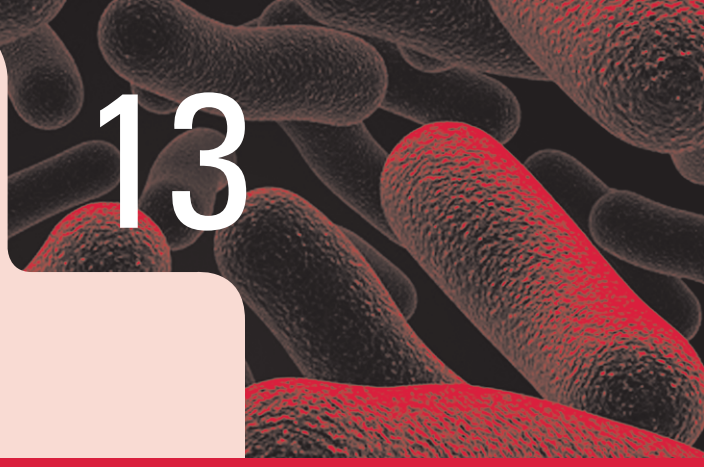

13

Antibodies

Introduction

Antibodies are globulin proteins (immunoglobulins) that are synthesized in serum and tissue fluids, which react specifically with the antigen that stimulated their production. Three types of globulins are present in the blood: alpha, beta, and gamma.

The antibodies are the gamma globulins. Antibodies are one of the major plasma proteins, and against infection often referred to as "first line of defense". The most important function of antibodies is to confer protection against microbial pathogens. Antibodies confer protection in the following ways:

1. They prevent attachment of microbes to mucosal surfaces of the host.
2. They reduce virulence of microbes by neutralizing toxins and viruses.
3. They facilitate phagocytosis by opsonization of microbes.
4. They activate complement, leading to complement-mediated activities against microbes.

Von Behring and Kitasato performed the first experiments that proved the physical existence of antibodies in 1890. They demonstrated that serum obtained from rabbits immunized with tetanus or diphtheria toxins could prevent disease in mice infected with such pathogens. The unknown substance that was present in serum and that provided protection on transfer was named "antitoxin" by Tizzoni and Cattani in 1891. Subsequently, experimental works by Paul Ehrlich and Jules Bordet demonstrated that a protective response could be generated even against whole cells (erythrocytes). The more inclusive term *antibody* subsequently replaced the term *antitoxin*.

Tiselius and Kabat accomplished the first successful attempt to identify antibody molecules in 1939. They demonstrated that hyperimmunization increased the concentration of γ-globulins in serum and that this fraction contained antibody activity. Because γ-globulins are large-molecular-weight proteins, it was suggested that further characterization of antibodies requires breaking them into smaller and easily handled fragments.

Porter in 1959, succeeded in digesting rabbit immunoglobulin G (IgG) with the proteolytic enzyme papain. These produced two distinct fragments: a monovalent fragment with antigen-binding activity, termed Fab (fragment antigen binding) and a second fragment that retained the antibody's effector functions and crystallized readily into a lattice, termed Fc (fragment crystallizable). Edelman and Poulik using a similar method splitted myeloma globulins into two distinct components, which subsequently were termed heavy (H) and light (L) chains.

The World Health Organization (WHO) in 1964 coined the term "immunoglobulin (Ig)" for the term antibody. The immunoglobulin includes not only antibody globulins but also the cryoglobulins, macroglobulins, and abnormal myeloma proteins. Thus, all antibodies are immunoglobulins but not all immunoglobulins may be antibodies.

Immunoglobulins

There are five classes of immunoglobulins: (*i*) immunoglobulin G (IgG), (*ii*) immunoglobulin M (IgM), (*iii*) immunoglobulin A (IgA), (*iv*) immunoglobulin E (IgE), and (*v*) immunoglobulin D (IgD). Myeloma proteins were first used for the amino acid sequencing of immunoglobulins. These proteins were also the first immunoglobulins that were subjected to crystallographic studies. They provided the first glimpses of the domain structure of the prototypic immunoglobulin.

