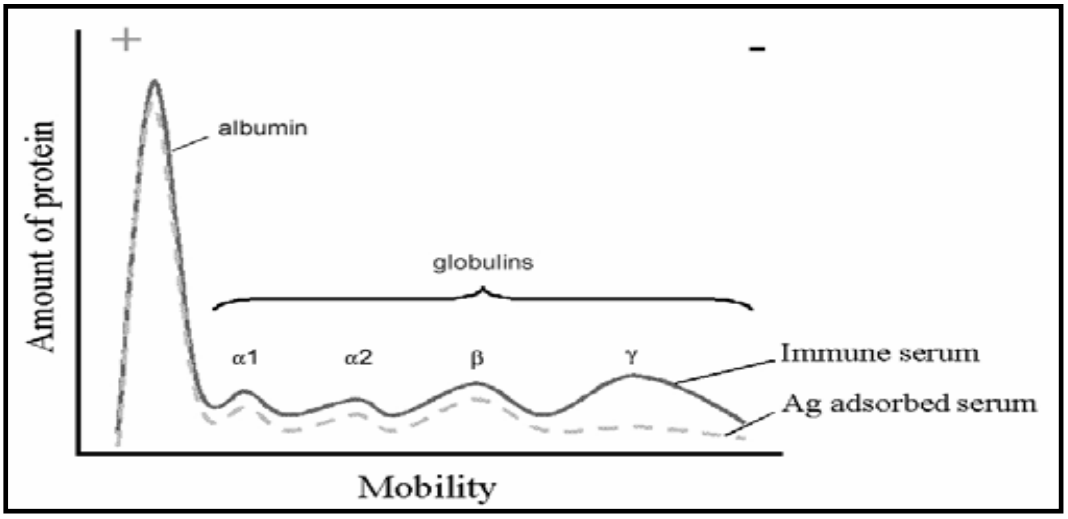
Course: Immunology

Lecturer: Dr. Weam Saad

Lecture: Immunoglobulins, structure and function and Antigens- Antibody Reactions

Immunoglobulins; Structure and Function

Immunoglobulins (Ig) or (Antibodies Ab) are Glycoprotein molecules, which produced by plasma cells in response to an immunogen and which function as antibodies and responsible for immunity. The immunoglobulins derive their name because when serum containing antibodies placed in an electrical field then the antibodies migrated with the globular proteins.



General functions of Immunoglobulins:

The general function is Ag binding - Immunoglobulins bind specifically to one or a few closely related antigens. Each immunoglobulin binds to a specific antigenic determinant. Antigen binding by antibodies is the primary function of antibodies and can result in protection of the host. Other effecter functions are:

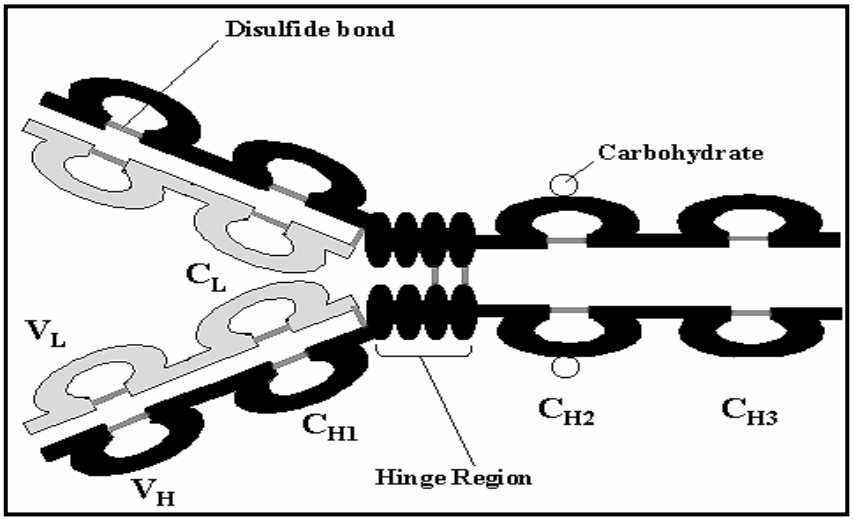
1. Fixation of complement - lysis of cells, release of biologically active molecules.

