Host-Pathogen Interaction (Immunology)
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Module No # 09
Lecture No # 46
Complement – Classic Pathway

Hi, so in previous session we have learned about the discovery of complement and what are the different pathways of complement and what are the various molecules involved in complement pathway? And now I will take you to individual pathway and in this session I will take you to the classical pathway. So this classical pathway is if you remember the previous session it is triggered by antigen antibody complex.

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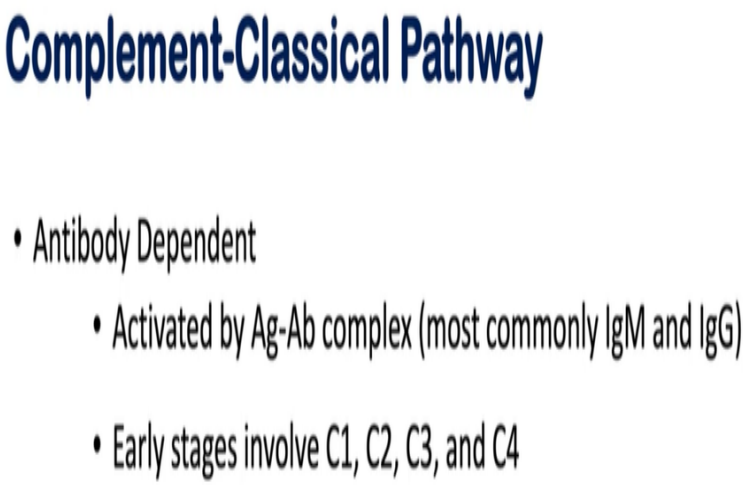

So let us look at how it is activated so basically this is antibody dependent this is the only complement pathway which is activated by antigen antibody complex therefore classical pathways antibody dependent activation pathway. So it is activated by various kinds of antibodies this is igM and igG. So igM is very effective in inducing the complement pathway compared to the igG.

And there are, several sub type of igG which you will learn when I will take up the antibody and not all subtype induces or activate the complement pathway some of this igG subclass can only activate the complement pathway. Here just one more information I would like to tell that igM has a more potential to activate complement pathway you will understand only one molecule of igM is needed in order to, activate the complement pathway.

On another hand in order to activate same level of this complement pathway 1000 igG molecule is needed. This is the one important information of course early stage activation needs the C 1, C 2, C 3 and C 4.

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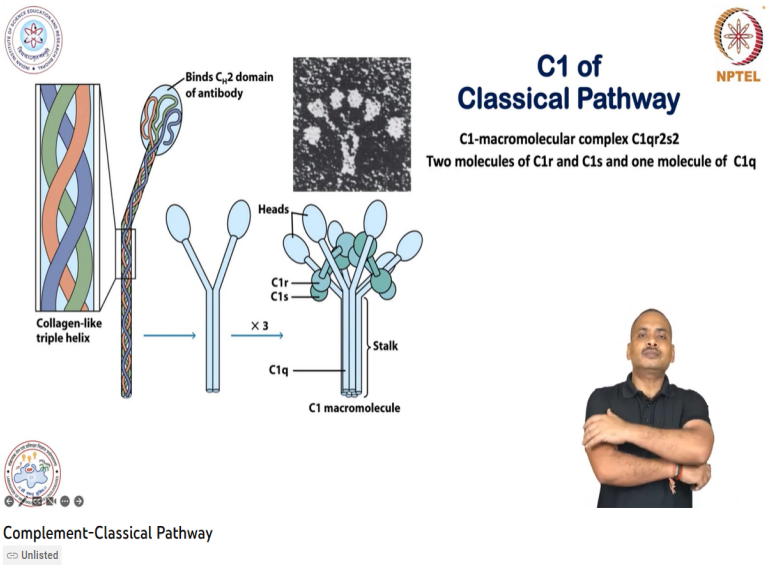

So I would like to discuss in more detail about C-1 so there are here you can see that there are various C-1 sub type. This is basically C-1 is a macro, molecular complex it is a quite big molecule as you can see here and this is basically consists of C-1-q and 2 unit of C-1-r and 2 unit of C-1-s. So this basically here you can see that there is a C-1-q and this C-1-q there is a more resolved schematic of C-1-q.