Structure of Immunoglobulins

Immunoglobulins show the following properties:

- They are glycoproteins.
- They are a complex structure of four polypeptide chains: two identical heavy (typically 55 kDa each) chains and two identical light chains (25 kDa each). This gives immunoglobulin an overall 'Y' or 'T' shape, which is the most widely recognized feature of immunoglobulin structure.
  - The terms "heavy" and "light" refer to the molecular weights of the chains. The heavy chains have a molecular weight of 50,000–70,000 Da, while light chains have a molecular weight of 25,000 Da. The heavy chains are longer, and light chains are shorter (Fig. 13-1).

Heavy chains

An immunoglobulin molecule has two heavy chains. Each heavy chain is made up of 420–440 amino acids. The two heavy chains are held together by one to five disulfide (S—S) bonds. Each heavy chain is bound to a light chain by a disulfide bond and by noncovalent bonds, such as salt linkages, hydrogen bonds, and hydrophobic bonds to form a heterodimer (H–L). Similar noncovalent interactions and disulfide bridges link the two identical heavy and light (H–L) chains to each other to form the basic four-chain $(H–L)_2$ antibody structure.

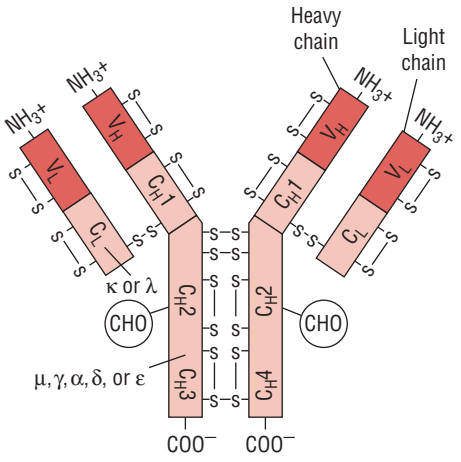

FIG. 13-1. Schematic diagram of monomer of the immunoglobulin.

TABLE 13-1 Classes of immunoglobulins and their heavy chains and subclasses

Class	Heavy chain	Subclasses
IgG	Gamma	γ_1, γ_2, γ_3, γ_4
IgM	Mu	None
IgA	Alpha	α_1, α_2
IgE	Epsilon	None
IgD	Delta	None

The heavy chains of a given antibody molecule determine the class of that antibody. For example, IgM contains mu (μ), IgG contains gamma (γ), IgA contains alpha (α), IgD contains delta (δ), and IgE contains epsilon (ε) heavy chains (Table 13-1). These heavy chains are structurally and antigenically distinct for each class of immunoglobulin. They differ in their size, carbohydrate content, and as antigens.

Light chains

An immunoglobulin molecule has two light chains. Each light chain is made up of 220–240 amino acids. Light chain is attached to the heavy chain by a disulfide bond. The light chains are structurally and chemically similar in all classes of immunoglobulins. They are of two types: kappa (κ) and lambda (λ). These two types differ in their amino acids present in constant regions. Each immunoglobulin has either two κ or two λ chains but never both. The κ and λ chains are present in human serum in a ratio of 2:1.

Variable and constant regions

Each polypeptide chain of an immunoglobulin molecule contains an amino terminal part and a carboxy terminal part. The amino terminal part is called the variable region (***V region***) and the carboxy terminal part is called the constant region (***C region***).

Both heavy and light chains contain variable and constant regions. These regions are composed of three-dimensional folded structures with repeating segments, which are called ***domains***. Each heavy chain consists of one variable (VH) and three constant (CH) domains. IgG and IgA have three CH domains (CH1, CH2, and CH3), whereas IgM and IgE have four domains (CH1, CH2, CH3, and CH4). Each light chain consists of one variable (VL) and one constant domain (CL).

Variable region: The amino-terminal half of the light or heavy chain, consisting of 100–110 amino acids, is known as variable or *V regions* (VL in light chains and VH in heavy chains). V region is different for each class of immunoglobulin.

