Lecture 4 Adaptive immunity (specific immune defense)

Adaptive immunity :is described as a dual system, with humoral and cellular components. Humoral immunity primarily involves B cells and neutralizes foreign body outside human cells. Cellular immunity primarily involves T cells and deals with foreign body inside cells. Both involve specialized immune cell receptors that recognize antigens(foreign body), followed by activation and production of cells, chemical messengers, and other factors that help destroy the antigen in question or allow the body to remember it later, for speedier future interactions.

A crucial element of the adaptive immune system is its ability to differentiate between normal "self" cells and "nonself." the adaptive system tailors its fight to specific pathogens, toxins, or other substances. The first time the adaptive immune system meets and combats a particular antigen is called the primary response, which involves a lag or latent period of 4 to 14 days. Later interactions with that same cell or substance will cause a secondary response, which is faster and more effective as a result of the "memory" formed during the primary response.

Humoral Immunity

The term humoral immunity derives from the word humors, an ancient name for body fluids such as blood, phlegm, black bile, and yellow bile. Humoral immunity describes immune actions taking place in these extracellular fluids, brought about by protective molecules called antibodies. Another term for antibody is immunoglobulin (Ig). Antibodies recognize and combat foreign molecules called antigens.

Humoral immunity involves B lymphocytes, more commonly known as B cells. Immunoglobulins corresponding to specific antigens coat the surfaces of B cells. Activated B cells secrete the same specific immunoglobulin that reacts with a particular antigen component of a virus, bacterium, toxin, or other extracellular material in body tissue fluids and blood.

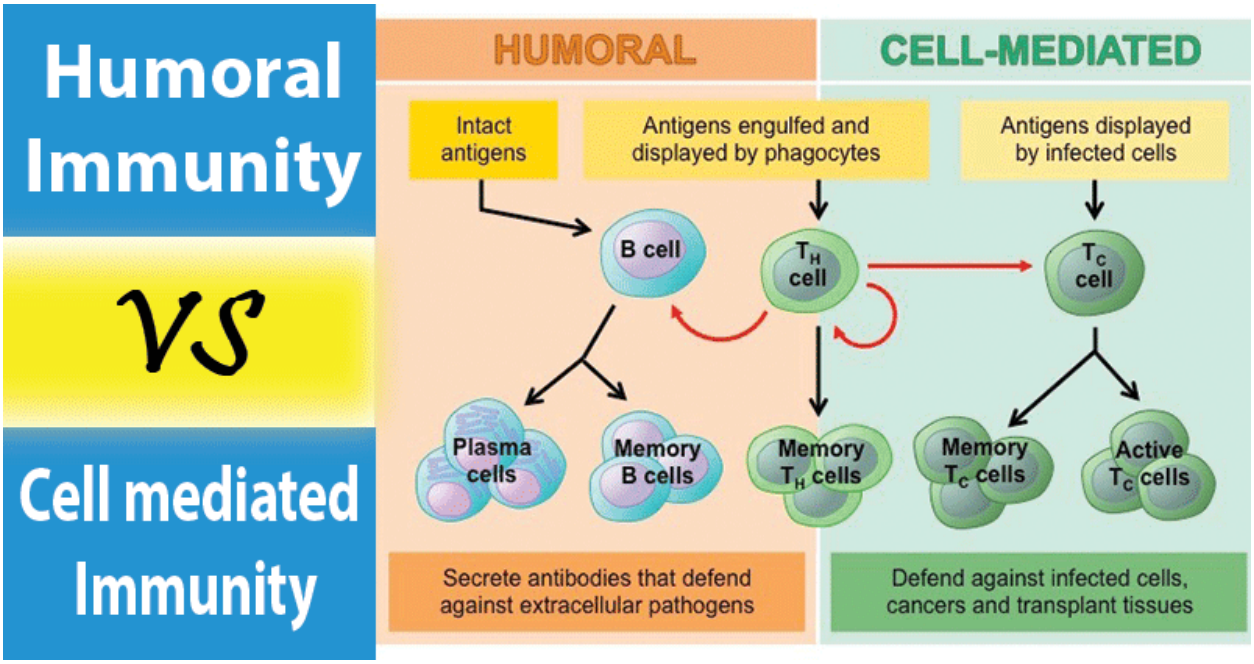
Because humoral immunity fights invaders outside cells, efforts tend to focus on bacteria that live extracellularly (as well as their toxins) and on viruses before they penetrate a target cell. B cells were named for the bursa of Fabricius, the specialized organ of birds where researchers first observed these cells. In humans, lymphocytes are initially produced in the fetal liver.

