LECTURE: 21

Title IMMUNOGLOBULINS FUNCTIONS & THEIR RECEPTORS

LEARNING OBJECTIVES:

The student should be able to:

- **Determine predominant immunoglobulin isotypes in serum.**
- **Determine the predominant immunoglobulin isotypes in secretions.**
- **Determine the predominant immunoglobulin involved in allergy.**
- **Determine the location of the IgD immunoglobulin.**
- **Determine the serum concentrations of human IgM, IgA, IgG, IgE, and IgD immunoglobulins.**
- **Determine which immunoglobulin is predominant in the primary, and which is predominant in secondary immune response?**
- **Determine which immunoglobulin isotype can cross the placenta?**
- **Determine which immunoglobulin isotype protect the gastrointestinal tract of the new born baby in the early life, and where it found?**
- **Determine the major opsonizing immunoglobulin.**
- **State the two different types of human IgA.**
- **Determine which is important in the mucosal surfaces IgA1 or IgA2.**
- **Identify the predominant serum IgA, and indicate in which form it exists.**
- **Enumerate the locations of the sIgA**
- **Describe the secretory component and indicate its functions.**
- **Identify structurally largest immunoglobulin and its locations.**
- **Enumerate the different functions of the IgM immunoglobulin.**
- **Determine the one antibody is made for ABO blood group.**
- **Identify the predominant antibody produced by the fetus.**
- **Determine the most efficient antibody in activating complement system.**
- **Determine which antibody which is not opsonic but enhances the opsonization process 1000-fold more than the IgG, and indicate how?**
- **Enumerate the functions of the immunoglobulin IgE.**
- **Enumerate the different immunoglobulin cell surface receptors on body cells.**

LECTURE REFRENCE:

1. TEXTBOOK: ROITT, BROSTOFF, MALE IMMUNOLOGY. 6th edition. Chapter 4. pg. 65-83.

2. TEXTBOOK: ABUL K. ABBAS. ANDREW H. LICHTMAN. CELLULAR AND MOLECULAR IMMUNOLOGY. 5TH EDITION. Chapter 9 .pg 189-214.

IMMUNOGLOBULINS FUNCTION AND THEIR RECEPTORS

INTRODUCTION

One of the most important characteristics of the immune system is the production of soluble proteins (glycoproteins), that migrate through the blood circulation into different parts of the body (thus present in the serum & tissue fluids) and some are present on the surface of the B-lymphocytes act as receptors for specific antigens. The antibodies perform many biological functions related to the protection and body's immunity against pathogens. These soluble proteins are the antibodies, and they belong to a class of protein called "globulins" due to their "globular structure". Antibodies present in the γ-globulin fraction of serum [when serum is subjected to electrophoresis (separation of proteins according to their charges in an electrical field), proteins which migrate faster to the anode (+ve) is called α–globulin, and β–globlulin, while those migrate but slower, towards the anode is called γ–globulin] (Figure). Later it was shown that antibody activity is present not only in the gamma-globulin fraction but also in a slightly more anodic area. Today antibodies are collectively known as immunoglobulins (Igs).

Electrophoretic mobility of serum proteins

Immunoglobulins are produced & secreted by antibody forming cell (AFCs) which is the differentiated B-lymphocytes and is called plasma cells in response to an exposure (contact = binding) to an antigen. They react specifically with that antigen in vivo or in vitro and are hence a part of the adaptive immune response (humoral immunity). The antibody on the surface of the precursor B-cell has the same binding specificity of the secreted antibody by the plasma cell (Figure).

BIOLOGICAL AND CHEMICAL PROPERTIES OF IMMUNOGLOBULINS

Immunoglobulins fall into **five classes (isotypes)**, based on certain structural differences (**Table-1**)

Feature	IgG	IgA	IgM	IgD	IgE
Sedimentation Coefficient	7S	7S, 9S, 11S	19S	7S	8S
Molecular Weight (kD)	150	160, 395	900	185	200
Heavy Chain Type	gamma	Alpha	mu	delta	Epsilon
Molecular Formulas	H_2L_2	H_2L_2 H_4L_4JSC	$H_{10}L_{10}J$	H_2L_2	H_2L_2
Valence	2	2, 4	5 (10)	2	2
Concentration in Serum (mg/ml)	8-16	1.4-4	0.5-2	0-0.4	0.02-0.5
Percentage of Total Ig in Serum	80	13	6	0-1	0.002
Carbohydrate Content	3%	8%	12%	13%	12%
Complement Activation	+++ (C1)	+ (Alt)	+++++ (C1)	-	-
Binds Fc Receptor (FcR)	MP, PMN, B	-	-	-	Mast Cells
Crosses Placenta	+++	-	-	-	-
Hypersensitivity	Types II, III	-	Types II, III	-	Type I
Cell Receptor on:	Mature B Cells	Mature B Cells	Immature and mature B Cells	Mature B Cells	Mature B Cells

Table-1 The function of Immunoglobulins

Each class also has certain unique biological and chemical properties

A. IgG. IgG is the major immunoglobulin in human serum, accounting for approximately 75% of the total normal serum immunoglobulin pool at a concentration of approximately 1200 mg/dl.