The variable regions of both light and heavy chains consist of three highly variable regions known as ***hypervariable regions***. The antigen combining sites Fab of the antibody molecule that consists of only 5–10 amino acids each are present in the hypervariable region of both the light and heavy chains. These antigen-binding sites are responsible for specific binding of antibodies with antigens. The high specificity of antibodies is primarily due to the presence of these hypervariable regions.

Constant region: The carboxyl-terminal half of the molecule is called the constant (C) region. It consists of two basic amino acid sequences. The Fc fragment, found to crystallize under low ionic conditions, is present in the constant region of heavy chain.

The constant region of the heavy chain has many biological functions. It is responsible for activation of the complement, binding to cell surface receptors, placental transfer, and many other biological activities.

The constant region of the light chain has no biological function.

A single antibody molecule has two identical heavy chains and two identical light chains, H2L2, or a multiple (H2L2)*n* of this basic four-chain structure. Subisotypes exist for α and γ chains, and this leads to the existence of subclasses of the respective immunoglobulins.

Treatment of Immunoglobulins with Proteolytic Enzymes

The immunoglobulin molecule can be broken into a number of "sections" or "fragments" by action of proteolytic enzymes. The proteolytic enzyme papain cleaves just above the interchain disulfide bonds linking the heavy chains, whereas the enzyme pepsin cleaves just below these bonds, thereby generating different digestion products. For example, peptide bonds in the "hinge" region are broken on treatment of antibody molecule with papain, resulting in production of two identical Fab fragments and one Fc fragment. The Fab fragments produced during cleavage monovalently bind to the antigen. Treatment with pepsin cleaves immunoglobulin but at a different site, producing an Fc fragment and two Fab fragments, F $(ab)_2$, which upon exposure to reducing conditions are separated into Fab monomeric units.

Immunoglobulin Antigen Determinants

There are three major types of immunoglobulin antigen determinants: isotypes, allotypes, and idiotypes.

Isotypes

The *isotype* of an immunoglobulin refers to the particular constant region of the light- or heavy-chain of the immunoglobulin. Immunoglobulins are classified on the basis of various heavy chain isotypes. Heavy chains are distinguished by the presence of heavy chain markers, such as μ, γ, α, δ, and ε in the immunoglobulins IgM, IgG, IgA, IgD, and IgE, respectively. The light chains are also distinguished by isotype markers, such as κ and λ. Isotypes are present in all members of a species.

Allotypes

The *allotype* refers to allelic differences in both the variable and constant regions of immunoglobulin. The allotype markers are present on the constant regions of light and heavy chains. They are Am on α heavy chains, Gm on γ heavy chains, and Km on κ light chains. Allotype markers are absent on μ, δ, and ε heavy chains and on λ light chains. More than 25 Gm types, 3 Km allotypes, and 2 Am on IgA have been described. Allotypes are present in some but not all members of a species and are inherited in a simple Mendelian fashion.

Idiotypes

The *idiotype* refers to a specificity that is associated with the variable region. Idiotype markers are found on the hypervariable region of the immunoglobulin. Idiotypes are specific for each antibody molecule. Anti-idiotypic antibodies produced against Fab fragments prevent antigen–antibody interaction.

Biosynthesis of Immunoglobulins

B lymphocytes and plasma cells take part in the synthesis of immunoglobulins. Resting B cells synthesize only small amounts of immunoglobulins that mainly get incorporated into cell membranes. Plasma cells, the most differentiated B cells, are specialized to produce and secrete large amounts of immunoglobulins. The synthetic capacity of the plasma cells is reflected by the abundant cytoplasm, which is extremely rich in endoplasmic reticulum.

Normally, heavy and light chains are synthesized in separate polyribosomes of the plasma cell. The amounts of heavy and light chains synthesized on the polyribosomes are usually balanced and so both types of chains are combined to produce complete Ig molecules, without excess of any given chain. The assembly of a complete Ig molecule is carried out either by associating one heavy and one light chain to form an H–L hemimolecule, and then joining two H–L hemi-molecules to form a single complete molecule (H2L2), or by forming H2 and L2 dimers that later associate to form the complete molecule.

