

IMMUNOGLOBULINS: TYPES, FUNCTIONS STRUCTURE AND BIOMEDICAL IMPORTANCE.

Immunoglobulins (Igs) are glycoprotein molecules also called antibodies (Abs), that are produced in response to foreign substances entering the living body- antigens or immunogens (viruses, bacteria, or toxins etc), binding to them and forming antigen-antibody complexes resulting in Ag elimination and protection of the body of the host). Igs are produced by the lymphocytes and are found in fraction of blood called gamma globulin. Gerald M. Edelman and Rodney Robert Porter are the notable researchers who worked extensively on purification and structural analysis of Igs, particularly the IgG type.

Igs are synthesized with a molecular arrangement that fits the shape of molecules on the antigens or immunogens, in order to allow effective binding of the Abs. Igs binding to Ags basically help to inactivate, weaken or enhance phagocytosis of Ags.

GENERAL FUNCTIONS

1. Antigen binding- Igs bind to specific Antigenic determinants (AD) on an antigen. They bind to at least 2 or in a few cases more Ads which are closely related and the number of ADs an Ab can bind to is referred to as its valency.
2. Most Igs mediate several effector functions which include fixation of complement that results to lyses of cells and release of biologically active molecules, binding of various cells to facilitate specific functions by bound cells e.g. phagocytic cells, lymphocytes, platelets etc.

Most effector functions of Abs are carried out after the Ab binds to Ags. Different Igs molecules can have different Ag binding properties because of different V_H and V_L regions.

BASIC STRUCTURE OF IMMUNOGLOBULINS

All Igs have the same basic structural units of 2 identical light chains and 2 identical heavy chains, the heavy and light chains are joined together by interchain disulphide bonds and non-covalent interactions. The number of interchain disulphide bonds varies among different Igs. Within the polypeptide chains i.e. the heavy and light chains there are also present intra-chain disulphide bonds. Amino acid sequence of both heavy and light chains of an Ig characterizes two distinct regions of the chains based on variability of the amino acid sequence, known as VARIABLE (V) and CONSTANT (C) regions. Light and heavy chains are composed of both a variable and constant region designated V_L and C_L (light chains) and V_H and C_H (heavy chains). The amino acid sequence of the variable region form the N-terminal ends of the chains and determine antigenic specificity of the Igs. Constant regions are the same for each specific class of Ig and carry the effector sites.

Light chain- V_L -about 100-110 amino acids, C_L -100-110 amino acids. There are two types of light chains, kappa and lambda, (κ and λ) the κ are twice as much as λ . There are also four classes of the λ chains. These chains weigh about 23KDa. Differences in the type of light chains also form a basis for grouping of Igs into various types. The variable region makes up half of the entire light chain and the constant region the remaining half.

Heavy chains- V_H -110 amino acids, C_H -330-440 amino acids. There are 5 types of heavy chains which defines the class of Igs, namely, Alpha, Gamma, Miu, Delta and Epsilon ($\alpha, \gamma, \mu, \delta, \epsilon$). the heavy chains are between 53-75KDa. the variable region makes up a quarter of the entire heavy chain while $\frac{3}{4}$ of the remaining chain is the constant region.

The hinge region is the area of the Ig where the arms of the Abs form a 'Y', it is a flexible region. Igs also have domains formed from folds of the globular region containing the intrachain disulphide bonds and they are V_L and C_L (light chain domains) and V_H and C_H (heavy chain domains), seen in the three dimensional images of the Ig. The constant region of light chain and the appropriate heavy chain form globular constant domains while the variable regions of light chain 1 and corresponding heavy chain interact to form globular variable domain.

Ig s also have attached to their C_H oligosaccharides and in other cases these carbohydrates are attached to other areas.

The variable regions of an Ig are also further divided into hypervariable or complementarity determining regions (CDRs) which distinguishes Abs with different specificities and is found on both light and heavy chains and the frame work regions lie between the CDRs. There are about 3 hypervariable regions on the V_L and 4 on the V_H , and these contribute to uniqueness of each antibody.

Proteolytic digestion of Igs have produced fragments which have been found useful in elucidating the structure-function relationship of the Ig.

Fab- also referred to as the antigen binding fragment, is gotten upon digestion of Ig with papain and its cleavage at the hinge region. It contains the antigen binding site synonymous to V_H and V_L which is particular to the kind of antigenic determinant the Ab will bind.

Fc- this is also called fragment crystallizable because it is readily crystallized and it contains the remainder of the two heavy chains. It contains different domains and which mediate effector functions of an Ig. Variations in the Fc determines the different classes of Igs.

The hinge region is between the Fab and the Fc portion and controls interactions between these portions.

$F(ab)_2$ - treatment of Igs with pepsin results in cleavage of the heavy chain, resulting in a fragment that contains both antigen binding sites, it is called $F(ab)_2$ because it is divalent. Fc portion is digested into small peptides by pepsin. The $F(ab)_2$ binds to Ag but does not mediate effector functions.

