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Immunoglobulin

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Abstract
An antibody (Ab), also known as an immunoglobulin (Ig), is a large, Y-shaped protein produced mainly by plasma cell that is used by the immune system to neutralize pathogens such as pathogenic bacteria and viruses. The antibody recognizes a unique molecule of the pathogen, called an antigen, via the fragment antigen binding (Fab) variable region. Each tip of the "Y" of an antibody contains a paratope (analogous to a lock) that is specific for one particular epitope (similarly, analogous to a key) on an antigen, allowing these two structures to bind together with precision. Using this binding mechanism, an antibody can *tag* a microbe or an infected cell for attack by other parts of the immune system, or can neutralize its target directly (for example, by inhibiting a part of a microbe that is essential for its invasion and survival). Depending on the antigen, the binding may impede the biological process causing the disease or may activate macrophages to destroy the foreign substance. The ability of an antibody to communicate with the other components of the immune system is mediated via its Fc region (located at the base of the "Y"), which contains a conserved glycosylation site involved in these interactions. The production of antibodies is the main function of the humoral immune system.
Key words: S Immunoglobulin, Antigen, Antibody, fab, Plasma cell, immune system, Immunity, serum, Lymphocytes

Introduction

Specific acquired immunity against infection is primarily a property of group of serum glycoproteins called as antibodies. These antibodies have been produced by a subpopulation of whites blood cells in the immune system called lymphocytes. These are small round cells, 6 to 7um in diameter, with a high nuclear to cytoplasmic ratio in their resting stage, and they are capable of expanding greatly in volume and activity in response to an antigen. This process is called lymphocyte activation. "Immunoglobulins are glycoproteins molecules that are produced by plasma cells in response to an immunogen and which function as antibodies. These are proteins which have demonstrable antibody activity and / or share a common antigenic specificity with any known antibody and are produced by cell that form antibody." [1]

1.2 Property

- These are protein molecules with demonstrable antibody activity.
- They are made of heterogenous group of proteins accounting for about 20 % of total plasma proteins.
- They are mainly γ – globulins but a few are β-globulins.

- They are two types: surface immunoglobulins – they are present on the surface of the lymphocytes where they act as specific receptor for the antigen, and secreted immunoglobulins these are the products of B lymphocytes and appear in the body fiuids (homors as antibodies). [2]

General Function of Immunoglobulins

A. Antigen binding

Immunoglobulins bind specifically to one or a few closely related antigens. Each immunoglobulin actually binds to a specific antigenic determinant. Antigen binding by antibodies is the primary function of antibodies and can result in protection of the host. The valency of antibody refers to the number of antigenic determinants that an individual antibody molecule can bind. The valency of all antibodies is at least two and in some instances more.

B. Effector Functions

Frequently the binding of an antibody to an antigen has no direct biological effect. Rather, the significant biological effects are a consequence of secondary "effector function of antibodies. The immunoglobulins mediate a variety of these effector functions. Usually the ability to carry out a particular effector function requires that the antibody bind to its antigen. Not every immunoglobulin will mediate all effector functions. Such effector functions include:

1. Fixation of complement - This results in lysis of cells and release of biologically active molecule.
2. Binding to various cell types - Phagocytic cells, lymphocytes, platelets, mast cells, and basophils have receptors that bind immunoglobulins. This binding can activate the cells to perform some function. Some immunoglobulins also bind to receptors on placental trophoblasts, which results in transfer of the immunoglobulin across the placenta. As a result, the transferred maternal antibodies provide immunity to the foetus and new born. [3]

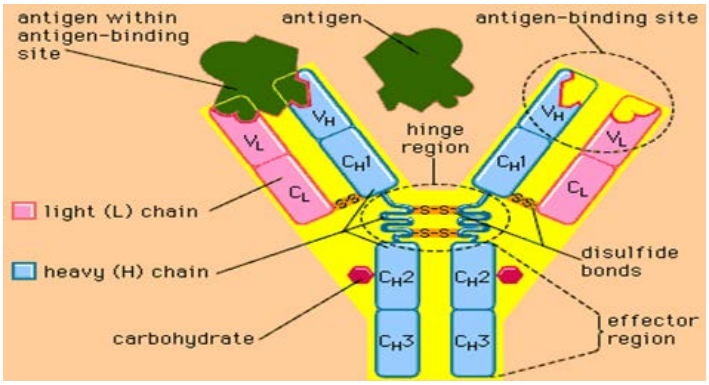

Figure 3.1: Structure of Immunoglobulin

The basic structure of the immunoglobulins can differ structurally:

They are glycoproteins and are composed of 82-96% polypeptide and 4-18% carbohydrates. The polypeptide part possesses the biological properties of antibodies.