Here you can see that there is a triple helix structure it is a collision triple helix structure I do not know if you studied, the biochemistry this triple helix structure is present in one more very important biomolecule which we call it as a collagen. So this collagen is rich in if you remember this is rich in proline as and this proline is basically not present as a proline it is present as a hydroxyproline.

And for making this proline to hydroxyproline there is a need of enzyme which needs the vitamin C, probably you may remember just I am giving you as information. So this C1q has this collagen like triple helix structure and this subunit basically binds with the antibody molecule and in antibody there is a one region which we call it as a C-H-2 domain. So what; is C-H-2 domain I will show you in subsequent slide it is better to understand the structure of antibody so that you are able to, understand the things much better.

And this C1-q is basically making a complex width here you can see that 2 subunit of C1r. And C1-s so this complex is verified by electron microscopy here you can see there is on top there is electron micrograph of this complex. Now let me show you the structure of antibody.

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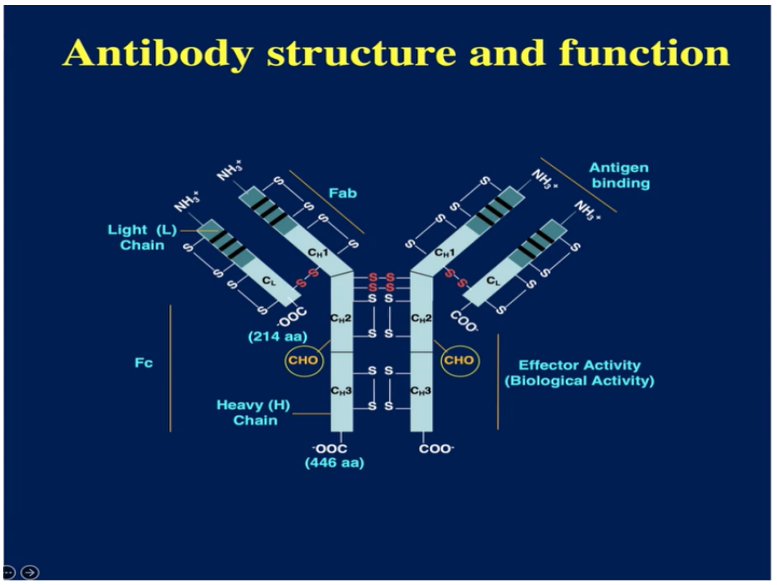

So this is just for a quick understanding I will again discuss this, structure when I will take the antibodies. So this is a one class of antibody the structure which I am showing this is mainly the immunoglobulin g the structure is more resembled with immunoglobulin g. So this immunoglobulin g is having a 2 light chain here you can see there are 2 light chain and it is basically consists of 214 amino acid and there is a 2 heavy- chain.

So this heavy chain if you see carefully there is a C-H-2 region and this C-H-2 region basically bind with C-1q ~~cubed~~. And this basically this light chain and heavy chain joined together by various interactions and one of the important direction interaction is by disulfide linkages. Here you can see that these 2 chains are basically linked by 2 disulfide linkages and, there is some antigen binding region which is present in both light chain and heavy chain.

So this antigen binding region basically bind with the antigen and then there will be some conformational changes taking place in this molecule and this conformational change will be noticed or that will also induce the conformational changes in C1q molecule. Our subunit of C1 complex this, conformational change will be detected or sensed somehow by this C1q and then it will interact.

So there is a effector region this I will discuss more in when I will take up the antibody. Just for your simple understanding you should remember there is a F a b part of antibody F a b

here you can see which is basically binding with the antigen and there is a F c portion. And this portion is, basically playing an important role in biological activity and just for your information antibody molecules are heavily glycosylated here you can you can see there is a CHO so this region is heavily glycosylated.

