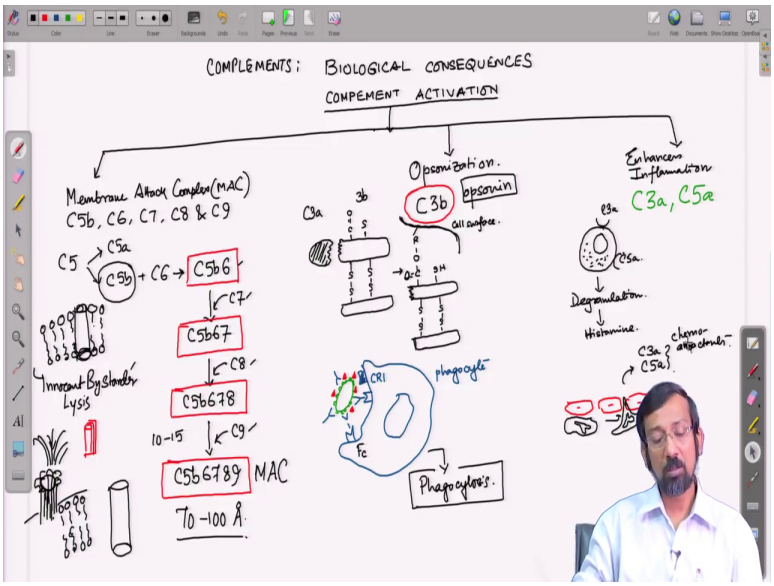

So after the activation of the complements, so complement activation that is what we learnt in our last class this occurs and this leads to at least three different consequences. So one of the major consequences that we know or we have told or discussed about is formation of the membrane attack complex or we also call it the MAC. Now how is this MAC formed and what

does it do? We have to understand what is this MAC is actually and what it does to the target cell.

A second thing is opsonization and a third thing is enhances inflammation. So these are the three major functions that the complement proteins perform among these this opsonization is an antibody driven process membrane attack complex it is primarily driven by other complement proteins. And what are the complement proteins that are involved the major complement proteins that are involved in this are C5b C6 C7 C8 and C9.

So now what does this membrane attack complex to and how is this formed C5 as I as we discussed in the from the last slide or in the last class that C3 is broken down to 3a and 3b and this 3b is the magic molecule. So this 3b is the central molecule this 3b can form 5 C5 convertase and it can function independently as well so that is it can have direct action on the cells. So this is one of the functions by which it has produced the C5b.

Now and this C5b which is produced on the surface of the cell it is a cleavage product of the C5 it has formed C5a and C5b. So once this a are produced we take this a here so C3a and C5a we put them here because they are the major mediators of inflammation. We will discuss about how they do the inflammation or mediate the inflammation later on but for the time being let us look into this membrane attack complex.

So what happens is the C5b when it the cleavage product is formed this 5b is a very labile product it is not very stable and it cannot survive like that otherwise it will be degraded. So it cannot survive like that for more than two minutes. So then it has to be protected or it has to be stabilized and who does that so it is being done by the C6. So C5 which is broken into C5a and C5b and the C5b then associates with C6 and forms what we call is C5b6.

Now this is a rather stable complex because C5 itself gets degraded very fast. So this cannot survive more than two minutes and now it forms this C5b6 complex now as soon as this 5b6 complex is formed immediately the C7 comes in and it binds to this C5b6 and forms the C5b6 7 complex and this C5b67 complex is kind of already competent enough to lies a cell or go into a

cell into the cell membrane why? Because as soon as this C5b6 complex is formed and it binds to the C7 unit then there is a structural transition.

So there is a structural transition a conformational change what we call normally in in terms of structure. So there is a quick conformational change and this conformational change actually exposes the hydrophobic patches or the hydrophobic residues on the C7 on the surface now that leads to imports more hydrophobicity on the surface and leading to its as this assembly of 5b6 5b67 to get inserted into the hydrophobic cell membranes.

You know because the cell membranes are usually they have a hydrophobic environment because of this lipid bilayers. So this kind of lipid bilayer is usually present in the membrane and something that has to go inside this lipid bilayer has to be hydrophobic. Any hydrophilic things cannot go in they have the these lipids they have a polar head and the non-polar tail and this non-polar tail or this hydrophobic tail does not accommodate anything or any charged molecules.