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)

Disulfide bonds

1. **Inter-chain disulfide bonds:** The heavy and light chains and the two heavy chains are held together by inter-chain disulfide bonds and by non-covalent interactions. The number of inter-chain disulfide bonds varies among different immunoglobulin molecules.

2. **Intra-chain disulfide binds:** Within each of the polypeptide chains there are also intra-chain disulfide bonds.

Variable (V) and Constant (C) Regions

When the amino acid sequences of many different heavy chains and light chains were
Compared, it became clear that both the heavy and light chain could be divided into two regions based on variability in the amino acid sequences. These are the:

1. Light Chain - V_L (110 amino acids) and C_L (110 amino acids)
2. Heavy Chain - V_H (110 amino acids) and C_H (330-440 amino acids)

Hinge Region

This is the region at which the arms of the antibody molecule form a Y. It is called the hinge region because there is some flexibility in the molecule at this point. **Domains**
Three dimensional images of the immunoglobulin molecule show that it is not straight, it is folded into globular regions each of which contains an intra-chain disulfide bond. These regions are called domains.

1. Light Chain Domains - V_L and C_L
2. Heavy Chain Domains - V_H, C_{H1} - C_{H3} (or C_{H4})

Oligosaccharides

Carbohydrates are attached to the C_{H2} domain in most immunoglobulins. However, in some cases carbohydrates may also be attached at other locations. [3] **Complementarity Determining Regions,**

Fragment Antigen Binding and Fragment, Crystallizable Regions

Some parts of an antibody have unique functions. The arms of the Y, for example, contain the sites that can bind two antigens (in general identical) and, therefore, recognize specific foreign objects. This region of the antibody is called the *Fab (fragment, antigen binding) region*. It is composed of one constant and one variable domain from each heavy and light chain of the antibody.[4] The paratope is shaped at the amino terminal end of the antibody monomer by the variable domains from the heavy and light chains. The variable domain is also referred to as the F_V region and is the most important region for binding to antigens. More specifically, variable loops of β-strands, three each on the light (V_L) and heavy (V_H) chains are responsible for binding to the antigen. These loops are referred to as the complementarity determining regions (CDRs). The structures of these CDRs have been clustered [5].

In the framework of the immune network theory, CDRs are also called idiotypes. According to immune network theory, the adaptive immune system is regulated by interactions between idiotypes. [6]

Immunoglobuln Class and Subclass

Immunoglobulin Class [2]

Based on the antigenic character of heavy chains the immunoglobulins are classified into various types, the important are:

1. Immunoglobulin G (IgG) – Gamma heavy chains
2. Immunoglobulin M (IgM) – Mu heavy chains
3. Immunoglobulin A (IgA) – Alpha heavy chains
4. Immunoglobulin A (IgD) – Delta heavy chains
5. Immunoglobulin E (IgE) – Epsilon heavy chains

Immunoglobulin Subclass: [2]

1. IgG subclass
a) IgG1
b) IgG2
c) IgG3
d) IgG4

2. IgA subclass
a) IgA1
b) IgA2

A. Immunoglobulin G

Structure:

The structure of all IgG's are monomer (7S immunoglobulin). There are four IgG

subclass (IgG1,IgG2,IgG3 and IgG4) that very chemically in their chain composition and number arrangement of interchain disulfide bonds.

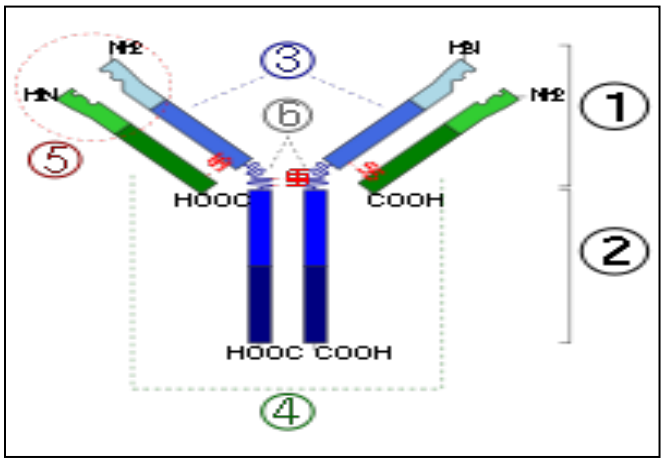

Figure 4.1: Structure of Immunoglobulin G

Schematic diagram of the basic unit of immunoglobulin (antibody)