While free light chains can be effectively secreted from plasma cells, free heavy chains are generally not secreted. The heavy chains are synthesized and transported to the endoplasmic reticulum, where they are glycosylated, but secretion requires combination with light chains to form a complete immunoglobulin molecule. If light chains are not synthesized or heavy chains are synthesized in excess, the free heavy chains combine through their CH1 domain with a heavy-chain-binding protein, which is believed to be responsible for their intracytoplasmic retention.

Both IgM and IgA are the polymeric antibodies, which have one additional polypeptide chain, the J chain. The J chain is synthesized by all plasma cells, including those that produce IgG. However, it is only incorporated to polymeric forms of IgM and IgA. It is believed that the J chain has some role in initiating polymerization. IgM proteins are assembled in two steps. First, the monomeric units are assembled. Then, five monomers and one J chain combine via covalent bonds to produce a pentameric molecule.

Metabolism of Immunoglobulins

Half-life (T 1/2) of immunoglobulin is one of the most commonly used parameters to assess the catabolic rate of immunoglobulins. The half-life corresponds to the time elapsed for a reduction to half of a circulating immunoglobulin concentration after equilibrium has been reached. This is usually determined by injecting an immunoglobulin labeled with a radioisotope (^{131}I).

The IgG is the immunoglobulin class with the longest half-life (average of 21 days), with the exception of IgG3. The IgG3 has a considerably shorter half-life (average of 7 days) that is nearer to that of IgA (5–6 days) and IgM (5 days).

The synthesis rate of IgA1 (24 mg/kg/day) is not very different from that of IgG1 (25 mg/kg/day), but the serum concentration of IgA1 is about one-third of the IgG1 concentration. This is explained by a fractional turnover rate three-times greater for IgA1 (24%/day). The highest fractional turnover rate and shorter half-life are those of IgE (74%/day and 2.4 days, respectively). The lowest synthesis rate is that of IgE (0.002 mg/kg/day, compared to 20–60 mg/kg/day for IgG).

Immunoglobulin Classes

The structure and biological functions of five classes of immunoglobulins (IgG, IgM, IgA, IgE, and IgD) are described below:

Immunoglobulin G

IgG is a 7S immunoglobulin with a molecular weight of 150,000 Da. It has a half-life of 23 days—longest among all the immunoglobulins. Other properties of the IgG are given in Table 13-2.

IgG is the most abundant class of immunoglobulins in the serum, comprising about 80% of the total serum immunoglobulin. There are four IgG subclasses IgG1, IgG2, IgG3, and IgG4—so numbered according to their decreasing concentrations in serum. Though the differences between these subclasses are minute, their functions vary as follows:

1. IgG1, IgG3, and IgG4 are special because these are the only immunoglobulins with the ability to cross the placental barrier. They play an important role in protecting the developing fetus against infections.
2. IgG3, IgG1, and IgG2, in order of their efficiency, are effective in the activation of the complement.

TABLE 13-2 Comparison of various properties of immunoglobulins

Characteristics	IgG	IgA	IgM	IgD	IgE
Structure	Monomer	Dimer	Pentamer	Monomer	Monomer
Percentage of total serum	80%	10–13%	5–8%	0.2%	0.002%
Location	Blood, lymph, and intestine	Blood, lymph, and B cell surface	Secretions	B cell surface, blood, and lymph	Bound to mast and basophil cell
Sedimentation coefficient	7	7	19	7	8
Molecular weight (kDa)	150	160	900	180	190
Carbohydrate (%)	3	8	12	13	12
Serum concentration (mg/mL)	12	2	1.2	0.03	0.00004
Half-life (days)	23	6–8	5	2–8	1–5
Heavy chain	$\gamma_1, \gamma_2, \gamma_3, \gamma_4$	α_1, α_2	μ	Δ	ε
Light chain	κ or δ	κ or δ	κ or δ	κ or δ	κ or δ
Complement binding	Classical pathway	Alternate pathway	Classical pathway	None	None
Placental transport	+	−	−	−	−
Present in milk	+	+	−	−	−
Seromucous secretion	−	+	−	−	−
Heat stability (56°C)	+	+	+	+	−
Binding to tissue	Heterologous	None	None	None	Homologous

3. IgG1 and IgG3 bind with high affinity to Fc receptors on phagocytic cells and thus mediate opsonization. IgG4 has an intermediate affinity for Fc receptors and IgG2 has an extremely low affinity.