1. Structure

a. IgG is a **monomer** consisting of identical pairs of H and L chains linked by disulfide bridges (**Figure-1**).

b. Four subclasses of IgG have been identified, based on H chain differences: subclasses IgG1, IgG2, IgG3, and IgG4 correspond to H chains γ_1, γ_2, γ_3, and γ_4.

2. Biological and chemical properties

a. Most IgG subclasses have a molecular weight of 150 kDa and an S value of 7S; IgG3 is slightly larger, at 170 kDa.

b. Most serum IgG is IgG1.

c. IgG is the only immunoglobulin that can cross the placenta in humans; therefore, maternal IgG provides most of the protection of the newborn during the first months of life [secondary IgA (sIgA) in colostrum protects the infant's gastrointestinal tract].

d. IgG molecules are capable of being complement by the classical pathway (except for IgG4, which activates by the alternative pathway). The binding site for complement component C1q is in the C_H2 domain.

e. IgG is the major antibody produced in the secondary immune response.

(1) IgG has a half-life of approximately 21 days (IgG3 has a half-life of only 7 days).

(2) Effective antitoxic immunity is exclusively IgG.

f. IgG is the major opsonizing immunoglobulin in phagocytosis; neutrophils have receptors for the Fc fragments of IgG1 and IgG3.

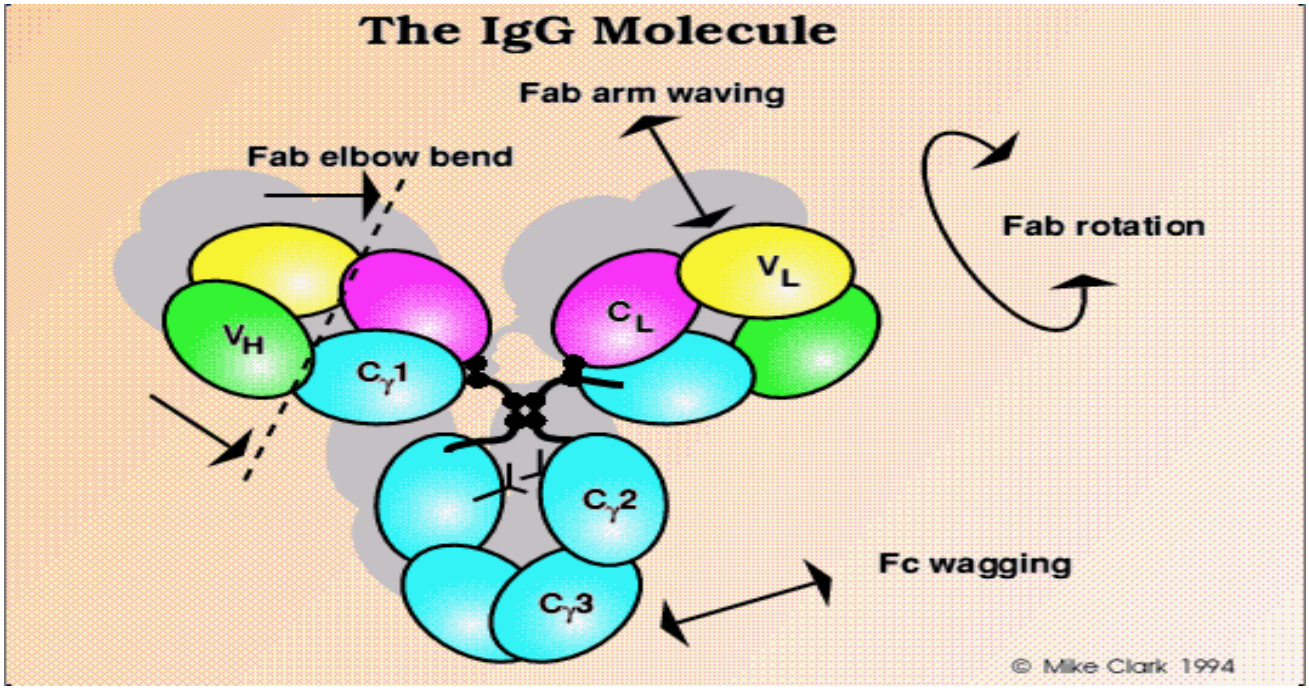

Figure-1 the basic structure of immunoglobulin

B. IgA. IgA is present in two forms: one in the serum and the other in various body secretions.

1. Serum IgA, at concentration of approximately 200 mg/dl, accounts for about 15% to 20% of the total normal serum immunoglobulin pool.