1. Fab
2. Fc
3. heavy chain (consist of VH, CH1, hinge, CH2 and CH3 regions: from N-term)
4. light chain (consist of VL and CL regions: from N-term)
5. antigen binding site
6. hinge regions
7. (*) -S-S- mean disulfide bonds.
8. IgG antibodies are large molecules of about 150 k Da composed of four peptide chains. It contains two identical class γ heavy chains of about 50 k Da and two identical light chains of about 25 k Da, thus a tetrameric quaternary structure. The two heavy chains are linked to each other and to a light chain each by disulfide bonds. The resulting tetramer has two identical halves, which together form the Y-like shape. Each end of the fork contains an identical antigen binding site. The Fc regions of IgGs bear a highly conserved N-glycosylation site. The N-glycans attached to this site are predominantly core-fucosylated diantennary structures of the complex type. In addition, small amounts of these N-glycans also bear bisecting GlcNAc and α-2,6-linked sialic acid residues.[10]

Subclass

There are four IgG subclasses (IgG1, 2, 3, and 4) in humans, named in order of their abundance in serum (IgG1 being the most abundant). [11]

Table 4.1: Subclass of IgG

Name	Percent	Crosses placenta easily	Complement activator	Binds to Fc receptor on phagocytic cells
IgG1	66%	yes (1.47)†	second-highest	high affinity
IgG2	23%	no (0.8)†	third-highest	Extremely low affinity
IgG3	7%	yes (1.17)†	Highest	high affinity
IgG4	4%	yes (1.15)†	No	intermediate affinity

Property:

- IgG is the major immunoglobulin in human serum, accounting for 70 to 75 % of the immunoglobulin. Its has a molecular weight of 150,000 daltons. Its presents
- in blood plasma and tissue fluids.
- Its is distributed approximately equally between the intravascular and extravascular compartments . it has a half-life of approximetly 23 days.
- The IgG class acts against bacteria and viruses by opsonising the invaders and neutralizing toxins.
- IgG participates in most immunological reactions such as complement fixation , precipitation and it is the only immunoglobulin molecule able to cross to the placenta and provide naturally acquired immunity for the newborn.
- IgG binding to cells – Macrophages,monocytes , PMNs and some lymphocytes have Fc receptors for the Fc region of IgG. 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. [12] [13]

Function

Antibodies are major components of the immune system. IgG is the main antibody isotype found in blood and extracellular fluid allowing it to control infection of body tissues. It binds many kinds of pathogen--including viruses, bacteria, and fungi--and protects the body against them using several immune mechanisms: For example, agglutination and immobilization, complement activation (classical pathway), opsonization for phagocytosis, and neutralization of toxins. It also plays an important role in antibody-dependent cell-mediated cytotoxicity (ADCC) and intracellular antibody-mediated proteolysis, in which it binds to TRIM21 (the receptor with greatest affinity to IgG in humans) in order to direct marked virions to the proteasome in the cytosol. IgG is also associated with Type II and Type III Hypersensitivity.

B. Immunoglobulin M Structure

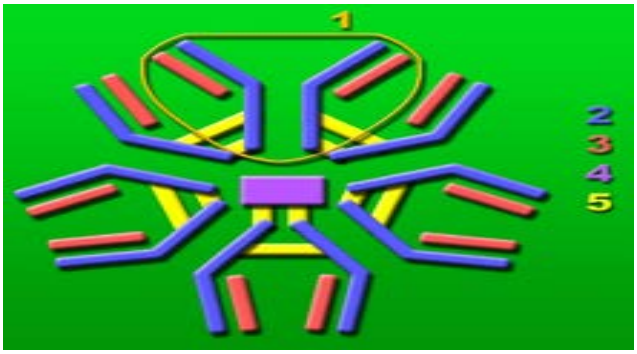

Figure 4.2: Structure of IgM

IgM (Immunoglobulin M) antibody molecule consisting of 5 base units.

1. Base unit.
2. Heavy chains.
3. Light chains.
4. J-chain.
5. Intermolecular disulfide bonds.

IgM scheme. Heavy chains are blue; light chains are yellow. [16]

Property:

- IgM accounts for the 10 % of serum immunoglobulins. Its has a half-life of about five days. Its has a molecular weight 900,000 daltons.