Two γ chains, along with two κ or γ light chains, joined together by disulfide bonds, comprise an IgG molecule as follows:

- The γ chain is a 51-kDa, 450-amino acid residue heavy polypeptide chain.
- It consists of one variable VH domain and a constant (C) region with three domains designated CH1, CH2, and CH3.
- The hinge region is situated between CH1 and CH2.
- Proteolytic enzymes, such as papain and pepsin, cleave an IgG molecule in the hinge region to produce Fab and F (ab´) 2 and Fc fragments.

There are four subclasses of IgG in humans with four corresponding γ chain isotypes designated γ-1, γ-2, γ-3, and γ-4. IgG1, IgG2, IgG3, and IgG4 show differences in their hinge regions and differ in the number and position of disulfide bonds that link two γ chains in each IgG molecule. There is only a 5% difference in amino acid sequence among human γ chain isotypes, exclusive of the hinge region. Cysteine residues, which make it possible for interheavy (γ) chain disulfide bonds to form are found in the hinge area. IgG1 and IgG4 have two interheavy chain disulfide bonds, IgG2 has 4, and IgG3 has 11. The IgG, is distributed equally in the intra- and extravascular compartments.

Key Points

IgG shows the following biological activities:

- In response to infection, IgG antibodies appear late after appearance of IgM antibodies, but persists for a longer period.
- It confers protection against the microorganisms that are present in the blood and tissues. It is distributed equally in the intra- and extravascular compartments.
- It is the only immunoglobulin that crosses the placenta; hence, it confers natural passive immunity to the newborns.
- It takes part in precipitation, complement fixation, and neutralization of toxins and viruses.
- It binds to microorganisms and facilitates the process of phagocytosis of microorganisms.

Immunoglobulin M

IgM constitutes about 5–8% of total serum immunoglobulins. It is distributed mainly intravascularly. It is a heavy molecule (19S) with a molecular weight varying from 900,000 to 1,000,000 Da (***millionaire molecule***). It has a half-life of 5 days (Table 13-2).

IgM is basically a pentamer, composed of five immunoglobulin subunits (monomeric subunits, IgMs) and one molecule of J chain. Each monomeric IgM is composed of two light chains (κ or γ light chains) and two heavy chains (μ). The heavy chains are larger than those of IgG by about 20,000 Da, corresponding to an extra domain on the constant region

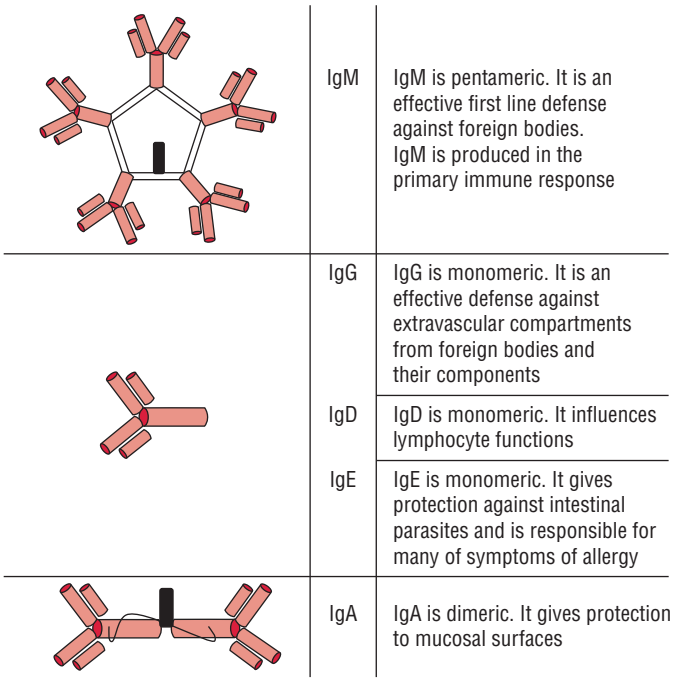

FIG. 13-2. Schematic diagram of immunoglobulins and their functions.