a. Structure

(1) In humans, over 80% of serum IgA exists in a monomeric form with an S value of 7S.
(2) The rest exist as dimers, trimers, or tetramers. In these polymeric forms of IgA, the monomeric units are linked by disulfide bonds and J chains.

b. Biological and chemical properties

(1) IgA does not bind complement via the classic pathway but may do so via the alternative pathway.
(2) IgA has a half-life of 6 days.
(3) IgA can be inactivated by an IgA protease produced by gonococci, meningococci, pneumococci, and Haemophilus influenzae.

2. Secretory IgA (sIgA) is the predominant immunoglobulin in various secretions (saliva; tears; colostrum; bronchial, genitourinary, and intestinal secretions).

a. Structure

(1) The sIgA molecule consists of two monomeric units plus J chain and secretory component (**Figure-2)**. It has an S value of 11S.

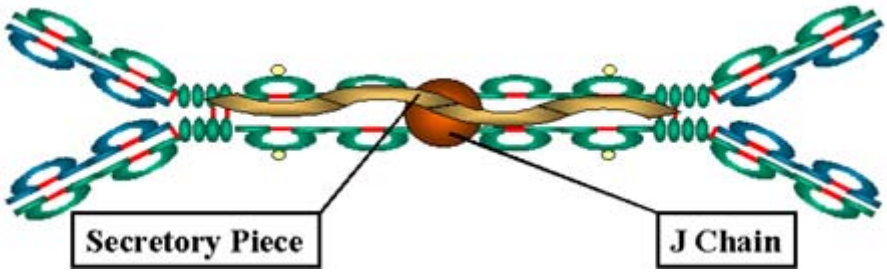

Figure-2 Secretory IgA (sIgA) molecule has a dimeric structure plus J chain plus secretory component.

(a) Secretory component (secretory piece) is a polypeptide chain with a molecular weight of about 70 kDa.
(b) It is joined to sIgA by disulfide bonds.
(c) It serves as a receptor for IgA on the surface of epithelial cells lining exocrine glands and is important in the secretion of sIgA.

(2) The dominant subclass of IgA is **sIgA2,** the form shown in **figure-2**. The sIgA2 molecule is unique for its absence of H-L chain bonds; this subclass instead has L-L bonds.

b. biological and chemical properties

(1) Secretory component is synthesized by exocrine epithelial cells and enables dimeric IgA to pass through the mucosa tissues into the secretions.

(a) The epithelial cells bear an IgA-specific receptor.
(b) After binding IgA, the receptor-IgA complex is internalized by endocytosis, transported across the cell cytoplasm, and extruded into the external secretions.
(c) As the complex is extruded, proteolytic cleavage of the receptor leaves a fragment, the secretory component, attached by a disulfide bond to the IgA dimer.
(d) Secretory component appears to protect IgA from mammalian proteases.

(2) Secretory IgA functions in several ways.

(a) It protects mucosal surfaces by reacting with adhesion molecules on the surface of potential pathogens and interfering with their adherence and colonization.
(b) It may also opsonize foreign particles, as polymorphonuclear neutrophils (PMNs) have FcαR in their membranes.

C. IgM. IgM represents about 8% to 10% of the total serum immunoglobulins and is present in normal serum at a concentration of approximately 120 mg/dl.

1. Structure

a. With an S value of 19S, IgM has a **pentameric** structure (**Figure-3**) consisting of five monomeric units linked by a J chain and by disulfide bonds at the Fc fragment.
b. IgM is easily dissociated by reducing agents, forming five monomeric units of 7S IgM.