So anything that is hydrophobic that will very nicely accommodate here. So similarly this kind of a complex can very easily go inside. Now sometimes this as I was telling you that most of the time this complement activation process and the assembly of these complement proteins they take place on the surface of the cell. But sometimes they are also taking place not only on the surfaces but also in isolated complexes.

And if so happens then sometimes these isolated complexes which can move around actually they can go and create the same damage to a cell which is not the target cell but it is nearby this target cell. And that can happen when this C5b67 is already formed and once the C5b67 is already formed it can go and get inserted into the membrane of a nearby cell which is not the target cell and this phenomenon is sometimes described as innocent bystander lysis.

So you know innocent bystander means the one that is standing by there is standing next to it is innocent but it just gets affected so it is it is just a faulty thing or a mistake of the system that can happen sometime that it can kill an innocent cell instead of the target cell. This can also happen and this phenomenon is known as the innocent bystander lysis this can usually happen starting

from this 5b67 which is competent enough to go into the cell membrane and can cause the lysis of the cell.

So now the next step is once this 5b67 is formed then the next complement protein the C8 immediately binds 5b678 complex is formed and again this complex undergoes a similar conformational change the C8 and which is a outermost part so they come one after the other and they form our tubular structure like this and the C8 which is now the outermost one it can also undergo a structural transition.

And then what it happens is it allows binding of C9 now the C9 usually binds in huge number it is not a single say night. So it can bind like 10 to 15 C9 molecules can bind together and form something what would look like something like this and a hollow cylindrical structure like this will be formed. Now this structure can go into the cell membrane and that would lead to a damage of the cell membrane.

So there will be a hole or a pore formation on the cell membrane leading to in rushing fluids leading to disturbance in the in the tonicity so the cells will basically there will be in rushing fluids and the cells will swell and the cells will finally die. So they will burst and die so what is formed here is C5b 6 7 8 9 and this is nothing but the membrane attack complex. So this membrane attack complex this usually has approximately the size ranges in the range of 70 to 100 angstrom.

The size is approximately in the range of 70 to 100 angstrom and it looks like a cylindrical structure and this cylindrical structure gets inserted on the membrane of the cell and forms a channel or a pore and allows the entry of the fluids and leading to bursting of the cell or and finally leading to killing of the cells. So this is one of the way that the cells that the complement system actually can destroy the cells directly.

So after the activation pathway the final product that is formed is the C5b associates with the C6 and that in turn associates with 7 8 and 9 and finally it forms the C5b 6 7 8 9 complex and this 56789 complex is known as the membrane attack complex and this membrane attack complex as

the name suggests it attacks the membrane it goes and gets inserted into the membrane and leads to killing of the cell.

But usually these events they do not happen to our normal cells they usually happen to the target cells. So the system is very well designed to recognize the target cell only sometimes as I told it can so happen that these complexes are formed not formed on the cell or the target cell and can lead to what we know what is known as the innocent bystander lysis. So lysis the cell that is standing next to it, so this can also happen sometime but usually does not happen and why it does not happen we will discuss in our next classes.

So let us look into the other process by which complement activation actually shows is its effect so it is biological consequence that is by opsonization. So again C3b we will come across this C3b molecule several times because the C3b is the central and the wonder molecule. Now how does this C3b look like? So this C3b usually there is an internal thioester linkage by which it can actually have or get an attachment to the cell or the target cell.

So this is how the C3b looks like and this is the 3b the 3b and this is C3 a so this this portion is a C3 and this is the soluble part and this C3a goes here. So this is a soluble C3a and this remains bound to the membrane how, to consider this as a membrane. So it reacts with this free hydroxyl or the amine groups and it can remain bound like this and this is how the C3b can get bound to the surface of the target cell if this is the target cell for example.

If this is the surface of the target cell so and that is how it can even coat the cell surface. So for example if there is a pathogen if this is the pathogen for example a bacteria it can get coated by the C3b molecules directly by this by this interaction. And then of course there are antibodies which are produced there are antibodies that are produced and they can also bind to the target cell. Now this target cell or the target pathogen is then recognized by the phagocytic cells.

So the phagocytic cells or the phagocytes so let us call this the phagocyte. These phagocytic cells they can recognize this by specialized receptors like the complement receptors the Cr1 for example. They can recognize by these complement receptors as well as there are this FC

receptors which can bind to this region of the antibodies. So when there is these two reactions occurring together. So when there is an antibody binding to the surface of the target cell as well as C3b molecule which is also known as an opsonnin.