(CH4). Two subclasses of IgM (IgM1 and IgM2) are described, which differ in their μ chains. IgM1 consists of μ_1 and IgM2 consists of μ_2 chains (Fig. 13-2).

The immunoglobulin μ chain is a 72 kDa, 570-amino acid heavy polypeptide chain comprising one variable region, designated VH, and a four-domain constant region, designated CH1, CH2, CH3, and CH4. The μ chain does not have a hinge region. A "tail piece" is located at the carboxy terminal end of the chain. It comprises 18-amino acid residues. A cysteine residue at the penultimate position of a carboxy terminal region of the μ chain forms a disulfide bond that joins to the J chain. There are five N-linked oligosaccharides in the μ chain of humans.

Monomeric IgM, with a molecular weight of 180,000 Da, is expressed as membrane-bound antibody on B cells. As mentioned earlier, the J chain found in the IgM molecule was believed to play a major role in the secretion of its polymerized form. Being present on the membrane of B cells, IgM acts as the antigen-binding molecule in the antigen–antibody complex.

Because of its pentameric structure with 10 antigen-binding sites, serum IgM has a higher valency than the other isotypes. An IgM molecule can bind 10 small hapten molecules; however, because of steric hindrance, only five or fewer molecules of larger antigens can be bound simultaneously.

Treatment of serum with 2-mercaptoethanol destroys IgM without affecting IgG antibodies. This forms the basis for differential estimation of IgM and IgG antibodies in serum pretreated with 2-mercaptoethanol.

Key Points

IgM shows the following biological activities:

- Pentameric IgM, because of its high valency, is more efficient than other isotypes in binding antigens with many repeating epitopes, such as viral particles and red blood cells.
- It is more efficient than IgG in activating complement. Complement activation requires two Fc regions in close proximity, and the pentameric structure of a single molecule of IgM fulfills this requirement.
- IgM is the first immunoglobulin produced in a primary response to an antigen. The immunoglobulin confers protection against invasion of blood by microbial pathogens. Deficiency of IgM antibodies is associated with septicemia.
- IgM antibodies are short lived and disappear early as compared to IgG. The presence of IgM antibody in serum, therefore, indicates recent infection.
- It is also the first immunoglobulin to be synthesized by a neonate in about 20 weeks of age. IgM is not transported across the placenta; hence, the presence of IgM in the fetus or newborn indicates intrauterine infection. The detection of IgM antibodies in serum, therefore, is useful for the diagnosis of congenital infections, such as syphilis, rubella, toxoplasmosis, etc.

Immunoglobulin A

IgA is the second major serum immunoglobulin, comprising nearly 10–15% of serum immunoglobulin. It has a half-life of 6–8 days (Table 13-2).

IgA consist of α heavy chain that confers class specificity on IgA molecules. The α chain is a 58-kDa, 470-amino acid residue heavy polypeptide chain. The chain is divisible into three constant domains, designated CH1, CH2, and CH3, and one variable domain, designated VH. Hinge region is situated between CH1 and CH2 domains. An additional segment of 18-amino acid residues at the penultimate position of the chain contains a cysteine residue where the J chain can be attached through a disulfide bond. IgA occurs in two forms: serum IgA and secretory IgA.

Serum IgA: It is present in the serum and is a monomeric 7S molecule with a molecular weight of 60,000 Da. It has a half-life of 6–8 days. It has two subclasses, IgA1 and IgA2, which are two α-chain isotypes α-1 and α-2, respectively. The α-2 chain has two allotypes, A2m (1) and A2m (2), and does not have disulfide bonds linking heavy to light chains. Differences in the two α chains are found in two CH1 and five CH3 positions. Thus, there are three varieties of α-heavy chains in humans.