IMMUNOGLOBULINS TYPES AND CLASSES.

Based on differences in the amino acid sequences in the constant region of the heavy chains there are five classes of Igs.

1. IgG- gamma heavy chain

2. IgM-miu heavy chain
3. IgA- alpha heavy chain
4. IgD- delta heavy chain
5. IgE- epsilon heavy chain.

In each class of Ig small differences in the constant regions of the heavy chain still occur, leading to subclasses of the Igs e.g. IgG1,IgG2,IgG3 etc.

IgG

All IgG are monomers, subtypes and subclasses differ in number of disulphide bonds and lengths of hinge region.

Properties.

1. It is the most versatile Ig and can carry out all functions of Ig molecules.
2. It is the major Ig in serum
3. It is also found/ the major Ig in extravascular spaces.
4. It is the only Ig that crosses the placenta.
5. It fixes complement although not all subclasses do this well.
6. It binds to cells and is a good poisoning(substance that enhances phagocytosis).

IgM

It normally exists as a pen tamer in serum but can also occur as a monomer. It has an extra domain on the mui chain (C_{H4}) and another protein covalently bound via S-S . called J-chain. This chain helps it to polymerize to the pentamer form.

Properties

1. It is the first Ig to be made by fetus in most species and new B cells when stimulated by Ags.
2. It is the 3rd most abundant Ig in serum.
3. It is a good complement fixing Ig leading to lyses of microorganisms
4. It is also a good agglutinating Ig, hence clumping microorganisms for eventual elimination from the body.

5. It is also able to bind some cells via Fc receptors.
6. B cells have surface IgMs , which exists as monomers and lacks J chain but have an extra 20 amino acid at the C-terminal that anchors it to the cell membrane.

IgA

Serum IgA is monomeric, but IgA found in secretions is a dimer having a J chain. Secretory IgA also contains a protein called secretory piece or T- piece, this is made in epithelial cells and added to the IgA as it passes into secretions helping the IgA to move across mucosa without degradation in secretions

Properties

1. It is the second most abundant Ig in serum
2. It is the major class of Ig in secretions- tears, saliva, colostrums,mucus,and is important in mucosal immunity.
3. It binds to some cells- PMN cells and lymphocytes
4. It does not normally fix complement.

IgD

It exists as monomers.

Properties

1. It is found in low levels in serum and its role in serum is uncertain
2. It is found primarily on B cells surface and serves as a receptor for Ag.
3. It does not fix complement.

IgE

It occurs as a monomer and has an extra domain in the constant region.

Properties

1. It is the least common serum Ig, but it binds very tightly to Fc receptors on basophils and mast cells even before interacting with Ags.
2. It is involved in allergic reactions because it binds to basophils and mast cells.
3. It plays a role in parasitic helminthic diseases. Serum levels rise in these diseases. Eosinophils have Fc receptors for IgEs and when eosinophils bind to IgEs coated helminthes death of the parasite results.

BIOMEDICAL IMPORTANCE OF IGS

IgG- Increases occur in:-chronic granulomatous infections and infections of all types, hyperimmunization, liver disease, severe malnutrition, dysproteinemia, rheumatoid arthritis etc.

Decreases occur in:-agammaglobulinemia, lymphoid aplasia, selective IgG, IgA deficiency, IgA myeloma and chronic lymphoblastic leukemia.

IgM. Increases occur in: - Waldenstrom's macroglobulinemia, Trypanosomosis, Actinomycosis, Bartonellosis, Malaria, Lupus erythromatosis, Rheumatoid arthritis, Dysgammaglobulinemia etc

Decreases occur in: - Agammaglobulinemia, lymphoproliferative disorders, lymphoid aplasia, IgG and IgA myeloma and chronic lymphoblastic leukemia.

