Assistant Prof. Dr. Ekhlass N. Ali

Advanced Immunology

ANTIBODY

The basic structure of the antibody molecule is depicted in Figures 1 and. It consists of a four-chain structure divided into two identical heavy (H) chains with a molecular weight of 25 kDa. Each chainis composed of *domains* of 110 amino acids and is connected in a loop by a disulfidebond between two cysteine residues in thechain. The amino acid N-terminal domains of the heavy and light chains include the antigen-binding site. The amino acids of these variable domains vary between different antibody molecules and are thus known as the *variable* (V) regions. Most of these differences reside in the *hypervariable* areas ofthe molecule and are usually only six toten amino acid residues in length. When the hypervariable regions in each chain come together along with the counterparts on the other pair of H and L chains, theyform the antigen-binding site. This part of the molecule is unique to the molecule and is known as the *idiotype determinant*.

In any individual, 106 to 107 different antibody molecules can be composed from 103 different heavy and light chains of the variable regions. The part of the molecule next to the V region is called the constant (C) region made up of one domain in the light chain (C1) and three or four in a heavy chain (CH). A Cl chain may consist of either two kappa (κ) or two lambda (λ) chains but *never* one of each. Of all the human antibody molecules, approximately 60%, are chains and 40% contain λ chains. Although there are no known differences in the functional properties of κ and λ chains, there are several different types of the CH domain. These differences are reflected in determining the class (isotype) of the antibody and thereby the physiological function of a particular antibody molecule.

The IgM molecule is the oldest class of immunoglobulin, and it is a large molecule consisting of five basic units held together by a J hain. The major role IgM plays is the intravascular neutralization of organisms, especially viruses. The reason for this important physiological role is that it contains **fiv e** complement-binding sites, resulting in excellent complement activation. This activation permits the segment removal of antigen–antibody complement complexes via complement receptors on phagocytic cells or omplement-mediated lysis of the organism. However, in contrast to the IgGmolecule, it has relatively low affinity binding to the antigen in question. Second, because of its size, it does not usually penetrate into tissues. In contrast, IgG is a smaller molecule that penetrates easily into tissues. There are four major classes of IgG: IgG1 and IgG3 activate complement efficiently and clear most protein antigens, including the removal of microorganisms by phagocytic cells. In contrast, IgG2 and IgG4 react mostly with carbohydrate antigens and are relatively poor opsonins. This is the only molecule that crosses the placenta to provide immune protection to the neonate. The major mucosal immunoglobulin, IgA, consists of two basic units joined by a J chain. The addition of a secretion molecule prevents its digestion by enzymes present in mucosal and intestinal secretions. Thus, IgA2 is the major IgA molecule in secretions and is quite effective in neutralizing antigens that enter via these mucosal routes.IgA1, the main IgA molecule in serum, **ishowever**, susceptible to inactivation by proteases and is thus less active for defense. Its function is unclear at present.Two other classes are worthy of note.IgD is synthesized by antigen-sensitive Bcells and is involved in the activation ofthese cells by antigen. IgE is produced by plasma cells and binds to specific IgE receptorson most cells and basophiles. This molecule plays an extremely important role in allergic reactions and expelling intestinal parasites, which is accomplished by increasing vascular permeability and inducing chemotactive factors following mast cell degranulation. Given this extraordinary ability to generate large numbers of antibody molecules, how does the immune system recognize all pathogens, including past, present, and future? This diversity is achieved by the way in which the genetics of antibody production is arranged (Figure 3).The light and heavy chains are carried on different **hromosomes.**

The heavy chain genes are carried on chromosome 14. These genes are broken up into coding systems called *exons* with intervening segments of silent segments called *entrons*. The exons represent the central region of the heavy chain and a large number of V regions. Between the V and D genes are two small sets of exons called the D and J. With each single B cell, one V gene is joined to one D and J in the chromosome. The product, the VH domain, is then joined at the level of RNA processing to Cu and the B cell makes an IgM molecule. By omitting the Cu gene and joining VHDJ to a Cλ an IgG molecule is produced. This enormous versatility allows the cell to make IgM, IgD, IgG, IgA, or IgE in sequence while using the same variable regions (see Figure 4). The heavy chain gene recombinations are controlled by two recombination activity genes called RAG1 and RAG2. If these genes are eliminated by "knock-out" techniques in mice, profound immunodeficiency status occurs in these animals, characterized by absent mature B and T cells. Thus, the diversity of antigen binding is achieved by the large number of V genes available and their combination with different D and L genes to provide different antibodies. Furthermore, the inherited set of genes may be increased by somatic mutation during multiple divisions of lymphoid cells, thereby increasing the number of antibody specificities to 1014, which far exceeds the number of B cells (1010) in the body.