2. Binding to various cell types - phagocytic cells, lymphocytes, platelets, mast cells, and basophils have receptors that bind immunoglobulins and the binding can activate the cells to perform some function. Some immunoglobulins also bind to receptors on placental trophoblasts. The binding results in transfer of the immunoglobulin across the placenta and the transferred maternal antibodies provide immunity to the fetus and newborn.

Structure of Immunoglobulins:

The basic structure of the immunoglobulins is illustrated in the Figure bellow. Although different immunoglobulins can differ structurally, they are built from the same basic unit.

A**. Heavy and Light Chains -** All immunoglobulins have a four chain structure as their basic unit. They are composed of two identical light chains (23Kd) and two identical heavy chains (50-70Kd)



B. Disulfide bonds:

1. Inter-chain
2. Intra-chain

C. Variable (V) and Constant (C) Regions:

They could be divided into two regions based on variability in the amino acid sequences.

1. Light Chain - VL (110 aa) and CL (110 aa).
2. Heavy Chain - VH (110 aa) and CH (330-440 aa).

D. Hinge Region:

The region at which the arms of the antibody molecule forms a **Y** is called the hinge region because there is some flexibility in the molecule at this point.

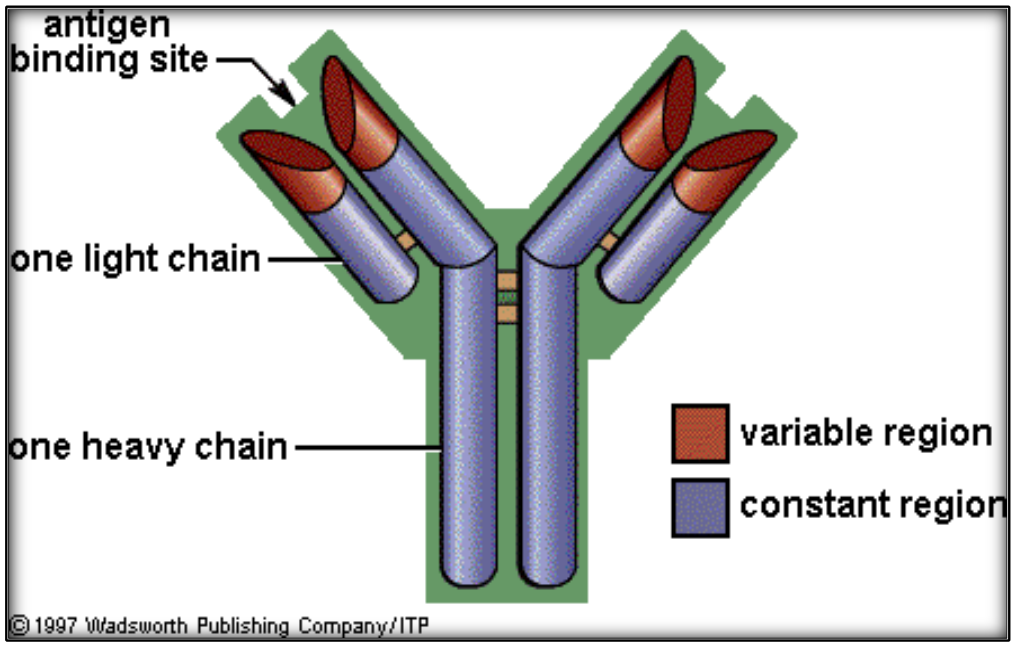
E. Domains

F. Oligosaccharides

Structure of the variable regions: These regions composed from:

A. Hypervariable (HVR) regions

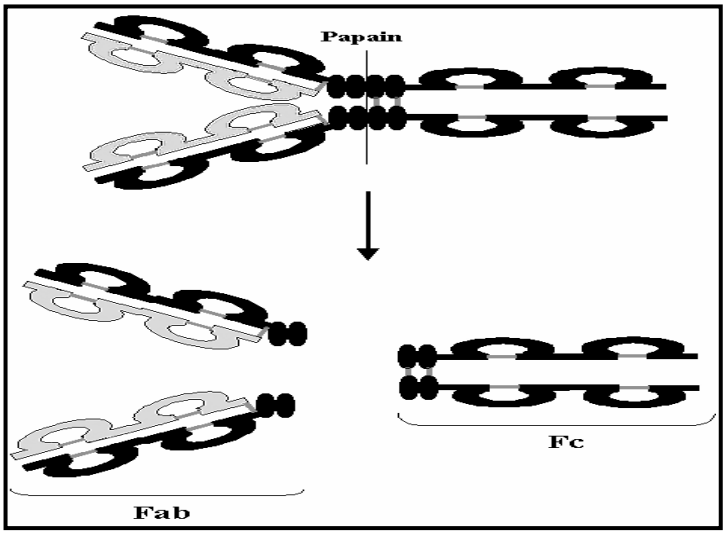
B. Framework regions



Immunoglobulin Fragments:

Immunoglobulin fragments produced by proteolytic digestion are useful in understanding structure/function relationships in immunoglobulins.

1) Fab region: can results after digestion with papain and breaks the immunoglobulin molecule in the hinge region before the H-H inter-chain disulfide bond. These regions are Antigen binding sites of the antibodies.
2) Fc region: can results after digestion with papain which produces a fragment that contains the remainder of the two heavy chains this fragment was called Fc because it was easily crystallized. This region has receptors on immune cells surfaces help in attaching of Immunoglobulins on immune cells surface.



General Immunoglobulins classes:

The immunoglobulins can be divided into 5 different classes based on differences in the amino acid sequences in the constant region of the heavy chains. All immunoglobulins within a given class will have very similar heavy chain constant regions. These differences can be detected by sequence studies or more commonly by serological techniques (i.e. by the use of antibodies directed to these differences).

1. IgG - Gamma (γ) heavy chains
2. IgM - Mu (μ) heavy chains
3. IgA - Alpha (α) heavy chains
4. IgD - Delta (δ) heavy chains
5. IgE - Epsilon (ε) heavy chains

In addition, the classes of immunoglobulins can be divided into subclasses based on small differences in the amino acid sequences in the constant region of the heavy chains. These subclasses can be differentiated serologically too.

Isotypes: They are antigenic determinants that characterize classes and subclasses of heavy chains and types and subtypes of light chains.

Allotypes: They are antigenic determinants specified by allelic forms of the Ig genes.

Properties of Immunoglobulins (Abs) classes:

1. IgG immunoglobulin:

Structure: Monomer, have4 subclasses (IgG1, IgG2, IgG3 and IgG4), the subclasses differ in the number of disulfide bonds and length of the hinge region.

Properties:

1) IgG is the major Ig in serum - 75% of serum Ig is IgG.
2) IgG is the major Ig in extra vascular spaces.
3) Placental transfer - IgG is the only class of Ig that crosses the placenta. Transfer is mediated by receptor on placental cells for the Fc region of IgG. Not all subclasses cross equally; IgG2 does not cross well.
4) Able to fix complement - Not all subclasses fix equally well; IgG4 does not fix complement
5) Binding to cells - Macrophages, monocytes, PMN's and some lymphocytes have Fc receptors for the Fc region of IgG. Not all subclasses bind equally well; IgG2 and IgG4 do not bind to Fc receptors. A consequence of binding to the Fc receptors on PMN's, monocytes and macrophages is that the cell can now internalize the antigen better. The antibody has prepared the antigen for eating by the phagocytic cells. The term opsonin is used to describe substances that enhance phagocytosis. IgG is a good opsonin. Binding of IgG to Fc receptors on other types of cells results in the activation of other functions.