- IgM is the first immunoglobulin made during B-cell maturation and the first secreted into serum during primary antibody response.
- IgM is so large size, it does not leave the bloodstream or cross the placenta, the presence of IgM in foetus or new born indicates intrauterine infection and detection is useful in the diagnosis of congenital infection such as syphilis, rubella, HIV infection and toxoplasmosis.

Expression:

In germline cells, the gene segment encoding the μ constant region of the heavy chain is positioned first among other constant region gene segments. For this reason, IgM is the first immunoglobulin expressed by mature B cells.

It is also the first immunoglobulin expressed in the foetus (around 20 weeks) and also phylogenetically the earliest antibody to develop.

Clinical Significance:

IgM antibodies appear early in the course of an infection and usually reappear, to a lesser extent, after further exposure. IgM antibodies do not pass across the human placenta (only isotype IgG).

These two biological properties of IgM make it useful in the diagnosis of infectious diseases. Demonstrating IgM antibodies in a patient's serum indicates recent infection, or in a neonate's serum indicates intrauterine infection (e.g. congenital rubella).

C. Immunoglobulin A Structure

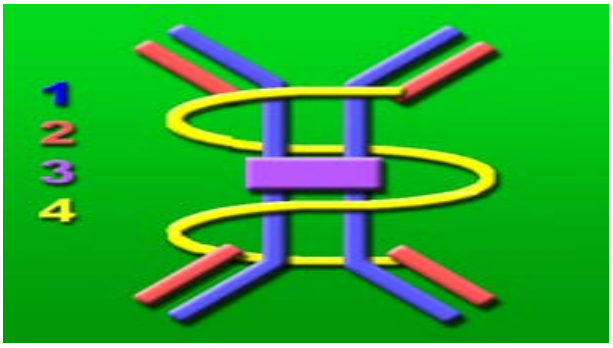

Figure 4.3: Structure of IgA

The dimeric IgA molecule.

H-chain

L-chain

J-chain

Secretory component[20]

- Serum IgA vs. secretory IgA.

Propery

- IgA is account for 10 to 13%of serum immunoglobulin . normal serum level is 0.6 - 4.2 mg/ml. It is half-life of 6 - 8 days
- IgA occurs in two forms serum IgA and secretory IgA

Serum IgA- a monomeric 7s molecule , MW about 160,000 daltons.

Secretory IgA- secretions secretory IgA is important in local (mucosal) immunity. It is found on mucosal surface and in secretions is a dimer form.MW about 390,000 daltons.

- Normally IgA does not fix complement, unless aggregated.
- IgA can binding to some cells - PMN's and some lymphocytes
- The protection of respiratory and gastrointestinal mucous membranes and external body secretion such as a tears ,saliva, seminal fluid ,urine and colostrums is accomplished by IgA.
- IgA may act as a first line defense agaist bacteria and viruses may also neutralize allergens.

IgA Activity

- The high prevalence of IgA in mucosal areas is a result of a cooperation between plasma cells that produce polymeric IgA (pIgA), and mucosal

epithelial cells that express an immunoglobulin receptor called the polymeric Ig receptor (pIgR). pIgA is released from the nearby activated plasma cells and binds to pIgR. This results in transportation of IgA across mucosal epithelial cells and its cleavage from pIgR for release into external secretions.

- In the blood, IgA interacts with an Fc receptor called FcαRI (or CD89), which is expressed on immune effector cells, to initiate inflammatory reactions. Ligation of FcαRI by IgA containing immune complexes causes antibody-dependent cell-mediated cytotoxicity (ADCC), degranulation of eosinophils and basophils, phagocytosis by monocytes, macrophages, and neutrophils, and triggering of respiratory burst activity by polymorphonuclear leukocytes.[23]

Transport

- Polymeric IgA (mainly the secretory dimer) is produced by plasma cells in the lamina propria adjacent to mucosal surfaces. It binds to the polymeric immunoglobulin receptor on the basolateral surface of epithelial cells, and is taken up into the cell via endocytosis. The receptor-IgA complex passes through the cellular compartments before being secreted on the luminal surface of the epithelial cells, still attached to the receptor. Proteolysis of the receptor occurs, and the dimeric IgA molecule, along with a portion of the receptor known as the secretory component, are free to diffuse throughout the lumen. In the gut, it can bind to the mucus layer on top of the epithelial cells to form a barrier capable of neutralizing threats before they reach the cells. .[24]

