12.2: Antigens and Epitopes

Skills to Develop

1. Define antigen and immunogen.
2. State what antigens are composed of chemically.
3. List 3 characteristics an antigen must have to be immunogenic.
4. Define epitope.
5. Briefly describe how the body recognizes an antigen as foreign.
6. Compare B-cell receptors and T-cell receptors in terms of how they recognize epitopes.
7. In terms of infectious diseases, list 2 categories of microbial materials that may act as an antigen.
8. List 3 groups of noninfectious materials that may act as an antigen.
9. Define the following:
   a. endogenous antigen
   b. exogenous antigen
   c. autoantigen
   d. hapten

An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes. An immunogen is an antigen that is recognized by the body as non-self and stimulates an adaptive immune response. For simplicity, both antigens and immunogens are usually referred to as antigens.

To be immunogenic, an antigen must possess three characteristics:

- be of high molecular weight,
- exhibit chemical complexity, and
• exhibit foreignness (recognized as non-self by the body).

Chemically, antigens are large molecular weight proteins (including conjugated proteins such as glycoproteins, lipoproteins, and nucleoproteins) and polysaccharides (including lipopolysaccharides). These protein and polysaccharide antigens are found on the surfaces of viruses and cells, including microbial cells (bacteria, fungi, protozoans) and human cells.

### Epitopes of an antigen

The actual portions or fragments of an antigen that react with receptors on B-lymphocytes and T-lymphocytes, as well as with free antibody molecules, are called epitopes or antigenic determinants. The size of an epitope is generally thought to be equivalent to 5-15 amino acids or 3-4 sugar residues.

Some antigens, such as polysaccharides, usually have many epitopes, but all of the same specificity. This is because polysaccharides may be composed of hundreds of sugars with branching sugar side chains, but usually contain only one or two different sugars. As a result, most "shapes" along the polysaccharide are the same (see Figure 1).

Other antigens such as proteins usually have many epitopes of different specificities. This is because proteins are usually hundreds of amino acids long and are composed of 20 different amino acids. Certain amino acids are able to interact with other amino acids in the protein chain and this causes the protein to fold over upon itself and assume a complex three-dimensional shape. As a result, there are many different "shapes" on the protein (see Figure 2). That is why proteins are more immunogenic than polysaccharides; they are chemically more complex.

A microbe, such as a single bacterium, has many different proteins (and polysaccharides) on its surface that collectively form its various structures, and each different protein may have many different epitopes. Therefore, immune responses are directed against many different epitopes of many different antigens of the same microbe. (For example, a bacterial cell wall alone may contain over 100 different epitopes.) Even simple viruses possess many different epitopes. (see Figure 3).

### Recognizing an antigen as foreign

As we saw earlier in Unit 5, the B-lymphocytes and T-lymphocytes are the cells that carry out the immune responses. The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope (similar to interlocking pieces of a puzzle).

a. B-cell receptors

The antigen receptors on the cytoplasmic membrane of B-lymphocytes are called B-cell receptors and are actually antibody molecules made by that cell and anchored to the outer surface of its cytoplasmic membrane. As will be seen in a later section, antibodies are "Y"-shaped macromolecules composed of four glycoprotein chains connected to one another by disulfide (S-S) bonds and noncovalent bonds (see Figure 4). Additional S-S bonds fold the individual glycoprotein chains into a number of distinct globular domains (see Figure 5).
The two tips of the "Y" are referred to as the Fab portions of the antibody (see Figure 4 and Figure 5). The first 110 amino acids or first domain of both the heavy and light chain of the Fab region of the antibody provide specificity for binding an epitope on an antigen. Because they recognize molecular shapes that occur as a result of the 3-dimensional folding of an antigen, B-cell receptors can bind directly to epitopes on peptide, protein, polysaccharide, nucleic acid, and lipid antigens.

The bottom part of the "Y", the C terminal region of each glycoprotein chain, is called the Fc portion. The Fc portion has a constant amino acid sequence that defines the class and subclass of each antibody. The terminal portion of the Fc region of the B-cell receptor is the part that becomes anchored to the cytoplasmic membrane of B-lymphocyte (see Figure 6).

b. T-cell receptors

The receptors on the membrane of T-lymphocytes are called T-cell receptors or TCRs. They are analogous to the B-cell receptor, but are composed of just two glycoprotein chains, each having a variable domain and a constant domain (see Figure 7).

Unlike B-cell receptors that can directly bind to epitopes on antigens, the T-cell receptor or TCR of most T4-lymphocytes and T8-lymphocytes can only recognize peptide epitopes from protein antigens presented by the body's own cells by way of special molecules called MHC molecules as seen in Figure 6. The terminal portion of the variable domains provides specificity for binding peptides of protein antigens after the protein has been unfolded, broken into peptides, and bound to a MHC molecule, while the terminus of the constant region becomes anchored to the cytoplasmic membrane of the T-lymphocyte.

The TCR of CD4^CD8^- T-lymphocytes and non-MHC restricted CD4^+ and CD8^+ lymphocytes can recognize epitopes of lipid or glycolipid antigens after they have been attached to CD1 molecules on antigen-presenting cells or in some cases, epitopes directly on antigens.