2. IgM immunoglobulin:

Structure - IgM normally exists as a pentamer but it can also exist as a monomer. IgM has an extra domain (another protein molecule) covalently bound via the S-S bond called the J chain. This chain functions in polymerization of the molecule into a pentamer.

Properties

a) IgM is the third most common serum Ig.
b) IgM is the first Ig to be made by the fetus and the first Ig to be made by B cells when it is stimulated by antigen.
c) Due to its pentameric structure, IgM is a good complement fixing Ig. Thus, IgM antibodies are very efficient in leading to the lysis of microorganisms.

d) IgM is also a good agglutinating Ig. Thus, IgM antibodies are very good in clumping microorganisms for elimination from the body. IgM binds to some cells via Fc receptors. Cell surface IgM functions as a receptor for antigen on B cells.

3. IgA immunoglobulin:

Structure - Serum IgA is a monomer but IgA found in secretions is a dimer. When IgA is found in secretions is also has another protein associated with it called the secretory piece or T piece (sIgA), this secretory piece is made in epithelial cells and is added to the IgA as it passes into the secretions. The secretory piece helps IgA to be transported across mucosa and also protects it from degradation in the secretions.

Properties:

a) IgA is the second most common serum Ig.
b) IgA is the major class of Ig in secretions - tears, saliva, colostrum, mucus. Since it is found in secretions secretory IgA is important in local (mucosal) immunity.
c) IgA does not fix complement.

4) IgD immunoglobulin:

Structure: IgD exists only as a monomer.

Properties:

a) IgD is found in low levels in serum; its role in serum uncertain.
b) IgD is primarily found on B cell surfaces where it functions as a receptor for antigen.
c) IgD does not bind complement.

5) IgE immunoglobulin:

Structure: IgE exists as a monomer.

Properties:

a) IgE is the least common serum Ig since it binds very tightly to Fc receptors on basophils and mast cells even before interacting with antigen.
b) Involved in allergic reactions - As a consequence of its binding to basophils and mast cells, IgE is involved in allergic reactions. Binding of the allergen (allergy antigen) to the IgE on the cells results in the release of many

pharmacological mediators and cytokines that result in allergic symptoms e.g.histamin.

c) IgE also plays a role in parasitic helminth diseases. Since serum IgE levels rise in parasitic diseases, measuring IgE levels is helpful in diagnosing parasitic infections. Eosinophils have Fc receptors for IgE and binding of eosinophils to IgE-coated helminths results in killing of the parasite.

d) IgE does not fix complement.

Antigens- Antibody Reactions

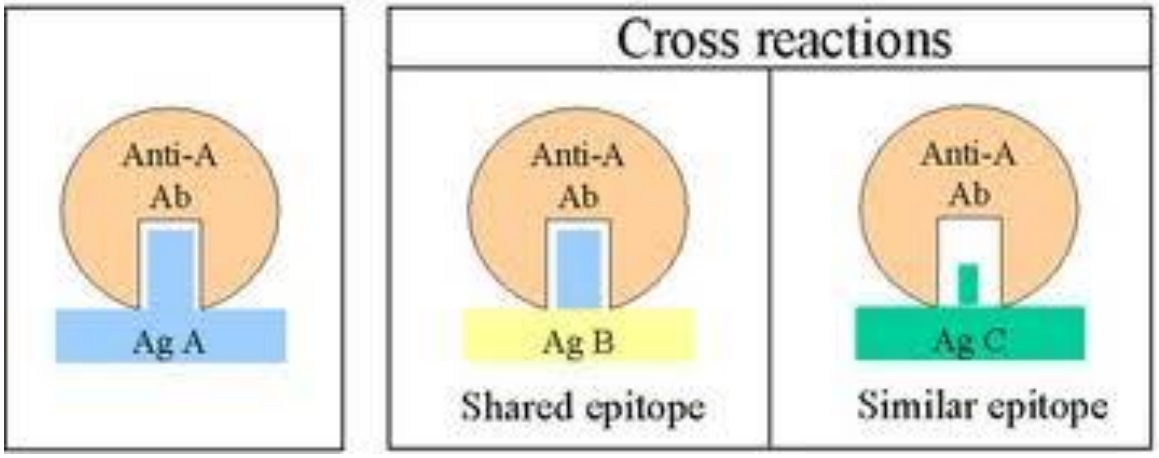
It is a specific reaction between an antibody (produced by B-cells and secreted by plasma cells) and any antigen then forming Ag-Ab Complex. The antigenic determinant or epitopes are recognized by the Ag binding site of the antibody at the variable region, then Antigens are bound to antibodies through weak and non-covalent interactions such as electrostatic interactions, hydrogen bonds, Van der Waals forces, and hydrophobic interactions.