Secretory IgA: It is a dimer or tetramer and consists of a J-chain polypeptide and a polypeptide chain called secretory component, or SC, or secretory piece (Fig. 13-3). The SC is a polypeptide with a molecular weight of 70,000 Da and is produced by epithelial cells of mucous membranes. It consists of five immunoglobulin-like domains that bind to the Fc region domains of the IgA dimer. This interaction is stabilized by a disulfide bond between the fifth domain of the SC and one

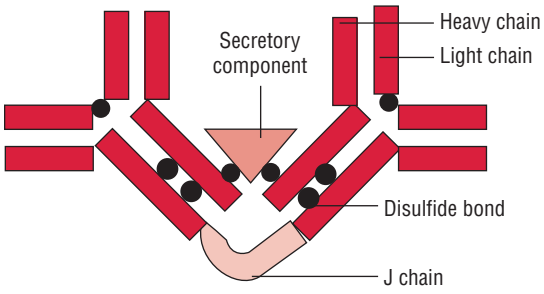

FIG. 13-3. Schematic diagram of immunoglobulin A (IgA).

of the chains of the dimeric IgA. IgA-secreting plasma cells are concentrated along mucous membrane surfaces. The daily production of secretory IgA is greater than that of any other immunoglobulin. Secretory IgA is the major immunoglobulin present in external secretions, such as breast milk, saliva, tears, and mucus of the bronchial, genitourinary, and digestive tracts. IgA activates the complement not by classical pathway but by alternative pathway.

Key Points

Secretory IgA shows the following biological activities:

- It protects the mucous membranes against microbial pathogens. It serves an important effector function at mucous membrane surfaces, which are the main entry sites for most pathogenic organisms. Because it is polymeric, secretory IgA can cross-link large antigens with multiple epitopes.
- Binding of secretory IgA to bacterial and viral surface antigens prevents attachment of the pathogens to the mucosal cells, thus inhibiting viral infection and bacterial colonization. Complexes of secretory IgA and antigen are easily entrapped in mucus and then eliminated by the ciliated epithelial cells of the respiratory tract or by peristalsis of the gut.
- Breast milk contains secretory IgA and many other molecules that protect the newborns against infection during the first month of life. Because the immune system of infants is not fully functional, breast-feeding plays an important role in maintaining the health of newborns.
- Secretory IgA has shown to provide an important line of defense against bacteria (such as *Salmonella* spp., *Vibrio cholerae*, and *Neisseria gonorrhoeae*) and viruses (such as polio, influenza, and reovirus).

Immunoglobulin E

IgE constitutes less than 1% of the total immunoglobulin pool. It is present in serum in a very low concentration (0.3 μg/mL). It is mostly found extravascularly in lining of the respiratory and intestinal tracts. IgE is an 8S molecule with a molecular weight of 190,000 Da and half-life of 2–3 days. Unlike other immunoglobulins that are heat stable, IgE is a heat-labile protein—easily inactivated at 56°C in 1 hour (Table 13-2).

Two ε heavy polypeptide chains, along with two κ or two λ light chains, fastened together by disulfide bonds, comprise

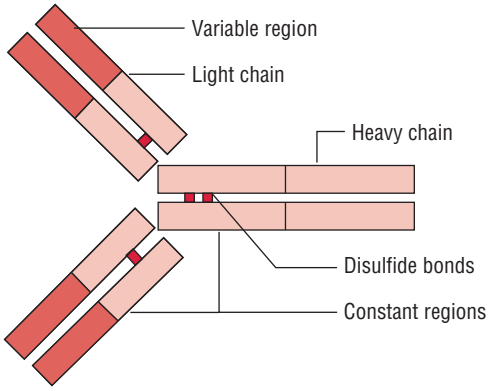

FIG. 13-4. Schematic diagram of immunoglobulin E (IgE).

an IgE molecule. The ε chain is a 72-kDa, 550-amino acid residue polypeptide chain. It consists of one variable region, designated VH, and a four-domain constant region, designated CH1, CH2, CH3, and CH4. This heavy chain does not possess a hinge region. In humans, the ε heavy chain has 428 amino acid residues in the constant region (Fig. 13-4). IgE does not cross the placenta or fix the complement.