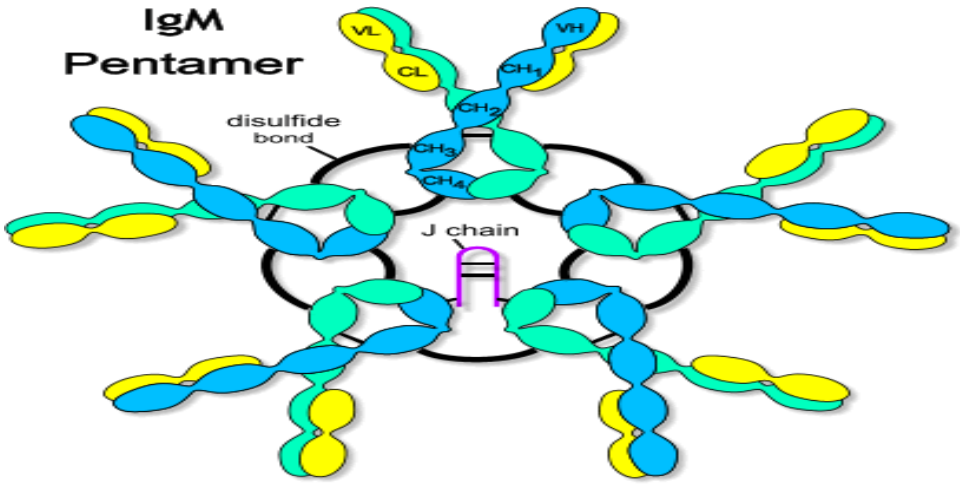

Figure-3 Immunoglobulin-M pentamer structure, linked by the J chain at the Fc fragment.

2. Biological and chemical properties

a. IgM is the first antibody that an immunologically committed B lymphocyte can produce. It has a half-life of approximately 10 days.

(1) IgM will appear in the B cell membrane (followed shortly by IgD) prior to an encounter with its homologous epitope.
(2) IgM is the predominant antibody in the early (primary) immune response to most antigens.
(3) IgM is the predominant antibody produced by the fetus. An elevated IgM level in the cord serum of a newborn (normal level, approximately 10 mg/dl) may indicate that the fetus was infected before birth.

b. IgM is the only antibody made to certain carbohydrate antigens, such as the ABO blood group antigens on human erythrocytes.
c. IgM is the most efficient immunoglobulin at activation complement proteins in lytic reactions.
d. IgM is not intrinsically opsonic, since phagocytic cells do not possess a receptor for the Fc portion of the μ chain. However, IgM enhances phagocytosis by causing the deposition of the C3b opsonin onto the surface where the IgM antibody resides.
e. Some IgM is synthesized locally in secretory tissues (e.g., parotid glands). **Secretory IgM,** like sIgA, can bind secretory component.

D. IgD. IgD represents less than 1 % of the total immunoglobulin pool and is present in trace amounts in normal serum (approximately 3-5 mg/dl).

1. Structure. IgD exists as a monomer; its S value is 7S.

a. Structure studies are difficult because of the low serum levels and because IgD is susceptible to enzymatic degradation (**Figure-4**).
b. One unique structure feature is the presence of only a single H-H interchain bond, along with two H-L interchain bonds.