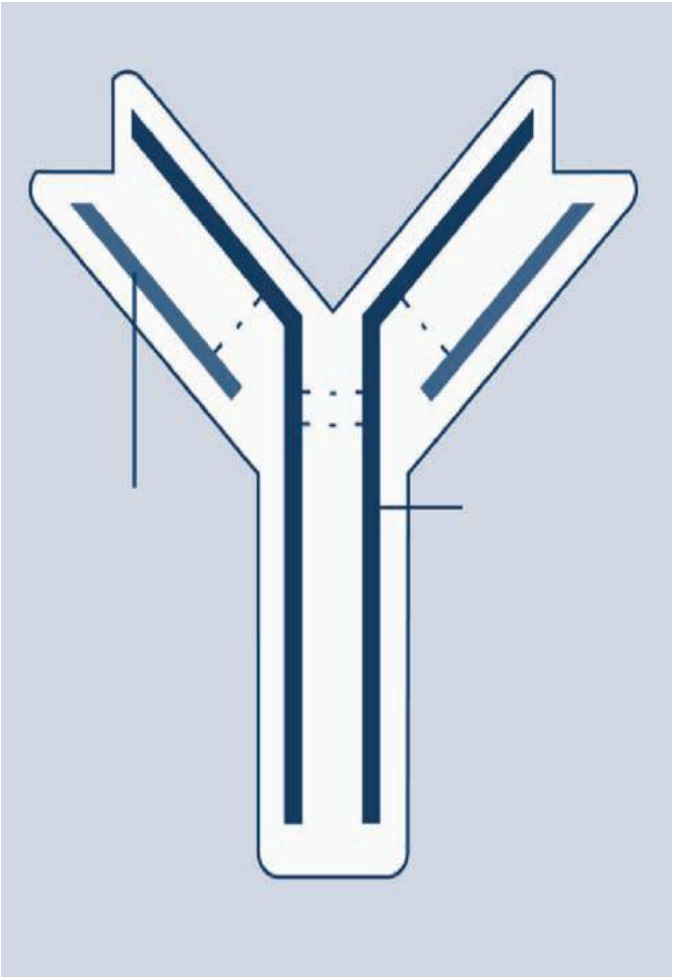


Figure 1 : Heavy and light chains of an IgG antibody. An IgM antibody would be a pentameric structure of an IgG molecule.