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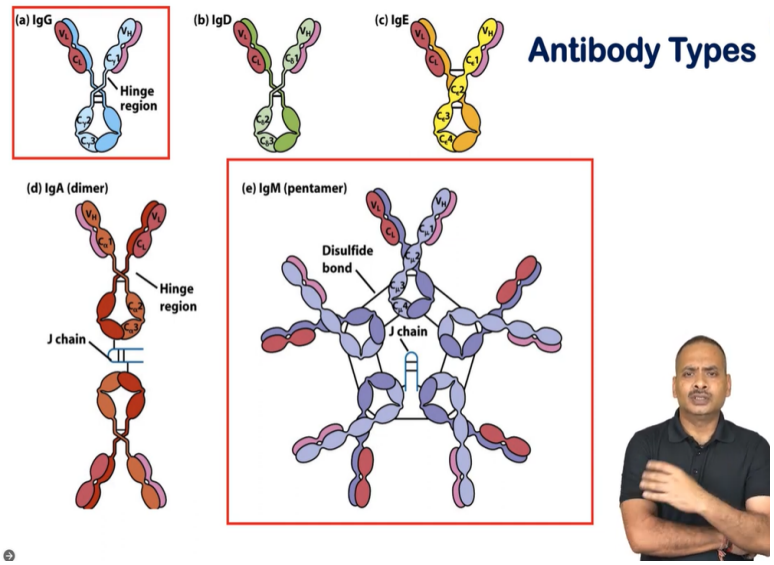

And there are several kinds of antibody here you can see that there are 5 kinds of antibody that is IgG, IgD, IgE, IgA and IgM. So among these several kind IgM is as I told you in previous slide that IgM is a very strong in making this classic or activating this classical pathway and this IgM is basically pentameric in nature. So you can see that there are 5 basic unit of antibodies are joining together and that makes a IgM.

And this is very strong this has a more potential to activate the classical pathway compared to the, another molecule which is a IgG basically Ig stands for immunoglobulin and m is a type.

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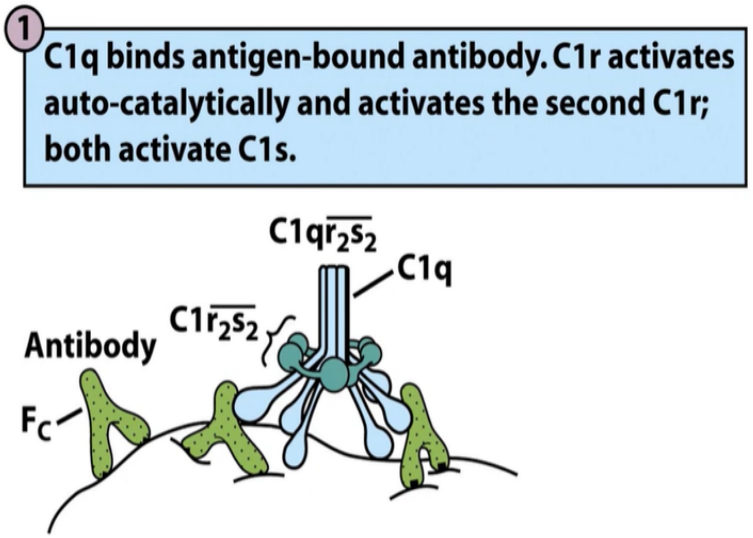

So this is just basic information about the antibody now I will talk how this classical pathway get activated? Here you can see there is a very beautiful schematic and this is a this is a quite self-explanatory. Here C1q basically binds with CH2 domain or CH2 portion of antigen antibody which is, bound with antigen. And this when it is binding then C1r get activate and once it will be activate there will be a ~~con~~ auto catalytic activity.

And this auto catalytic activity basically activates second C1r molecule and eventually the both activate C1s component of C1 complex here you can see there is a very good schematic.