By about the third month of fetal development, the site of B cell creation and maturation (known as schooling) becomes the red bone marrow. Once mature, B cells are found primarily in the blood and lymphoid organs.

Cellular immunity

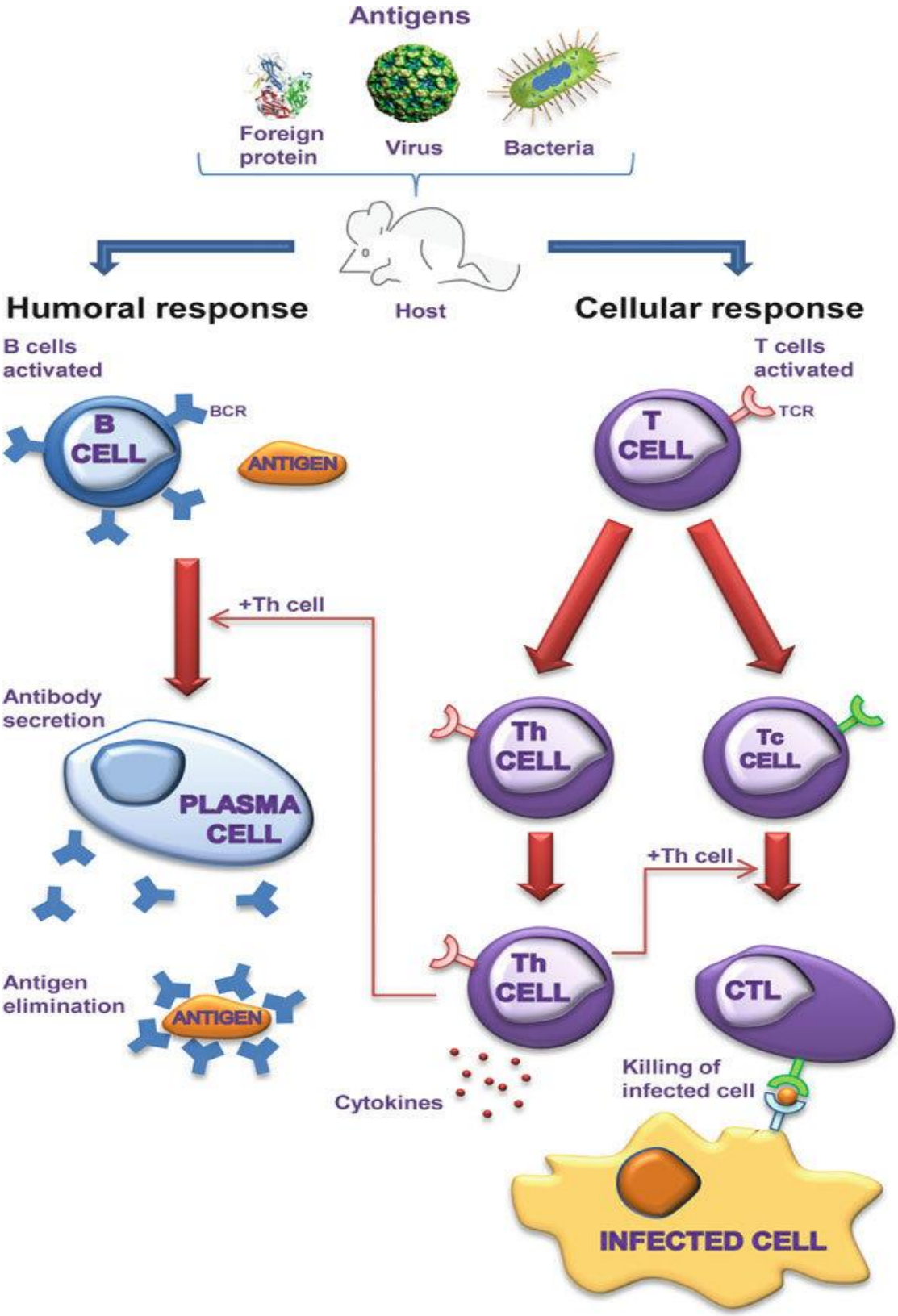
T lymphocytes, or T cells, are the basis of cellular immunity, also called cell-mediated immunity. T cells do not directly bind to antigens. Instead, phagocytic cells, such as macrophages or dendritic cells, process and present antigenic peptides to them. T cells have T cell receptors (TCRs) that recognize an antigenic peptide attached to a specialized presenting molecule on a cell. When T cells are activated, some destroy target cells that present a particular antigenic peptide. Others can proliferate and secrete chemical messengers, called cytokines (discussed next), that induce other cells to perform a function.