Pathology

- Decreased or absent IgA, termed selective IgA deficiency, can be a clinically significant immunodeficiency.
- *Neisseria gonorrhœae* (which causes gonorrhea), *Streptococcus pneumoniae*, and *Haemophilus influenzae* type B all releases a protease which destroys IgA.
- IgA nephropathy is caused by IgA deposits in the kidneys. It is not yet known why IgA deposits occur in this chronic disease. Some theories suggest an abnormality of the immune system results in these deposits.
- Celiac disease involves IgA pathology due to the presence of IgA antiendomysial antibodies.[24]

D. Immunoglobulin D Structure

The structure of IgD exists only as a monomer similer to IgG structure. Immunoglobulin D (IgD) is an antibody isotype that makes up about 1% of proteins in the plasma membranes of immature B-lymphocytes where it is usually coexpressed with another cell surface antibody called IgM. IgD is also produced in a secreted form that is found in very small amounts in blood serum. Secreted IgD is produced as a monomeric antibody with two heavy chains of the delta (δ) class, and two Ig light chains. [25]

Property

- IgD account for hardly 1% of the total serum immunoglobulins.MW- about180,000 daltons.
- IgD antybodies does not fix compliment and cannot cross the placenta .
- IgD is primarily found on B cell surfaces where it functions as a receptor for antigen. IgD on the surface of B cells has extra amino acids at C-terminal end for anchoring to the membrane. It also associates with the Ig-alpha and Ig-beta chains.
- It appears to act as a primary receptor for specific antigen on the surface of fetel lymphocytes destined to becomes a antibody forming cells in adult life.

Function

- IgD was recently found to be present in species from cartilaginous fish to human (probably with the exception of birds). This nearly ubiquitous appearance in species with an adaptive immune system demonstrates that IgD is as ancient as IgM and suggests the notion that IgD has important immunological functions.
- In B cells, IgD's function is to signal the B cells to be activated. By being activated, they are ready to take part in the defense of the body in the

immune system. During B-cell differentiation, IgM is the exclusive isotype expressed by immature B cells. IgD starts to be expressed when the B-cell exits the bone marrow to populate peripheral lymphoid tissues. When a B-cell reaches its mature state, it co-expresses both IgM and IgD. It is not well understood whether IgM and IgD antibodies are functionally different on B cells. Cδ Knockout mice (mice that have been genetically altered so that they do not produce IgD) have no major B-cell intrinsic defects. IgD may have some role in allergic reactions. [25]

- Recently, IgD was found to bind to basophils and mast cells and activate these cells to produce antimicrobial factors to participate in respiratory immune defense in human. It also stimulates basophils to release B-cell homeostatic factors. This is consistent with the reduction in the number of peripheral B cells, reduced serum IgE level and defective primary IgG1 response in IgD knockout mice.

Method of Coexpression

- In the human Heavy-Chain Locus, 3' of the V-D-J cassette is a series of C (for constant) genes, each conferring to an Ig isotype. The Cμ [IgM]gene is 3' and closest to the V-D-J cassette, with the Cδ gene appearing 3' to Cμ.
- A Primary mRNA transcript will contain the transcribed V-D-J cassette, and the Cμ and Cδ genes, with introns in between them.
- Alternative splicing can then occur, causing a selection of either Cμ or Cδ to appear on the functional mRNA (μ mRNA and δ mRNA respectively). Alternative splicing is thought to be possible due to two Polyadenylation sites, one appearing between the Cμ and Cδ, and the other 3' of Cδ (polyadenylation in the latter site would cause Cμ to be spliced away along with the intron). The precise mechanism of how the polyadenylation site is chosen remains unclear.
- The resulting functional mRNA will have the V-D-J and C regions contiguous, and its translation will generate either a μ heavy chain or δ heavy chain. The heavy chains then couple with either κ or λ light chains to create the final IgM or IgD antibody. .[26]

D. Immunoglobulin E

Immunoglobulin E (IgE) is a class of antibody (or immunoglobulin "isotype") that has been found only in mammals. IgE is a dimeric antibody with 4 Ig-like domains (Cε1-Cε4).[27] Its main function is immunity to parasites such as parasitic worms [28] like *Schistosoma mansoni*, *Trichinella spiralis*, and *Fasciola hepatica*,[29][30][31] and may be important during immune defense against certain protozoan parasites such as *Plasmodium falciparum*.[32]