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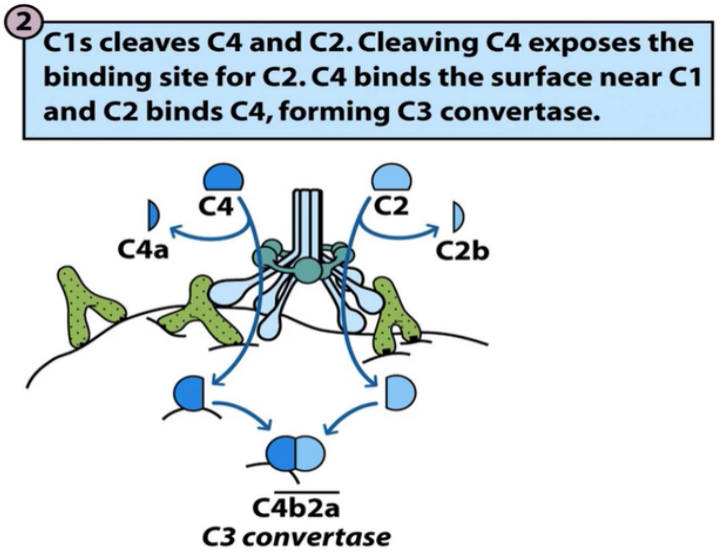

Second step will be one this C1s is get activated then this cleaves the complement C4 and C2. So C4 and, C2 once it will be cleaved then this will basically C4 exposes the binding site for C2 and this C4 binds the surface near C1 and C2 binds C4 and forming. If you remember the

aim of activation of complement is to generate C3 convertaseers and here the C3 convertagse is basically C-4-b-2 a, and this has an enzymatic activity. So once there will be a lot of C-4-b2a this will convert lot, of C-3 into C-3a and C-3b and 3b will be coated over the microbial pathogen.

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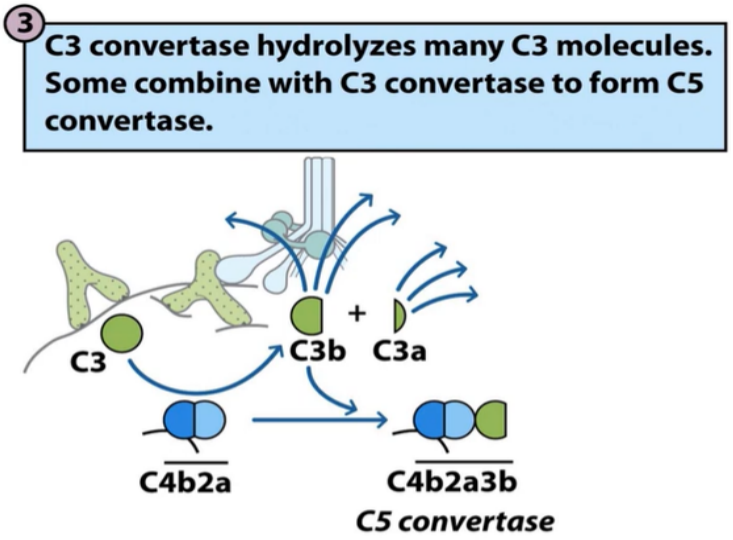

The third step is which is quite obvious and quite clear that this C3 converters as I explained you hydrolyze or breaks the C3 molecule into basically it will generate the C3a and C3b. And C3-b will be coated over the over the target microbe nd-and then it will be RReadilyidly phagocytose. Another thing that will also, generate the C5 convertaseers so C3b which is interacting with C4b2a which has already enzymatic activity it will interact with C3b, and it will acquire another enzymatic activity that is enzymatic activity for making C5 break and that is and that enzyme will be C5 convertase.

So C5 convertaseconverters I will repeat again the C3 convertaseconverters basically make a lot of C3b so, one future of the C3b molecule will be coating to coating the microbe and then it will be phagocytose. Another aim is to make a C5 convertaseconverters so this C5 convertaseconvertage is generated when C3 convertaseconvert is which is C4b and C2a which is having a C3 convertaseconvert is this will interact with C-3b and that will generate the C5 convertaseconverter is activity .