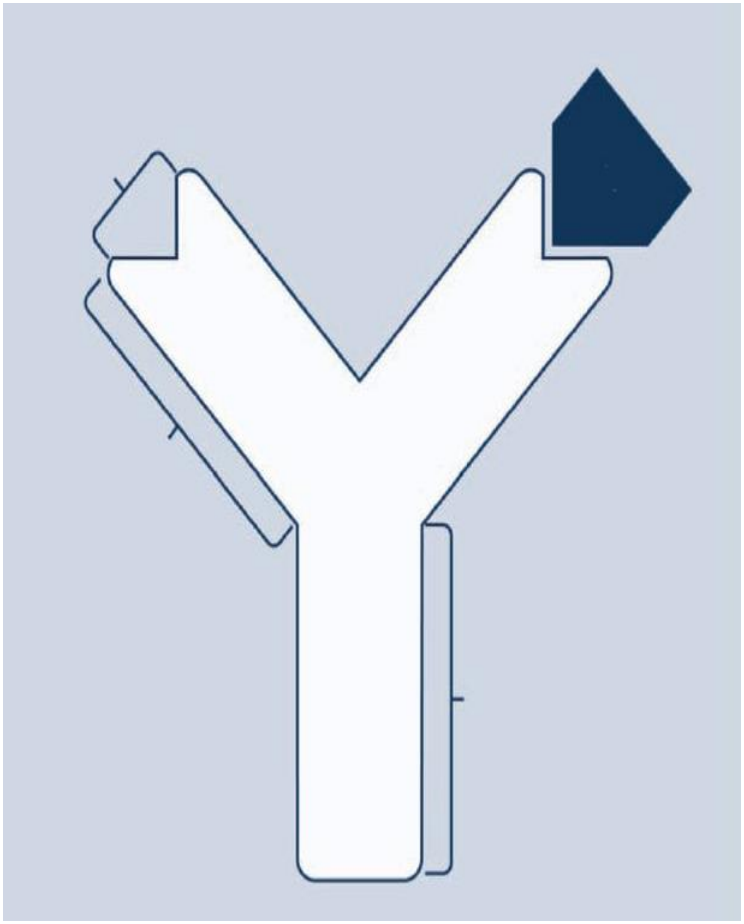


Figure 2 : Antigen-binding sites and antigen binding in an IgG antibody. Hinge region allows for rotational and lateral movements of the two antigen binding sites.

Figure 3 : The genetics of antibody production.

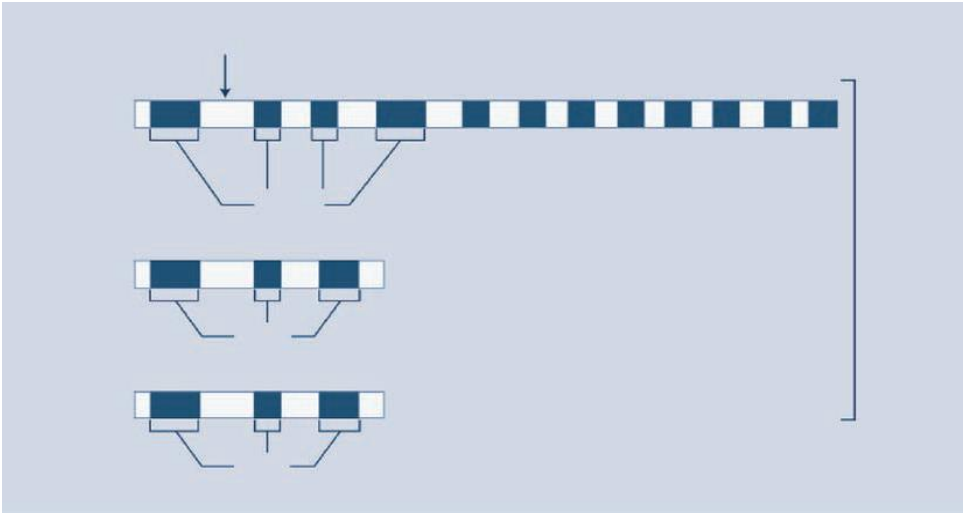
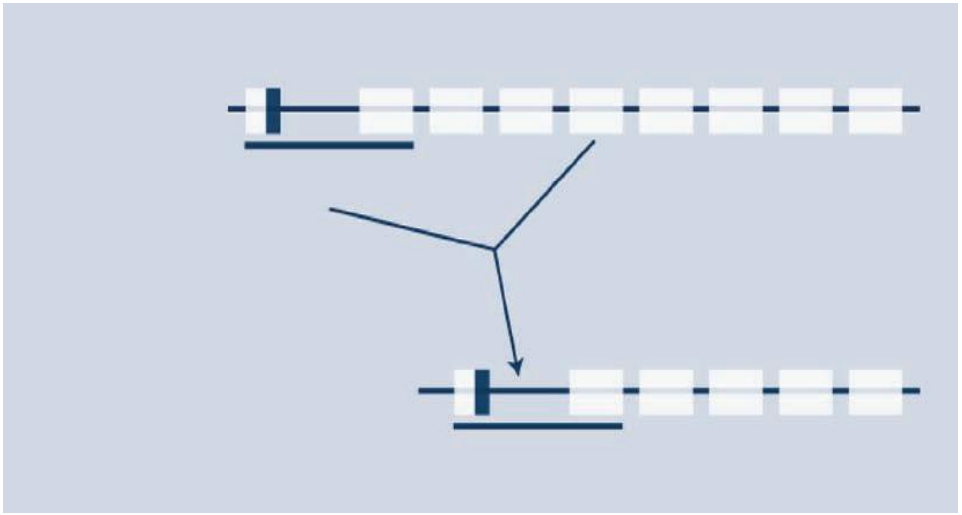


Figure.4: Recombination events necessary for generation of class and subclass switching.



