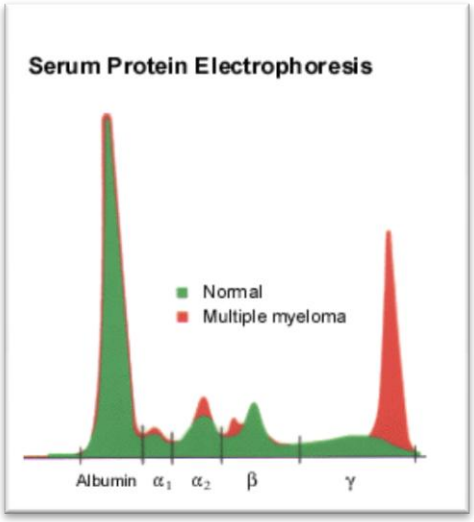
IMMUNOGLOBULINS

Immunoglobulin (Ig) has a common name which is "Antibody (Ab)", but actually we should say Ig, why? Because the proteins, which are involved, are actually globular proteins "known as globulins" and since they're involved in the immune system we called them Ig.

If we do a serum electrophoresis of serum proteins, we'll find the albumin (1st one to be observed), $\alpha 1$, $\alpha 2$, β, γ. So the last one to the right is the γ peak .Since most of the Ig migrate to the γ region, we called Ig "gammaglobulins".

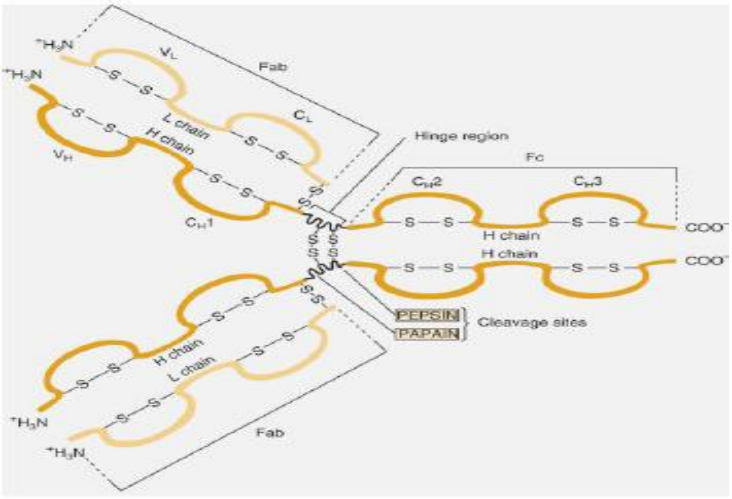


If we look at the Ig molecule ,it consists of 2 pairs of **identical** chains (polypeptide chains).If we put a line through the middle, it'll look like something on the mirror (mirror image).The ***light chain*** is the small one, the other (the larger one) is the ***heavy chain.***

So, there are 2 identical light chains & 2 identical heavy chains in Ig molecule. There're **disulfide bonds** that keep them together .Ig is represented as Y-shaped.

There're 2 terminals of the polypeptide:

1) NH2 terminal (amino-terminal) 2) COOH terminal (carboxylic terminal)

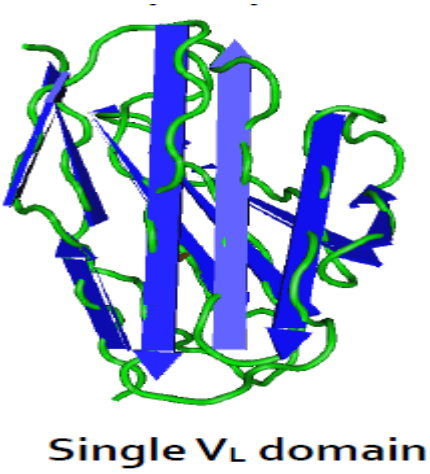


Light chain ~22-23 KDa whereas the heavy chain ~55-60 KDa

Light chain is made of 2 segments/domains.

REMEMBER: *Domain*: - is a specific structure that actually belongs to the Ab (Ig) and forms part of many of the molecules that have a role to play in the immune response.

So we've many molecules that have this domain structure and they're referred as member of the **super immunoglobulin family.**


Single V_L domain

This domain is actually a schematic representation, but in deep, each is made of β-pleated structure. The polypeptide runs in strands and loops. Light chain is made of 2 domain, one domain at the NH2 terminal and the other at the COOH terminal. This structure of strands and loops is maintained by the disulfide bonds and known as" β-pleated structure", which is considered the base of the domain , giving the whole of the Ig accounts for the globular structure.

Number of amino acids that constitute the domain ~110-120 a.a

When we come back to the Ig molecule, we find that the light chain is made of 2 domains, the domain which is on the outside ⟹ ***Variable domain*** (there're changes in the a.a) but the one that's inner to that ⟹ ***Constant domain*** (fixed, NOT changed).