And eventually the C5 convertaseconverters will be C4b to a and 3b so this C5, convertaseconverters is needed for generating lot of C5a and C5b.

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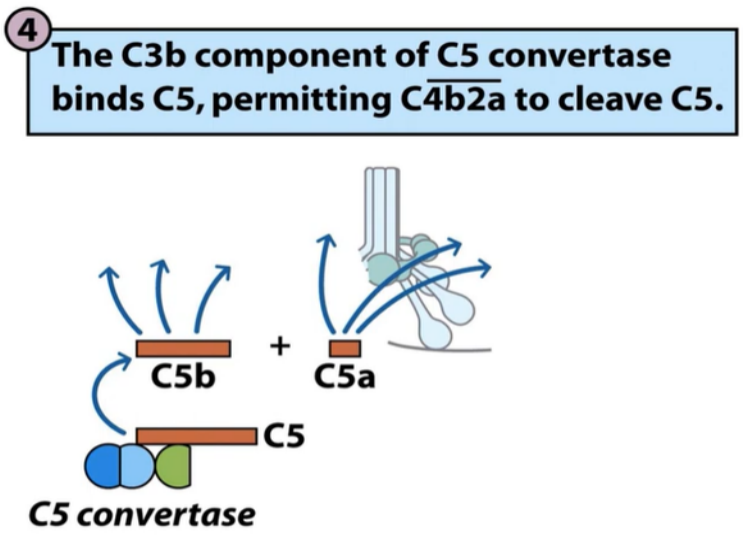

So here you can see that this there will be a generation of C5b and C5a so this the C3b component of C5 convertase~~convert~~ is bind with C5 permitting the C5 C4b2a to cleaves C5. And this C5 convertase~~converter~~ is or C5b binds with C6 and initiate the formation of membrane attack complex. Here you can see that this membrane attack complex is, formed and then and this is basically supported by C9. And this C9 basically make a pore in the target cells and this C9 is a basically making the membrane attack complex.

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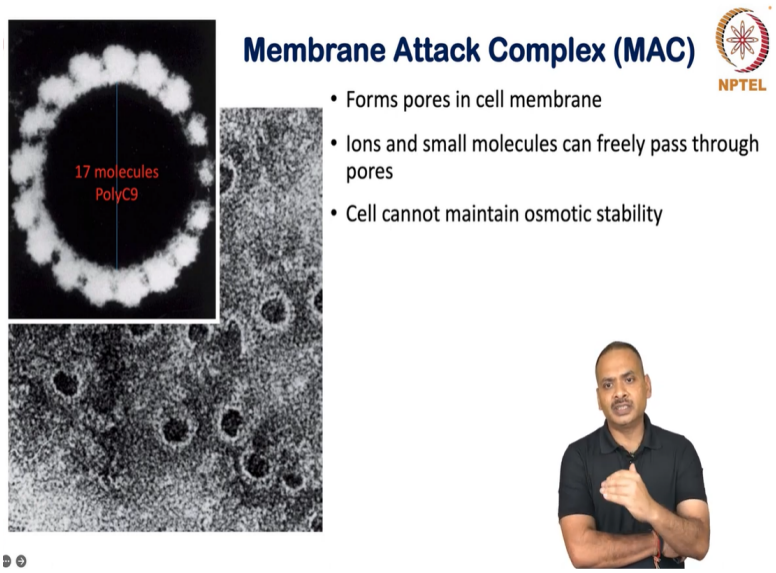

So there is a lot of evidences about this membrane attack complex here you can see this is electron micrograph and this electron micrograph is showing a big pore in the target cell. And basically there is a 17, molecules of poliey C9e and this poliey C9 basically makes a pore. So this membrane attack complex it will make a pore in cell membrane of target cell. And iron

and a small molecule can freely pass through this pore and the cell cannot maintain the osmotic stability and eventually the cell will die.

So this is all about the classical pathway in subsequent session I will talk about, alternative pathway and Lectin pathway. And I will also talk about the disease associated with complement dysregulation thank you.