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# IMMUNOGLOBULINS: COMPOSITION AND STRUCTURE

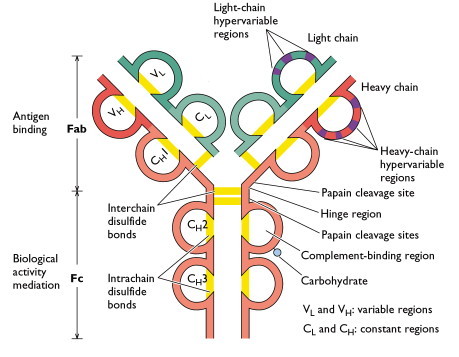
The ultimate aim of the immune organs of the body is to recognize and react specifically with the ‘non-self substance, i.e. antigen and destroy it. Nature has evolved a unique protein molecule distributed widely in the body more so in serum, to perform these two different functions.

### ****COMPOSITION AND FUNCTIONAL CHARACTERISTICS OF IMMUNOGLOBULINS (IGs):****

* The immunoglobulins comprise of heterogeneous group of proteins, which account for approximately 20% of the total plasma proteins.
* Pro­tein molecules that combine specifically with antigens are termed as antibodies; collectively, proteins with antibody activity are referred to as immunoglobulins.
* They are produced in multicellular organisms in response to a foreign stimulus called antigen which may be a protein, a carbohydrate or any other substance.
* They are all produced by cells called B-lymphocytes.
* The immunoglobulin (Ig) be­longs to a large group of closely related globular glycoproteins. It is composed of polypeptide (82-96 %) and carbohydrate (4-18 %).
* It is a three-dimensional protein molecule, which is bilaterally symmetrical.
* Antibody molecules are extremely heterogeneous, which is demonstrated by amino acid sequence, electrophoretic and serological methods.

### BASIC STRUCTURE OF AN IMMUNOGLOBULIN:

* All immunoglobulin molecules consist of 2 identical light (L) chains and two identical heavy (H) chains, held together as a tetramer (L2H2) by inter-chain disulfide bonds.
* The arrangement of the four polypeptide chains in an immunoglobulin molecule gives it a “Y” shape.
* The half of the light chain towards N-terminal is called as variable region (VL-variable light) and the other half towards C-terminal end is called as constant regions (CL-constant light).
* Similarly one-quarter (1/4) of the heavy chain at the N-terminal end is called variable region (VL-variable heavy) and one-thirds (1/3) at the C-terminal is called constant region (CH-constant heavy).
* Each chain can be divided into domains or re­gions.
* In each of the two light chains there are two intra-chain disulphide bonds giving rise to two domains, one each in variable and constant regions.
* Similarly there are four intrachain disulphide bonds in the heavy chain giving rise to four domains in each of the heavy chain.
* One domain appears in each variable region of the heavy chain and three in constant regions.
* When immunoglobins are subjected to papain digestion, 3 fragments are produced, two of them retain the ability to bind with the antigen and hence they are called antigen binding fragments (Fab).
* The third one does not have such a capacity but it is easily crystallisable and hence called crystallization fragment (Fc).
* The point of papain cleavage is called the hinge region.
* There are two types of light chains known by the Greek letters kappa (k) and lambda (λ). An immuno­globulin has either k or λ, chain but not both.



* There are five (5) types of heavy chains designated as gamma (γ), alpha (α), meu (μ), epsilon (ԑ) and delta (δ).
* Depending upon the type of the heavy chain, five different types of immunoglobulin’s identified are

|  |  |
| --- | --- |
| IgG (contains γ) | C:\Users\welcome\Desktop\IG.jpg |
| IgA (contains α) |
| IgM (contains μ) |
| IgE (contains ԑ) |
| IgD (containing δ). |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | IgM | IgA | IgE | IgD |
| Heavy chain | γ (gamma) | μ (mu) | α (alpha) | ε (epsilon) | δ (delta) |
|  |  |  |  |  |  |
| Number of antigen binding sites | 2 | 10 | 4 | 2 | 2 |
| % of total antibody in serum | 80% | 6% | 13% | 0.002% | 1% |
| Fixes complement | YES | YES | NO | NO | NO |
| Distribution | Intravascular and extravascular | Mainly intravascular | Intravascular and secretions | Basophils and mast cells (in saliva and nasal secretions) | Lymphocyte surface |
| Function | Main blood antibody, neutralizes toxins, opsonization | Primary response, fixes complement. Monomer serves as B-cell receptor | Secreted into mucus, tears and saliva | Antibody of allergy and anti-parasitic activity | B cell receptor |

* Each type of heavy chain can combine with each type of light chain, but within the same antibody molecule, the two heavy and two light chains are of same type.