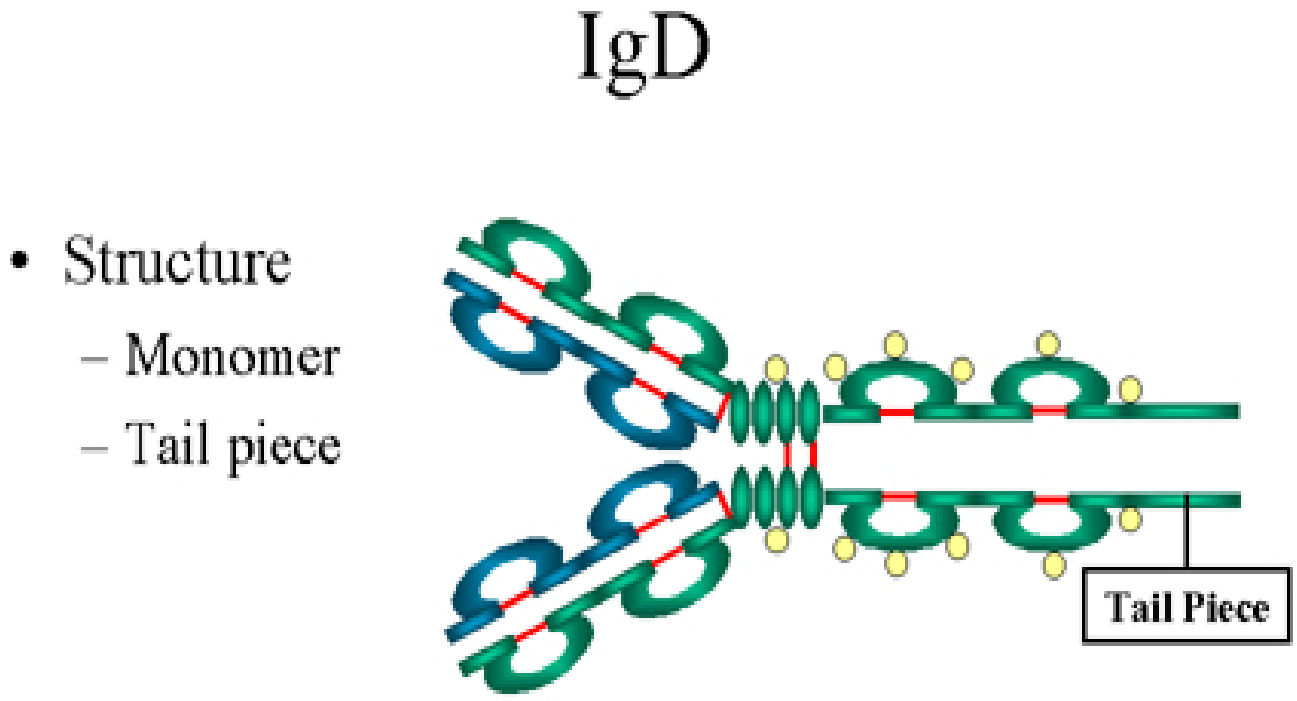

Figure-4 Immunoglobulin-D

2. Biological and chemical properties

a. IgD has a half-life of 2-3 days; it is heat and acid labile.
b. There is still controversy over the biological functions of IgD.

(1) IgD occurs I n large quantities on the B cell membrane and may, as an antigen receptor, be involved in B cell activation.
(2) The molecule may have some antibody activity for penicillin, insulin, and diphtheria toxoid.

E. IgE. IgE is present in trace amounts in normal serum (approximately 0.05 mg/dl), accounting for only 0.004 % of total serum immunoglobulins.

1. Structure. IgE is a monomer with the unusual feature that its fifth domain separates the two interchain H-H bonds.

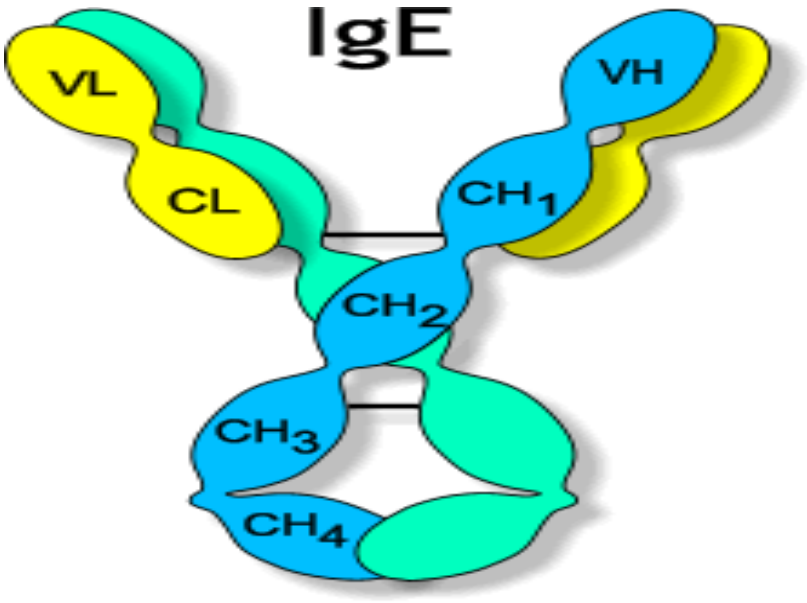

Figure-5 Immunoglobulin-E

2. Biological and chemical properties

a. IgE has a molecular weight of approximately 190 kDa and an S value of 8S.
b. IgE is produce by B cells and plasma cells in spleen, in lymphoid tissue of the tonsils and adenoids, and in the respiratory and gastrointestinal mucosa. It has a vascular half-life of 2-3 days.
c. IgE production begins in the fetus early in the gestational process; IgE does not cross the placenta.
d. IgE is associated with immediate hypersensitivity reactions (e.g., atopy and anaphylaxis).

(1) IgE is **homocytotropic:** is has an affinity for cells ("cytotropic") of the host species that produced it ("homo").

(a) This affinity is particularly strong for tissue mast cells and blood basophils.
(b) Fixation to these cells occurs via the Fc fragment (C_H3 and C_H4 domains).

(2) Upon combination with certain antigens (called **allergens,** because they generate allergy), IgE antibodies trigger the release of histamine and other mediators of atopic disease from the tissue mast cells.
e. IgE may also be important in immunity to certain helminthic parasites.
f. It is unable to activate complement via the classic pathway.
g. IgE is heat-labile at 56° C.