T cells owe their name to the thymus, the organ where these particular cells mature. Once mature, T cells are found in the same places as B cells—primarily in the blood and lymphoid organs. Cellular immune responses focus on recognizing antigens that have already entered a cell. This immunity is generally best at fighting viruses and some intracellular bacteria such as Listeria monocytogenes or Mycobacterium leprae.



HUMORAL IMMUNITY
VERSUS
CELL MEDIATED IMMUNITY

Characteristics	Humoral Immunity	Cell Mediated Immunity
Definition	The aspect of immunity, mediated by macromolecules found in the extracellular body fluids is called humoral immunity.	The aspect of immunity that identifies and destroys infected cells is called cell mediated immunity.
Pathogens	The humoral immunity protects against extracellular pathogens.	The cell mediated immunity protects against intracellular pathogens.
Main cells	The main cells, involved in the humoral immunity are the B-cells. These cells are generated and mature in the bone marrow.	The main cells, involved in the cell mediated immunity are the T-cells. These cells are generated in the bone marrow and complete their development in the thymus.
Activation	The end result of the activation is the differentiation of plasma B-cells, secreting antibodies.	The end result of the activation is the secretion of cytokines.
Onset	Rapid	Delayed


Antigens
Foreign protein
Virus
Bacteria
Host
Humoral response
Cellular response
B cells activated
T cells activated
B CELL
BCR
ANTIGEN
T CELL
TCR
+Th cell
Antibody secretion
PLASMA CELL
Th CELL
Tc CELL
+Th cell
Th CELL
CTL
Antigen elimination
ANTIGEN
Cytokines
Killing of infected cell
INFECTED CELL

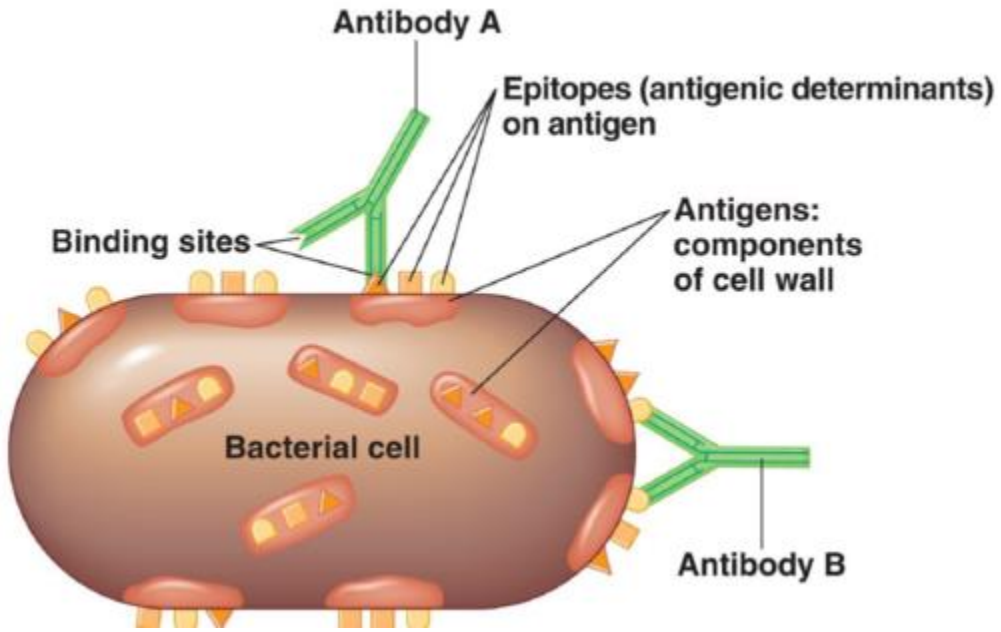
Antigens:

Antigens are Substances that induce production of antibodies are called antigens (short for antibody generators). Most antigens are either proteins or large polysaccharides. Lipids and nucleic acids are usually antigenic only when combined with proteins and polysaccharides. Pathogens can have multiple antigenic sites.

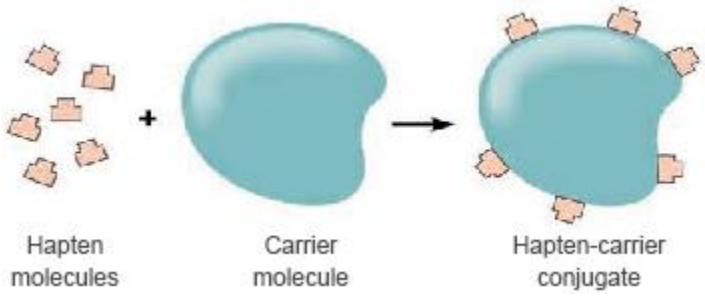
Components of invading microbes—such as capsules, cell walls, flagella, fimbriae, bacterial toxins, and viral coats—all tend to be antigenic. However, a compound doesn't have to be part of an invading pathogen to be deemed antigenic by the immune system.

Nonmicrobial antigens may include pollen, egg white, blood cell surface molecules, serum proteins from other individuals or species, and surface molecules of transplanted tissues and organs.

Detection of an antigen provokes production of highly specific, corresponding antibodies. Generally speaking, antibodies react with specific regions on antigens called epitopes or antigenic determinants (Figure).



The nature of the interaction depends on the size, shape, and chemical structure of the binding site on the antibody molecule. Similarly, epitopes can be displayed by antigen presenting cells (such as when macrophages and dendritic cells present them to T cells). A bacterium or virus may have several epitopes that cause the production of different antibodies. Pathogenic bacteria characteristically possess a number of recognizable antigens called pathogen-associated molecular patterns (PAMPs). PAMPs serve as warning flags of an invading organism that the host can recognize by means of receptors. The best-known of these receptors is the extended family of Tolllike receptors (TLRs). A foreign substance that has a low molecular mass is often not antigenic unless it is attached to a carrier molecule. These low molecularmass compounds are called haptens (figure).



Once an antibody against the hapten has been formed, the antibody will react with the hapten independent of the carrier molecule. Penicillin is a good example of a hapten. This drug is not antigenic by itself, but some people develop an allergic reaction to it.

In these people, when penicillin combines with host proteins, the resulting combined molecule initiates an immune response. This concept has therapeutic applications. Conjugated vaccines, which combine an antigen with a protein, work in the same fashion.

* **Immunogen :** A substance that induces a specific immune response..
***Antigen (Ag) :** A substance that reacts with the products of a specific immune response

***Hapten :** Haptens are small molecules which could never induce an immune response when administered by themselves but which can when coupled to a carrier molecule.

Epitope or Antigenic Determinant : That portion of an antigen that combines with the products of a specific immune response.

Antigen vs. Immunogen

- Antigen
  - Any substance that can bind to an antibody or T cell receptor
- Immunogen
  - Any substance that can elicit an immune response
  - All immunogens are antigens
  - Not all antigens are immunogens, i.e. haptens

Immunogen, antigen, epitope, hapten

•Immunogen: a stimulus that produces a humoral or cell-mediated immune response

•Antigen: any substance that binds specifically to an antibody or a T-cell receptor

•Epitope: the portion of an antigen that is recognized and bound by an Ab or TCR/MHC complex (aka antigenic determinant)

•Hapten: a low molecular weight molecule that can be made immunogenic by conjugation to a suitable carrier

Factors influencing immunogenicity A- Contribution of the Immunogen

1. Foreignness : The immune system normally discriminates between self and non-self such that only foreign molecules are immunogenic.