Key Points

IgE shows the following biological activities:

- IgE is also known as reaginic antibody that mediates the type I immediate hypersensitivity (atopy) reactions.
- IgE is responsible for the symptoms of hay fever, asthma, and anaphylactic shock. IgE binds to Fc receptors on the membranes of blood basophils and tissue mast cells. Cross-linkage of receptor bound IgE molecules by antigen (allergen) induces basophils and mast cells to translocate their granules to the plasma membrane and release their contents to the extracellular environment—a process known as degranulation. As a result, varieties of pharmacologically active mediators are released and give rise to allergic manifestations.
- Localized mast-cell degranulation induced by IgE may also release mediators that facilitate a buildup of various cells necessary for antiparasitic defense.

Immunoglobulin D

IgD comprises less than 1% of serum immunoglobulins. It is a 7S monomer with a molecular weight of 180,000 Da. The half-life of IgD is only 2–3 days (Table 13-2). IgD has the basic four-chain monomeric structure with two δ heavy chains (molecular weight 63,000 Da each) and either two κ or two λ light chains (molecular weight 22,000 Da each) (Table 13-2).

Immunoglobulin δ chain is a 64-kDa, 500-amino acid residue heavy polypeptide chain consisting of one variable region, designated as VH, and a three-domain constant region, designated as CH1, CH2, and CH3. There is also a 58-residue amino acid residue hinge region in human δ chains. Two exons encode the hinge region. IgD is very susceptible to the action of proteolytic enzymes at its hinge region. Two separate exons

TABLE 13-3 Role of immunoglobulins in human defense

IgG	IgM	IgA	IgD	IgE
Enhances phagocytosis	Especially effective against microorganisms and agglutinating antigens	Localized protection on mucosal surfaces	Serum function not known	Allergic reaction
Neutralizes toxins and viruses	First antibody produced in response to initial infection		Present on B cells; and function in initiation of immune response	Possibly lysis of parasitic worms
Protects fetus and newborn				

encode the membrane component of δ chain. A distinct exon encodes the carboxy terminal portion of the human δ chain that is secreted. The human δ chain contains three N-linked oligosaccharides.

Table 13-3 summarizes roles of various immunoglobulins in human defense.

Key Points

IgD is present on the surface of B lymphocytes and both IgD and IgM serve as recognition receptors for antigens. The role of IgD in immunity continues to remain elusive.

Abnormal Immunoglobulins

Abnormal immunoglobulins are other structurally similar proteins that are found in serum in certain pathological conditions, such as multiple myeloma, heavy chain disease, and cryoglobulinemia and sometimes in healthy individuals also.

Multiple myeloma: Bence-Jones (BJ) proteins were the earliest abnormal proteins described in 1847 that were found in patients with multiple myeloma. These proteins are the light chains of immunoglobulins, hence occur as either κ or λ forms. In a patient, it may occur as either κ or λ but never in both the forms. BJ proteins have a peculiar property of coagulating at 60°C and redissolving again at a higher temperature of 80°C.

In multiple myeloma, plasma cells synthesizing IgG, IgA, IgD, or IgE are affected. Myeloma involving IgM-producing plasma cells is known as ***Waldenström's macroglobulinemia***. This condition is characterized by excessive production of the respective myeloma proteins (M proteins) and that of their light chains (BJ proteins).

The study of myeloma proteins led to a great advancement in our understanding of immunoglobulin function. These "single" or "monoclonal" antibodies obtained from the sera of patients with multiple myeloma were used in many of the serologic and biochemical studies of the 1950s and 1960s. They remained the major source of homogeneous immunoglobulins until the development of the hybridoma in 1974. The serologists injected them into animals and produced antisera that were used to study some of the basic properties of antibodies. For example, the immune sera were absorbed with other myeloma proteins and were used to identify isotypic, allotypic, and idiotypic specificities.

Heavy chain disease: Heavy chain disease is a different disorder, which is a lymphoid neoplasia, characterized by an excess production of heavy chains of the immunoglobulins.

Cryoglobulinemia: Cryoglobulinemia is a condition characterized by presence of cryoglobulins in blood. The condition may not be always associated with disease but is often found in patients with macroglobulinemia, systemic lupus erythematosus, and myelomas. Most cryoglobulins consist of either IgG or IgM or their mixed precipitates. In cryoglobulinemia, serum from patient precipitates on cooling and redissolves on warming.