Once a given B cell is preselected to producea particular VH and VL domain, all the ensuing progeny of that B cell will produce the same VH or VL domain. The sequence of events is as follows: initially, the B cell produces intracellular antigen-specific IgM, which becomes bound to the cell surface.
The B cell is now antigen responsive with exposure to a given antigen. The committed B cell begins producing a certain isotype or class of immunoglobulins and begins dividing, and all the progeny will produce the identical immunoglobulin molecules. These B cells will later mature into either plasma cells or long-term memory B cells.

T CELLS AND THEIR RECEPTORS

Each T cell is also committed to a given antigen and recognizes it by one of two TCRs. They may have TCR2s composed of gamma (γ) and delta (δ) chains or TCR2s composed of another heterodimer of alpha (α) and beta (β) chains. These TCR2s are associated with a group of transmembrance proteins on the CD3 molecule,which takes the antigen recognition signal inside the cell. Signal transduction via the CD3 complex is regulated by a series of kinases, which are associated with the tails of the CD3–TCR complex and regulate
phosphorylation. Deficiencies or blocks in the T-cell signaling pathways either atthe cell-surface complex or at the level of the kinases may result in various forms of immunodeficiency. Two other important antigens present on TCR2 cells recognize histocompatibility antigens and will be discussed later. The genes for TCR chains are on different chromosomes with the βand α molecules on chromosome 7, while the α and δ are on chromosome 14.

As seen in Figure.5, the four chains are made up of a variable region and a constant region similar to those observed with the immunoglobulins. The variable regions are also numerous and joined at D and J regions by RAG1 and RAG2. This permits a diversity of antigen recognition similar to that observed with immunoglobulin, but additional somatic mutation is not involved in T cells. These similarities have led to the concept that genes for antigen-specific T cells evolved in the same manner as immunoglobulin from a parent gene, and both are members of a super antigen family. The TCR complex recognizes small peptides presented to it by the MHC class I and II and depends on the type of T cell.

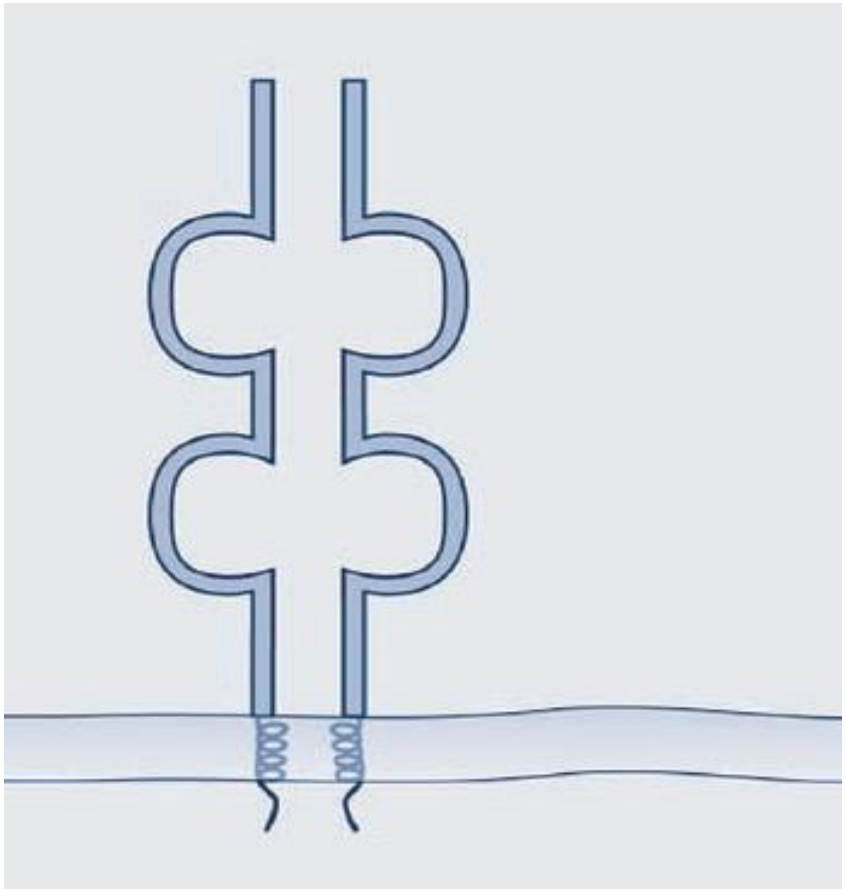


Figure 5: Diagram of the structure of a T-cell Receptor.