It also plays an essential role in the allergy disorder, and is especially associated with type I hypersensitivity.[33]

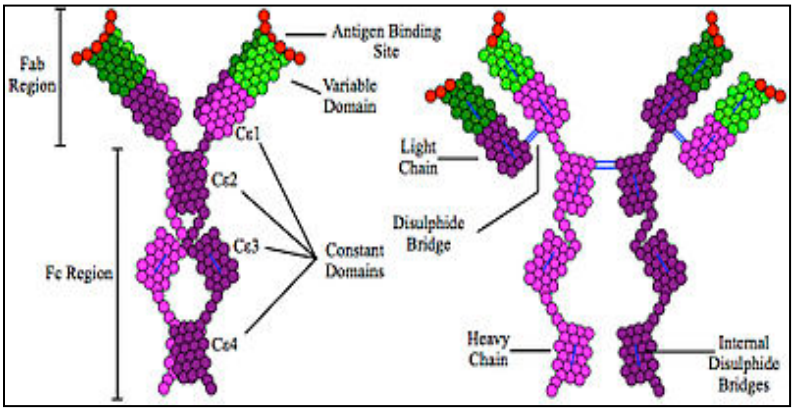

Figure 4.4: Structure of the IgE antibody

The role of mast cells in the development of allergy

Degranulation processes 1 - antigen; 2 - IgE antibody; 3 - FcεRI receptor; 4 - preformed mediators (histamine, proteases, chemokines, heparine); 5 - granules; 6 - mast cell; 7 - newly formed mediators (prostaglandins, leukotrienes, thromboxanes, PAF) [28]

Receptors

IgE elicits an immune response by binding to Fc receptors found on the surface of mast cells and basophils, and are also found on eosinophils, monocytes, macrophages and platelets in humans. Fcε has two types:

- FcεRI, the high-affinity IgE receptor
- FcεRII, also known as CD23, is the low-affinity IgE receptor

Physiology

There is much speculation into what physiological benefits IgE contributes, and, so far, circumstantial evidence in animal models and statistical population trends have hinted that IgE may be beneficial in fighting gut parasites such as *Schistosoma mansoni*, but this has not been conclusively proven in humans.

Although it is not yet well understood, IgE may play an important role in the immune system's recognition of cancer,[36] in which the stimulation of a strong cytotoxic response against cells displaying only small amounts of early cancer markers would be beneficial. Of course, if this were the case, anti-IgE treatments such as omalizumab (for asthma) might have some undesirable side effects.

Property

- IgE account for about 0.1% of total serum immunoglobulin.
- It is an 8s molecule MW about 190,000 daltons.
- Half-life is about 2 days .
- Located on the mast cells
- IgE molecules have four constant region domain ($c_\varepsilon 1$, $c_\varepsilon 2$, $c_\varepsilon 3$, and $c_\varepsilon 4$) two light chains
- IgE antybodies does not fix compliment and cannot cross the placenta.

Role in Disease

Atopic individuals can have up to 10 times the normal level of IgE in their blood (as do sufferers of hyper-IgE syndrome). However, this may not be a requirement for symptoms to occur as has been seen in asthmatics with normal IgE levels in their blood

P**harmacology**

IgE may be an important target in treatments for allergy and asthma.

Currently, severe allergy and asthma is usually treated with drugs (like anti-histamines) that damp down the late stages of inflammation and relax airway smooth muscle. However, these treatments are fairly broad in their action, so many have unpleasant side-effects; they may also inhibit important protective responses.

5. Antigenic Determinants on Immunoglobulins

Since antibodies are glycoproteins, they can themselves function as potent immunogens to induced an antibody response. The antigenic determinants , or epitopes on Ig molecules fall into three major categories which are located in characteristic portion of the molecule.