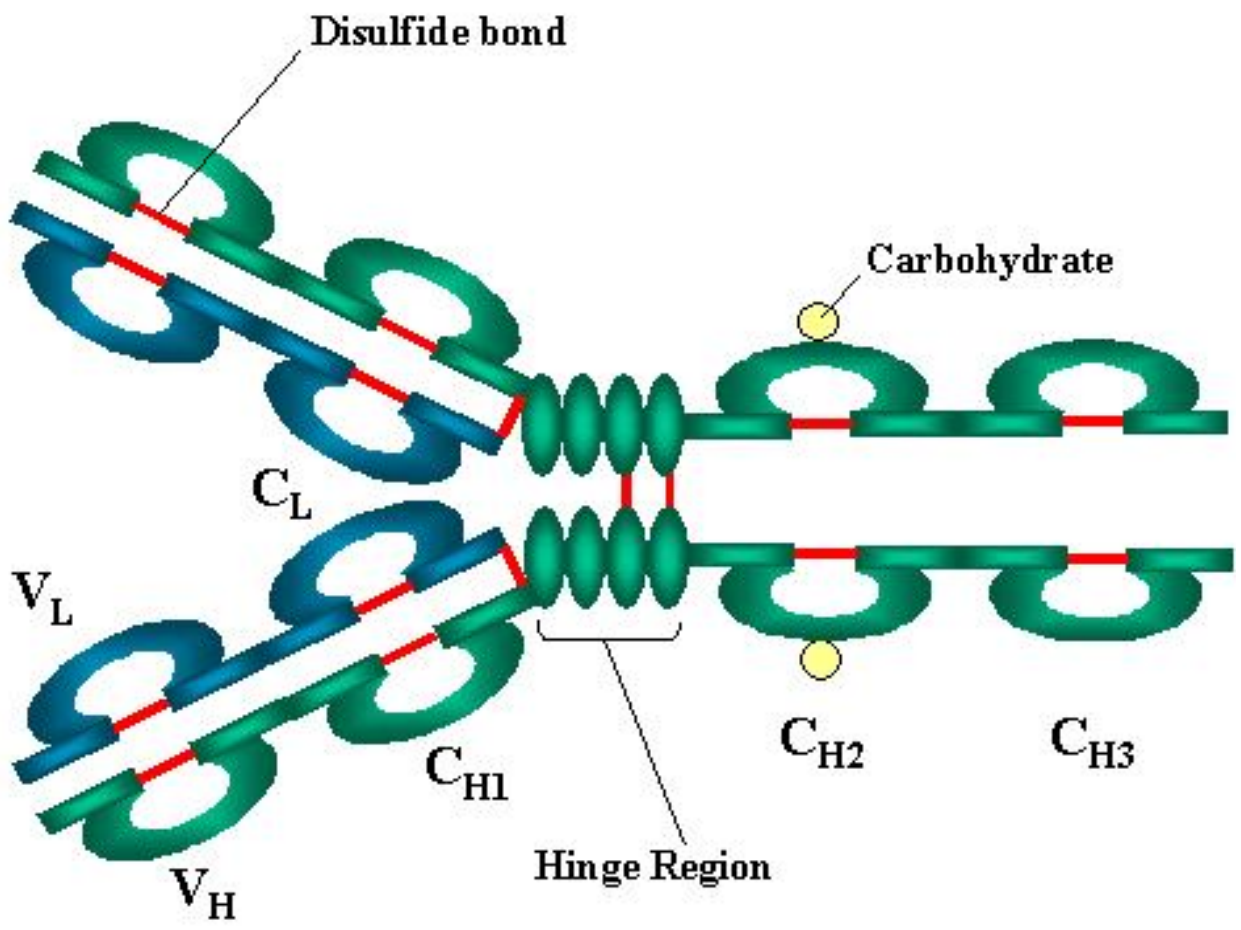
IgA Increases occur in:-Wiskott-Aldrich syndrome, cirrhosis of the liver, IgA myeloma, autoimmune disorders, rheumatoid arthritis, lupus erythromatosis etc

Decreases occur in: - hereditary ataxia Telangectasia, Ig deficiency states, malabsorbtion syndromes, lymphoid aplasia, IgG myeloma, chronic lymphoblastic leukemia etc.

IgD Increases occur in: - chronic infections, IgD myelomas

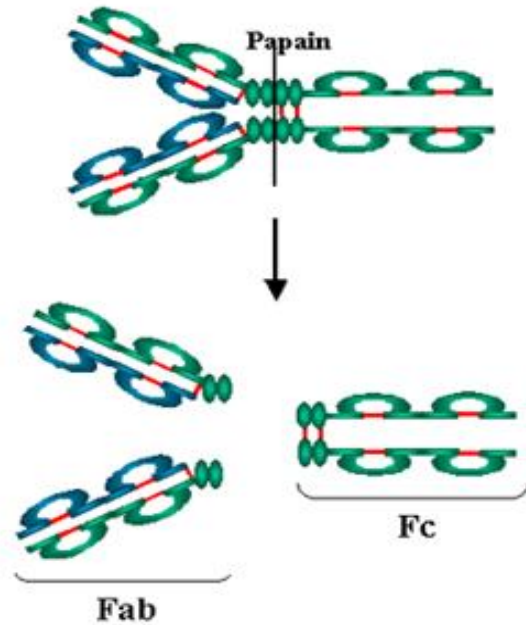
IgE Increases occur in:-atopic skin diseases e.g. eczema, hay fever, asthma, anaphylactic shock and IgE myelomas.

Decreases occur in:-congenital Agammaglobulinemia, Hypogammaglobinemia etc



Immunoglobulin Fragments: Structure/Function Relationships

- Fab
 - Ag binding
 - Valence = 1
 - Specificity determined by V_H and V_L
- Fc
 - Effector functions



IgM

- Structure

- Pentamer (19S)
- Extra domain (C_{H4})
- J chain