When we come to the heavy chain, we find on the arm of the Ig 2 domains; one is ***constant*** and the other is ***variable***. Also on the stem of the Ig, we've domains and this depends on the class of the Ig.

IgM & IgE : have 3 domains "so the total is (5) ;2 on the arm & 3 on the stem"

(1) Variable domain & (4) constant domains.

IgG ,IgA & IgD: have 2 domains "so the total is (4) ;2 on the arm & 2 on the stem"

(1) Variable domain & (3) constant domains.

In order to compensate the extra domain, there's a ***Hinge*** which is a bit elongated area , it's found in IgG, IgA, IgD and it's absent in IgM & IgE (because they've an extra domain

"4 constant domains"). Some people say that the hinge region is a remnant of a domain, so if it don't have 4 constant domains ,there must be a hinge which is a remnant of the 4th one that doesn't present.

If we applied a ***Papain*** to the Ig, it'll be splitted into 3 fragments; 2 identical Fab and 1 Fc. Fab(antigen-binding fragments) is the area where the contact between the paratope and epitope occurs .

REMEMBER: paratope: area on the Ig which contacts with the epitope on the antigen.

There're 2 Fab with the same specificity(they are the same, because both of them have the same heavy and light chains). The function of Fab is to recognize antigen.

Fc(crystallizable fragment) because when we leave it in a solution, it actually crystallizes. It is the stem of (Y)shaped Ig. The function of Fc is mediating the biological effect or function of the Ab, because Ig firstly recognize the antigen, after that they do an effect which is biological mediated by the Fc.

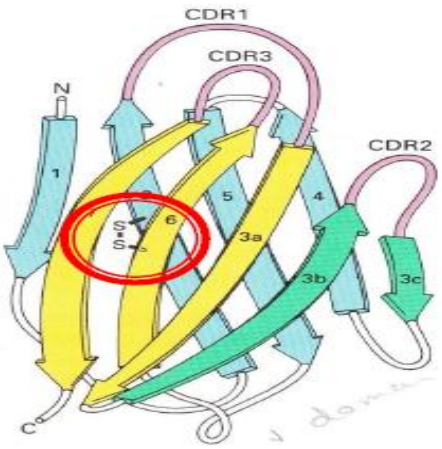
Variable domain has variability in the sequence of a.a (here the dr said that the domain has ~110 a.a and we've mentioned earlier that ~120 ! so it's not the accurate # but it's approximately between 110—120) and in certain areas there is a lot of variability.
but the constant domain do NOT change{the sequence of the a.a is the same}

The variability in the a.a sequence will produce variability in the electrostatic charges, hydrophobic forces, hydrogen bindings, Van der Waal's.

The specificity of the Ab is dictated by the sequence of a.a at the point of contact between the Ab & antigen.

There're 3 areas in these variable regions; one at 26 a.a ,2nd one at 53 a.a, the last one at 96 a.a

These regions are called ***Hypervariable regions*** which have a lot of variability. Another name for them is ***Complementarity-determining regions CDRs*** .



CDR1 → 26 CDR2 → 53 CDR3 → 96

They're far away from each other, but in the conformational status of the domain, they'll be close to each other. So we've a variable domain on the light chain with 3 CDRs.

Also the heavy chain has a variable domain which also has 3 CDRs.

The (3) CDRs of the light chain with the (3) CDRs of the heavy chain come together to make the paratope that's going to determine the complementarity between the Ab and the antigen.(Also we can say they'll produce a cleft that will bind the epitope on the antigen).

NOTES : – NOT only one a.a in the variable region will be changed.

– The loop has more than ONE a.a

We've 2 varieties of light chains (kinds):-

1) Kappa, K chains 2) Lambda, λ chains.

We've 5 classes/ kinds of heavy chains:

Class	Heavy chain
IgM	μ
IgG	γ
IgA	α
IgD	δ
IgE	ε

We've subclasses of IgG ; IgG1, IgG2, IgG3, IgG4
What does that mean?
The constant domains of the heavy chain bear slight differences from the others. What determines the isotype of the Ig is the heavy chain.

All the constant domains of IgM are the same but they differ from those of IgG, but sometimes, there'll be differences between IgGs themselves, as a result the subclasses(IgG1 ,IgG2 ,IgG3) will be created. {They've a similar function but can be slightly differ from each subclass}
Notice that we're talking about the a.a of the constant region, and as we know, the biological activity of the Ig lies in the Fc fragment, which is mainly constant.

We want variability for the detection of antigens but we do NOT need it for the performance (biological activity), which would be the same.
For example, if it's going to activate the complement, it should NOT be variable! (performance should be reserved)
Fc → constant domains with constant function.