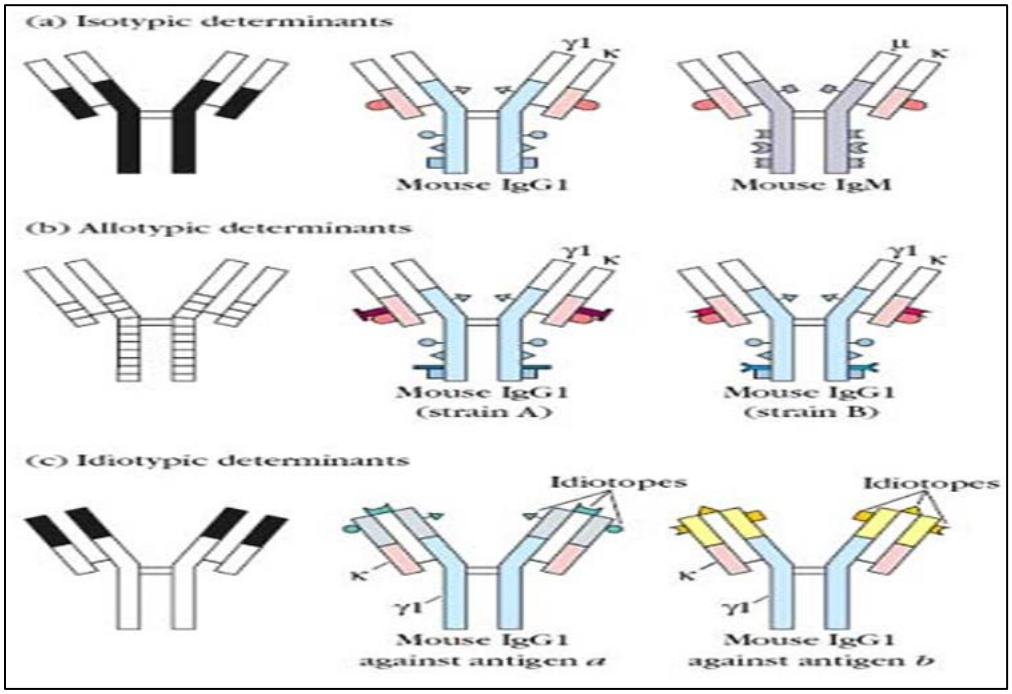

Figure 5.1: Structure of Antigenic Determinants on Immunoglobulin

5.1 Isotype

An antibody class is determined by the constant region sequence of the heavy chain. The five human isotype, designated IgA, IgD , IgG , IgE, IgM , exhibit structural and functional differences. Isotypic determinants are constant – region determinants that collectively define each heavy-chain class and subclass within a species. Each isotype is encoded by a separate constant-region genes, and all members of a species carry the same constant-region genes. Different species inherent different constant-region genes and therefore express different isotype. therefore, when an antibody from one species is injected into another species, the isotype determinants will be recognized as foreign, inducing an antibody response to the isotype determinants on the foreign antibody.

A. Occurrence

Isotypes are found in all normal individuals in the species. The prefix Iso means same in all members of the species. Some individuals with immunodeficiences may lack one or more isotypes but normal individuals have all isotypes.

B. Importance

Antibodies to isotypes are used for the quantitation of immunoglobulin classes and subclasses in various diseases, in the characterization of B cell leukemia and in the diagnosis of various immunodeficiency diseases.

5.2 Allotype

It is based on genetic difference among individuals. It depends on the existence of allelic from of the same gene. These alleles encode minor amino-acid difference, called allotypic determinants, that occur in some but not all, members of a species.

As a result of allotypy, a heavy or light chain constituent of any immunoglobulin can be present in some members of a species and absent in others. This situation contrasts with that of immunoglobulin classes or subclasses, which are present in all members of a species.

A. Importance

-Monitoring bone marrow grafts

Bone marrow grafts that produce a different

allotype from the recipient can be used to monitor the graft.

-Forensic medicine

Km and Gm allotypes are detectable in blood stains and semen and are useful in forensic medicine.

-Paternity testing

the immunoglobulin allotypes are one of the characteristics used in legal cases involving paternity.

5.3 Idotype

The unique amino-acid sequence of the variable domains of a given antibody can function not as an antigen-binding site but also as a set of antigenic determinants. The idiotype determinants are generated by the heavy – and light-chain variable regions. Each individual antigenic determinants of the variable region is refered to as an idotype.

A. Importance

-V region marker

Idiotypes are a useful marker for a particular variable region.

Regulation of immune responses

There is evidence that immune responses may be regulated by anti-Id antibodies directed against our own Id's.

-Vaccines

In some cases, anti-idiotypic antibodies actually stimulate B cells to make antibody and thus they can be used as a vaccine. This approach is being tried to immunize against highly dangerous pathogens that cannot be safely used as a vaccine.