2. Size : The most potent immunogens are usually large proteins. Generally, molecules with a molecular weight less than 10,000 are weakly immunogenic.

3. Chemical Composition : In general, the more complex the substance is chemically the more immunogenic it will be.

4. Physical form : In general particulate antigens are more immunogenic than soluble ones and denatured antigens more immunogenic than the native form.

5. Degradability : Antigens that are easily phagocytosed are generally more immunogenic.

B. Contribution of the Biological System

1. Genetic Factors : Some substances are immunogenic in one individual but not in others. The individuals may lack or have altered genes that code for the receptors for antigen on B cells and T cells.

2. Age : Age can also influence immunogenicity. Usually the very young and the very old have a diminished ability to mount and immune response in response to an immunogen.

C. Method of Administration

1. Dose : The dose of administration of an immunogen can influence its immunogenicity. There is a dose of antigen above or below which the immune response will not be optimal.

2. Route : Generally the subcutaneous route is better than the intravenous or intragastric routes. The route of antigen administration can also alter the nature of the response.

3. Adjuvants : Substances that can enhance the immune response to an immunogen are called adjuvants. The use of adjuvants, however, is often hampered by undesirable side effects such as fever and inflammation.

Chemical nature of immunogens :

A. Proteins : The vast majority of immunogens are proteins. These may be pure proteins or they may be glycoproteins or lipoproteins. In general, proteins are usually very good immunogens.

B. Polysaccharides : Pure polysaccharides and lipopolysaccharides are good immunogens.

C. Nucleic Acids : Nucleic acids are usually poorly immunogenic. However, they may become immunogenic when single stranded or when complexed with proteins.

D. Lipids : In general lipids are non-immunogenic, although they may be haptens.

Super antigens :

When the immune system encounters a conventional T-dependent antigen, only a small fraction of the T cell population is able to recognize the antigen and become activated (monoclonal/oligoclonal response). However, there are some antigens which polyclonally activate a large fraction of the T cells (up to 25%). These antigens are called superantigens. Examples of superantigens include: Staphylococcal enterotoxins (food poisoning), Staphylococcal toxic shock toxin (toxic shock syndrome) and Streptococcal pyrogenic exotoxins (shock).

Origin of antigens

1-Exogenous antigens : Exogenous antigens are antigens that have entered the body from the outside, for example by inhalation, ingestion, or injection. The immune system's response to exogenous antigens is often subclinical. By endocytosis or phagocytosis, exogenous antigens are taken into the antigen-presenting cells (APCs) and processed into fragments. APCs then present the fragments to T helper cells (CD4+) by the use of class II histocompatibility molecules on their surface.

2-Endogenous antigens : Endogenous antigens are antigens that have been generated within previously normal cells as a result of normal cell metabolism, or because of viral or intracellular bacterial infection. The fragments are then presented on the cell surface in the complex with MHC class I molecules. If activated cytotoxic CD8+ T cells recognize them, the T cells begin to secrete various toxins that cause the lysis or apoptosis of the infected cell.

3-Autoantigens : An autoantigen is usually a normal protein or complex of proteins (and sometimes DNA or RNA) that is recognized by the immune system of patients suffering from a specific autoimmune disease. These antigens should, under normal conditions, not be the target of the immune system, but, due to mainly genetic and environmental factors, the normal immunological tolerance for such an antigen has been lost in these patients.

4-Tumor antigens: Tumor antigens or neo-antigens are those antigens that are presented by MHC I or MHC II molecules on the surface of tumor cells. These antigens can sometimes be presented by tumor cells and never by the normal ones. In this case, they are called tumor-specific antigens (TSAs) and, in general, result from a tumor-specific mutation. More common are antigens that are presented by tumor cells and normal cells, and they are called tumor-associated antigens (TAAs)