Because of its opsonization function it is also known as an opsonin so it is primarily known as the option in so this kind of C3b molecules they coat the surface of the pathogen they coat the surface of this pathogen in as well as the antibodies which are formed these antibodies they also coat the surface of the pathogen. So when these two interactions are complete that leads to internalization or phagocytosis. So this makes phagocytosis complete so that would lead to finally internalization and phagocytosis.

So that is how the C3b actually the C3b molecule mediates opsonization so the C3b molecule usually the C3 the entire C3 it can remain bound to the surface of the cell and when there is a cleavage of this C3 by C3 convert is for example that would lead to C3a and C3b the C3a is usually the soluble part and the C3b is the insoluble part because it remains bound to the membrane.

So now this C3b can other than leading to formation of C5b and membrane attack complex and all these things the C3b can directly coat a pathogen surface it can go and bind to the surface of the pathogen by this kind of a linkage shown here. So it can go and bind to the pathogen surface and as well as the pathogen or the bacterium it can get coated by the antibodies and together they can bind to the receptors on the surface of the phagocytes.

So the Cr1 the complement receptor or the FC receptors and these FC receptors can bind to the FC region of the two bodies. So when these two types of bindings are complete then this phagocytosis can occur and the cell is then internalized and killed. A third process that the complement proteins initiates or the cleavage product of this complement proteins initiates is enhancing inflammation so they can bind to receptors that are expressed by this type of cells specialized cells which condenses granules or the granulocytes.

And binding of these receptors binding of this complement cleavage products can lead to degranulation. We will study more about Deccan relation your next classes so that leads to degranulation and releasing primarily histamine and other mediators of inflammation. Like for example prostaglandins so this process is known as the degranulation and this is primarily mediated by the soluble cleavage products or the smaller cleavage products like the C3a and C5a.

It can also lead to if you remember one of our very initial classes where we studied about the inflammation or the inflammatory responses and we have described about the extravasation of the neutrophils for example. So, the neutrophils the extravasation of neutrophils that also or migration of the neutrophils that can also be mediated by the cleavage products of the complement cleavage products or the soluble cleavage products like C3a and 5a.

So this can also act as chemo attractants and this can also enhance inflammation so they can bring more and more of these neutrophils more and more of these phagocytes the monocytes they can come to the site of action, so that leads to enhanced inflammation. So they can either lead to degeneration and release of the histamine and other mediators of inflammation like prostaglandins or they can also assist in migration of the leukocytes migration of primarily the neutrophils to the site of action and by that they can lead to enhancement of inflammation.

So what we learnt in this lecture today is that the complement system mediates its action. What we learnt in our last lecture is how the complement system gets activated what are the major activation pathway is how they cleave each other and gets activated. And what we learned today in this lecture is that how these activated complement proteins or the after activation how cleavage of these proteins can lead to.

Finally what are the biological consequences of this activation of the complement pathway and they can kill or destroy the target cells. So one of the ways it does is by formation of the membrane at a complex the MAC. A second way it does is by opsonization along with the antibodies it helps the antibodies as well so along with the antibodies it helps in engulfment of the pathogen or phagocytosis of the pathogen and the third is it can enhance inflammation.

So these are the three major ways that the complement protein actually performs their function. Now the question is so if these complement proteins can do so many things so many harmful things why do not they do it to our self cells to our own cells it targets the pathogen. It only creates membrane attack complex on the pathogen it only opsonise the pathogen or quotes the pathogen surface. So why or how this when there is no infection in the body the complement proteins are still there.

The complement proteins are still moving around. So why does these proteins even though they are moving around in the body they do not really attack the cells of our body or they do not really do anything any inflammation or anything. So, why this is happening, why the complement proteins do not perform these functions normally or do not get activated normally. So of course there is a reason and the reason is that there is a very tight regulation.

There is a very tight regulation and there is another class of proteins which are known as the regulator's. The regulators of complement activation the RCA, so this class of protein the regulators of complement activation this class of protein they do not allow the complements to even if there is a cleavage even if there is a breakage and formation of C3b availability of c4b even then there are regulators which will not allow the complement to perform all these functions or the complement system to perform all these functions.

And they are known as the RCS or the regulators of complement activation we will discuss about the RCS and the complement complex regulatory processes in our next lecture. So that is all for this lecture and thank you very much.