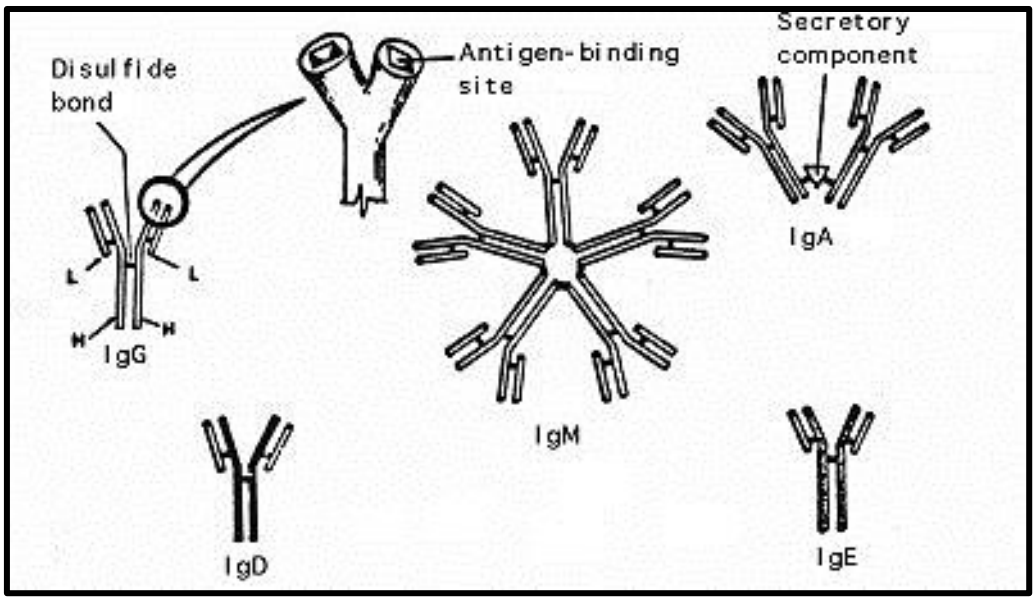
Ag+Ab → Ag-Ab Complex

Types of Antigens- Antibody Reactions

1. **Precipitation** (when the Ag is soluble).
2. **Agglutination** (when the Ag is insoluble or particulate).
3. **Complement Fixation** (during Complement classical pathway activation).
4. **Neutralization** (when the Ag is Toxin)
5. **Opsonization** (when the Ag is still on the cell surface and the Ab with the help of complement increase the susceptibility of foreign cell to be engulfed by Macrophages).

Cross reactivity - Cross reactivity refers to the ability of an antibody combining site to react with more than one antigenic determinant. Cross reactions occurs because the cross reacting antigen shares an epitope in common with the immunizing antigen or because it has an epitope which is similar in structure to one epitop on the immunizing antigen and that is called (multispecificity).


Anti-A
Ab
Ag A
Cross reactions
Anti-A
Ab
Ag B
Shared epitope
Anti-A
Ab
Ag C
Similar epitope


Disulfide bond
Antigen-binding site
Secretory component
L
L
H
H
IgG
IgA
IgM
IgD
IgE