Since the immune system of the body has no idea as to what antigens it may eventually encounter, it has evolved a system that possesses the capability of responding to epitopes of any conceivable antigen. During its development, each different B-lymphocyte and T-lymphocyte becomes genetically programmed to produce a B-cell receptor or T-cell receptor with a unique three-dimensional shape (see Figure 6).

It is estimated that the human body has the ability to recognize 10^7 or more different epitopes and make up to 10^9 different antibodies, each with a unique specificity. In order to recognize this immense number of different epitopes, the body produces 10^7 or more distinct clones of both B-lymphocytes and T-lymphocytes, each with a unique B-cell receptor or T-cell receptor. Among this large variety of B-cell receptors and T-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, any antigen the immune system eventually encounters. With the adaptive immune responses, the body is able to recognize any conceivable antigen it may eventually encounter.

Flash animation of epitopes reacting with specific B-cell receptors on B-lymphocytes.
Substances that act as antigens

In terms of infectious diseases, the following may act as antigens:

a. microbial structures, such as bacterial and fungal cell walls, protozoan cell membranes, bacterial and fungal capsules, microbial flagella, bacterial pili, viral capsids, viral envelope-associated glycoproteins, etc.; and

b. microbial toxins

Certain non-infectious materials may also act as antigens if they are recognized as "nonself" by the body. These include:

a. allergens, including dust, pollen, hair, foods, dander, bee venom, drugs, and other agents causing allergic reactions;

b. foreign tissues and cells from transplants and transfusions; and

c. the body's own cells that the body fails to recognize as "normal self," such as cancer cells, infected cells, cells involved in autoimmune diseases.

There are three broad categories of antigens: endogenous antigens, exogenous antigens, and autoantigens.

1. Endogenous antigens are proteins found within the cytosol of human cells. Examples of endogenous antigens include:
   a. viral proteins produced during viral replication;
   b. proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication;
c. proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells;  
d. tumor antigens produced by cancer cells; and  
e. self-peptides from host cellular proteins.

2. Exogenous antigens are antigens that enter from outside the body, such as bacteria, fungi, protozoa, and free viruses. These exogenous antigens enter macrophages, dendritic cells, and B-lymphocytes through phagocytosis or pinocytosis.

3. Autoantigens are any of an organism’s own antigens (self-antigens) that stimulate an autoimmune reaction, that is humoral immunity or cell-mediated against self.

A hapten is a small molecule that by itself is not immunogenic but can act as an antigen when it binds to a larger protein molecule. The hapten then acts as an epitope on the protein. For example with penicillin and poison ivy allergies, the penicillin molecules and the oil urushiol from the poison ivy plant function as haptens, binding to tissue proteins to form an antigen and stimulating an allergic immune response.

Exercise: Think-Pair-Share Questions
1. How is the body able to distinguish epitopes of microorganisms from “self” epitopes present as a part of our body?  
2. What is the difference between how B-lymphocytes and T-lymphocytes recognize antigens?

Summary
1. An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes.  
2. An immunogen is an antigen that is recognized by the body as non-self and stimulates an adaptive immune response.  
3. Chemically, antigens are large molecular weight proteins and polysaccharides.  
4. The actual portions or fragments of an antigen that react with receptors on B-lymphocytes and T-lymphocytes, as well as with free antibody molecules, are called epitopes.  
5. The size of an epitope is generally thought to be equivalent to 5-15 amino acids or 3-4 sugar residues.  
6. Polysaccharides antigens usually have many epitopes but all of the same specificity.  
7. Proteins antigens usually have many epitopes of different specificities.  
8. Immune responses are directed against many different epitopes of many different antigens of the same microbe.  
9. The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope.  
10. The antigen receptors on the cytoplasmic membrane of B-lymphocytes are called B-cell receptors and are actually antibody molecules made by that cell and anchored to the outer surface of its cytoplasmic membrane and is composed of composed of four interconnected glycoprotein chains.  
11. The receptors on the membrane of T-lymphocytes are called T-cell receptors or TCRs and are composed of just two glycoprotein chains.  
12. During its development, each different B-lymphocyte and T-lymphocyte becomes genetically programmed to produce a B-cell receptor or T-cell receptor with a unique three-dimensional shape.
13. The body produces 107 or more distinct clones of both B-lymphocytes and T-lymphocytes, each with a unique B-cell receptor or T-cell receptor and with this large variety of B-cell receptors and T-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, any antigen the immune system eventually encounters.

14. In terms of infectious diseases, microbial structures and microbial toxins act as antigens.

15. Certain noninfectious materials also act as antigens, including allergens, foreign tissues and cells from transplants and transfusions, and the body’s own cells that the body fails to recognize as “normal self,” such as cancer cells, infected cells, and cells involved in autoimmune diseases.

16. Endogenous antigens are antigens found within the cytosol of human cells such as viral proteins, proteins from intracellular bacteria, and tumor antigens.

17. Exogenous antigens are antigens that enter from outside the body, such as bacteria, fungi, protozoa, and free viruses.

18. Autoantigens are any of an organism’s own antigens (self-antigens) that stimulate an autoimmune reaction.

Contributors

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