#### Light Chains

* There exist two types of light chains; kappa (k) and lambda (A,).
* Light chain protein of the kappa type consists of 214 amino acids.
* All kappa chains have the same sequence in the carboxy terminal half of the molecule except that certain kappa chains have the amino acid leucine at position 191, while others have valine in this position.
* The amino acid sequence in the amino terminal half of the light chain is not same in different Ig.
* These two portions of the k light chain have been designated VK and CK respectively i.e. the segments of variable and constant amino acid sequence.
* Light chain proteins of either k or λ, type have the amino acid threonine at position 5, glutamine at position 6 and glycine at position 16.
* All kappa light chains have isoleucine at position 2 and leucine at position 11, all lambdas light chains have proline at position 7 and glutamine at position 17.
* Certain residues do not change from one portion to another, but some portions of the variable region show great variability in sequence composition and these are known as hyper variable regions or complementarity determining regions (CDRs) each containing 6 to 10 amino acids.
* Three regions of the VL segment show extreme sequence variability; these are located at positions 24 through 34; 50 through 56 and 89 through 97.
* The proportion of k and A, chains in immunoglobulin molecules varies from species to species being about 2:1 in human.
* A given molecule of immunoglobulin has either both the light chains as kappa or both of them as lambda, but never both. In humans 65% of the light chains are kappa and 35% are lambda.

**Heavy Chains:**

* Heavy chains consist of segments of variable (V) and constant (C) amino acid sequence composition; the VH segment of IgG consists of approximately 115 amino acids and CH segment of approximately 330.
* The CH segment in turn consists of three regions of approximately 110 amino acids termed CH1, CH2 and CH3.
* Four regions in VH region show marked variability in amino acid sequence composition and constitute the hyper variable regions of heavy chains.
* These regions are located at positions 31 through 37, 51 through 68, 86 through 91 and 101 through 109.
* The hyper variable regions (15-20%) are held in place by more conserved framework regions (80-85%).
* In an intact immunoglobulin, the hyper variable regions of a light chain and of heavy chain can be brought together in three dimensional spaces to form an antigen- binding surface.
* Because these sequences form a surface complementary to the three dimensional surface of a bound antigen, the hyper variable regions are also called complementarity determining regions (CDRs).
* The variable segment of the heavy chain also has certain residues, which appear in variant, for example, valine at position 2, leucine at 4, glutamine at 6 among others.
* In addition, certain residues permit the assignment of VH segments to 4 subgroups.
* These four VH segments are not restricted to one class or subclass of heavy chains but may be found in association with the CH regions of the γ, α, μ, δ or ԑ heavy chains.
* IgG molecule treated with the enzyme papain, in the presence of cysteine separated the molecule into two major fragments, Fab (fragment of antigen binding) which retained the antigen binding capacity of the intact molecule and Fc (fragment crystallizable) which did not combine with antigen but was readily crystallisable.
* Each fragment has a molecular weight of approximately 50,000 Daltons; Fab fragment accounted for approximately 2/3rd and the Fc fragment for 1/3rd of the papain digested IgG.

**J—Chains:**

* Multimeric IgM and IgA also contain an additional 15 KD polypeptide joining (J) chain, which is disulphide bonded to the tailpieces, stabilizing the multimer.
* All membrane immunoglobulin molecules regardless of isotype are believed to be monomeric, containing two heavy and two light chains.

**Secretory Component:**

* The secretory IgA has fourth polypeptide chain i.e. the secretory component (SC).
* The J and SC chain differ from each other antigenically and in amino acid composition and also from light and heavy chains.

**Hinge Region:**

* The basic four-chain structure of the immunoglobulin molecule is ‘Y’-shaped. However, it may change from a ‘Y’ to a ‘T’ shape depending on the reaction conditions.
* This is facilitated by the existence of a hinge region located between CH1 and CH2 in certain isotypes. The hinge may contain from about ten (in α1, α2, γ1; γ2 and y4) to over 60 (in y3 and δ) amino acid residues.
* There are intrachain disulphide bonds in the VL and CL segments of the light chain and the VH, CH1, CH2 and CH3 segments of the heavy chain.
* Thus in each segment, the intrachain disulphide bond establishes a loop involving approximately 60 amino acids.
* The segments of polypeptide immunoglobulin chains with homologous amino acid sequences are the domains.
* Light chains contain one variable domain (VL) and one constant domain (CL). Heavy chains contain one variable domain (VH) and either three or four constant domains (CH1, CH2, CH3 and CH4) depending on the antibody class.
* The constant region of heavy chain consists of three to four independent domains. Each chain is folded into recognizable loop-shaped zones created by intrachain disulphide bonds.
* These zones are termed as “domains’, which are folded over. Those of light chains consist of only one domain.
* These domains are numbered from 1 to 3 or 4.
* Both chains of heavy and light chains contain several homologous units of about 110 amino acid residues within each unit i.e. domain, an intrachain disulphide bond from a loop of about 60 AAs.