We've 4 subclasses of IgG & 2 subclasses of IgA (IgA1 & IgA2)
IgG1, IgG3, IgG4 ⟹ pass through the placenta but IgG2 cannot!
(Since there're differences in the constant domains)
IgG1, IgG2, IgG3 ⟹ activate the classical pathway of complement but IgG4 doesn't do that!
[The differences between the subclasses are very small in comparison to that in the classes of Ig (IgM, IgG,...)]

Idiotype:- the antigenicity of the paratope. We can produce Ab against the paratope itself, because it always changesand always new.
Anti-idiotype:- Ab produced against the paratope.

PROPERTIES & FUNCTIONS OF IMMUNOGLOBULINS:-

1)) Binding antigens and crossing them together.

If we've multivalent antigen, so we can get 1 Ab molecule with 2 antigens. (multivalent antigens with the same Abs), so we can cross-link antigens by means of Abs and this is an ***Immunocomplex***, which is a collection of antigen molecules with Ab molecules.

2)) Precipitation and Agglutination.

These immunocomplex will get bigger and bigger and they'll either precipitate or agglutinate; according to the nature of antigen; if it's soluble and after adding Ab to it, we'll have cross-linkages and then precipitation of this immunocomplex, but if the antigen is a particle or a cell, when we mix it with Ab, there'll be agglutination.

For example, if we've an antigen like RBCs (particle) and we produce against it Anti-A or Anti-B, RBCs will cross-link together and become bigger; they'll be coagulated and will be down in the bottom of the tube, and this is known as Agglutination.

3)) Opsonin (opsonization)
4)) ADCC (When it's cooperated with NK cells)
5)) Activation of complement system (not all Abs)
6)) Crossing the placenta
7)) Neutralization of toxins (Ab will block the active site of the toxins)
8)) Neutralization of viruses

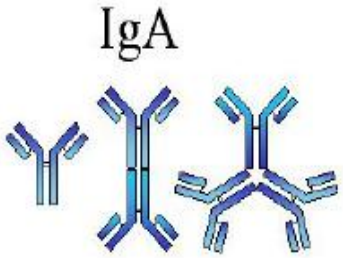
Viruses do have receptors like Influenza virus which has N receptors and H receptors, so it can adhere to the cells and the virus can go into the cell. But if we've Anti-H, the Ab will block the H and the virus cannot stick to the cell anymore, so the virus is neutralized and it'll produce No more infection.
Also, there's immobilization of bacteria; Abs against flagella, then they can be detected quickly by phagocytic cells and killed by them.

NOTE: The dr asked us to go and read about the properties and functions for each class of Ig, but here the dr mentioned the most important points about each one.

IgG:

-The most abundant Ig in the serum.
- Has the longest $t_{1/2}$ ~23 days.
- 4 subclasses "we've mentioned their major functions".
- Very good toxin neutralizer as well as viruses' neutralizer(IgA is better in this).
- Very versatile Ab.

IgM:



- Presents in the body as pentamer (5 molecules of IgM bind together by J-chain).

J-chain: a polypeptide molecule that join the Ig molecules together.

- The 1st Ab to be produced in the primary response.
- Very good agglutinating agent.
-Very good activator of the classical pathway of complement.
-But it's NOT good at neutralization of toxins, viruses...

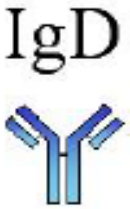
IgA:

-2 subclasses.

- Most of IgA which present in the serum is IgA1.
- Most IgAs are present in secretios, and the Most predominant IgA in the secretions is IgA2.

(It's more resistant to proteolysis by hydrolytic enzymes).

- It occurs as dimer or trimer in secretions, monomer in the serum.



In the secretions we've **J-chain** to join them together; also we've **secretin chain** which is NOT produced by plasma cells but by epithelial cells. Ig will be produced by the plasma cell with already J-chain (consist of 2 IgA), when it penetrates the epithelial cells of the mucosa to reach the lumen it acquires secretin. So the secretary portion or molecule facilitates the passage of IgA through the epithelial cells and gives protection from breaking down by enzymes.

IgD:

- Presents only on naïve B cells (The receptors on naïve B cells are for IgM & IgD).
- Its function is not clear. Some people say that is included in the activation of naïve B cells but it's not obvious!

IgE:

- Involved in parasitic analgesics.
- Found in a very little concentration in the serum; why?

Because all of the IgE bound to mast cells and basophiles (They have numerous specific receptors for IgE) .

- The biggest production of Igs is of IgA, (Don't confuse with IgG, IgG has the **highest** concentration in the serum), but its conc. Is little in the serum because it's secreted in saliva, tears, milk...
More IgA is produced in mucosal linings than all other types of antibody combined
It has a shorter half-life, but the main reason for its low conc. Is that it is secreted in body secretions.
the doctor said that we should read about each class of Igs, and that he only mentioned the most important points.

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