-Treatment of B cell tumours

Anti-idiotypic antibodies directed against an idiotype on malignant B cells can be used to kill the cells. Killing occurs because of complement fixation or because toxic molecules are attached to the antibodies. [39]

6. Clinical Applications of Human Immunoglobulins Class

A. IgG

1. Increases in:

a) Chronic granulomatous infections
b) Infections of all types
c) Hyperimmunization
d) Liver disease
e) Malnutrition (severe)
f) Dysproteinemia
g) Disease associated with hypersensitivity granulomas, dermatologic disorders, and IgG myeloma
h) Rheumatoid arthritis

2. Decreases in:

a. Agammaglobulinemia
b. Lymphoid aplasia
c. Selective IgG, IgA deficiency
d. IgA myeloma
e. Bence Jones proteinemia
f. Chronic lymphoblastic leukemia

B. IgM

1. Increases (in adults) in:

a)Waldenström'smacroglobulinemia
b)Trypanosomiasis
c)Actinomycosis
d)Carrión'sdisease(bartonellosis)
e)Malaria
f)Infectiousmononucleosis
g)Lupuserythematosus
h)Rheumatoidarthritis
I) Dysgammaglobulinemia (certain cases)

Note: In the newborn, a level of IgM above 20 ng./dl is an indication of *in utero* stimulation of the immune system and stimulation by the rubella virus, the cytomegalovirus, syphilis, or toxoplasmosis.

2. Decreases in:

a)Agammaglobulinemia
b) Lymphoproliferative disorders (certain cases)
c)Lymphoidaplasia
d)IgGandIgAmyeloma
e)Dysgammaglobulinemia
f) Chronic lymphoblastic leukemia

C. IgA

1. Increases in:

a)Wiskott-Aldrichsyndrome
b) Cirrhosis of the liver (most cases)
c) Certain stages of collagen and other

autoimmune disorders such as rheumatoid arthritis and lupus erythematosus
d) Chronic infections not based on immunologic deficiencies
e) IgA msyeloma

2. Decreases in:
a)Hereditary a taxiatelangiectasia
b)Immunologic deficiency states (*e.g.*, dysgammaglobulinemia, congenital and acquired agammaglobulinemia, and hypogammaglobulinemia)
c)Malabsorptionsyndromes
d)Lymphoidaplasia
e)IgGmyeloma
f)Acutelymphoblasticleukemia
g) Chronic lymphoblastic leukemia

D. IgD
1. Increases in:
a)Chronicinfections
b) IgD myelomas

E. IgE
1. Increases in:
a)Atopic skin diseases such as eczema
b)Hayfever
c)Asthma
d)Anaphylacticshock
e) IgE-myeloma

2. Decreases in:
a)Congenitalagammaglobulinemia
b) Hypogammaglobulinemia due to faulty metabolism or synthesis of immunoglobulins. [40]

Conclusion

"Immunoglobulins are glycoproteins molecules that are produced by plasma cells in response to an immunogen and which function as antibodies. These are proteins which have demonstrable antibody activity and / or share a common antigenic specificity with any known antibody and are produced by cell that form antibody."

These antibodies have been produced by a subpopulation of whites blood cells in the immune system called lymphocytes. Based on the antigenic character of heavy chains the immunoglobulins are classified into various types , the important are IgG ,IgM, IgA, IgD, IgE. Activated B cells produce soluble antibodies. Unactivated and memory B-cells produce surface, membrane-bound, antibodies.The membrane form is associated with two copies of Igα and Igβs , giving the B-cell receptor. Antibodies can recognize an extremely diverse set of antigens.A *single* B-cell produces antibodies that are *homogenous* in their specificity. This is one example of Allelic exclusion in the immune system. Although two copies of the gene are present (maternal and paternal), only one is used to express the protein.

Antibodies are glycoproteins, they can themselves function as potent immunogens to induced an antibody response. The antigenic determinants, or epitopes on Ig molecules fall into these major categories which are located in characteristic portion of the molecule , these are isotype , allotype ,idiotypic .The nature of antigen – antibody reaction are the combining site of an antibody is located in the Fab portion of the molecule and is constructed from the hypervariable regions of the heavy and light chains. Thus, our concept of antigen-antibody reactions is one of a key (*i.e.* the antigen) which fits into a lock (*i.e.* the antibody).The bonds that hold the antigen to the antibody combining site are all non-covalent in nature. These include hydrogen bonds, electrostatic bonds, Van der Waals forces and hydrophobic bonds. Multiple bonding between the antigen and the antibody ensures that the antigen will be bound tightly to the antibody.

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