Lect. 6 part 1

TYPES AND GRADES OF IMMUNITY: ADAPTIVE IMMUNIT

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THIS LECTURE DEALS WITH:

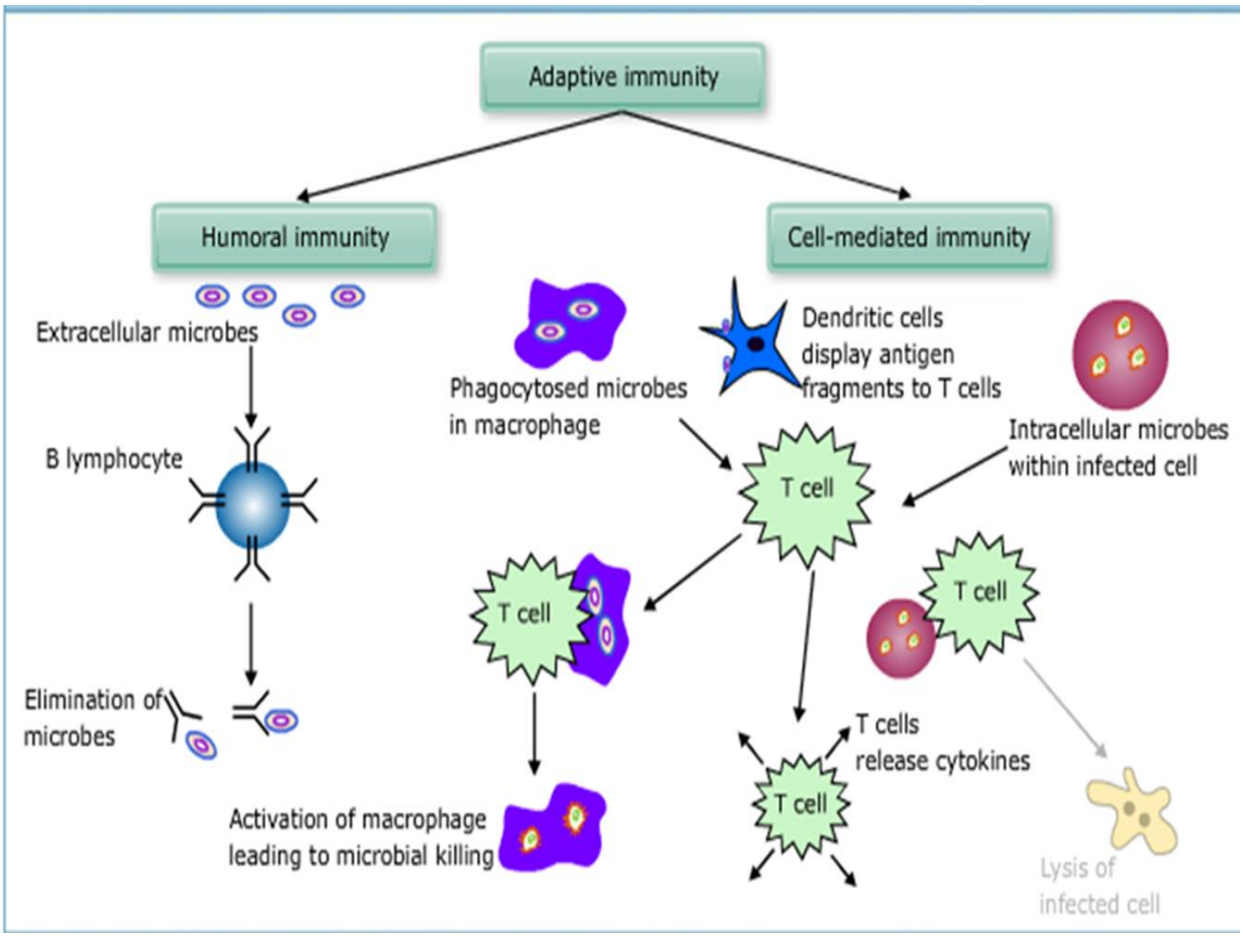
- **Adaptive immunity**
- **Types of adaptive immune response**
- **Features of adaptive immune responses**

Adaptive immunity

Adaptive immunity is specific for <u>different microbial and non-microbial antigens and increased by repeated exposures to antigen.</u>

1. In contrast to innate immunity, **<u>there are other immune responses that are stimulated by exposure to infectious agents</u>** and increase in greatness and defensive capabilities with each successive exposure to a particular microbe.
2. **<u>Because this form of immunity develops as a response to infection and adapts to the infection, it is called adaptive immunity</u>**.
3. The defining characteristics of adaptive immunity are exquisite **<u>specificity for distinct molecules and an ability to "remember" and respond more vigorously to repeated exposures to the same microbe.</u>**
4. The adaptive immune system is able to recognize and react to a large number of microbial and nonmicrobial substances.
5. In addition, it has **<u>an extraordinary capacity to distinguish between different, even closely related, microbes and molecules, and for this reason it is also called specific immunity.</u>**

6. It is also **<u>sometimes called acquired immunity, to emphasize that potent protective responses are "acquired" by experience.</u>**
7. the main components of adaptive immunity are cells called lymphocytes and their secreted products, such as antibodies. Foreign substances that induce specific immune responses or are recognized by lymphocytes or antibodies are called antigens



- **Compares between adaptive and innate immunity**

Types of immunity	Innate Immunity Always "on"	Adaptive Immunity Turned on by Antigens
Cells engaged	Macrophages, dendritic cells Neutrophils, NK cells*	**T and B cells**
Cell receptors	Preformed and directed against common microbial molecules	**Generated in response to foreign molecules**
Evolutionary history	Ancient	**Recent**
Onset	Rapid (min-hr)	**Slow (days-weeks)**
Specificity	Common microbial structures	**Unique antigens**
Potency	May be overwhelmed	**Rarely overwhelmed**
Memory	None	**Significant memory**
Effectiveness	**Does not improve**	**Improves with exposure**

TYPES OF ADAPTIVE IMMUNE RESPONSE

- **There are two types of adaptive immune responses:**
  - ***Humoral immunity:*** **Produced by B-lymphocytes and mediated by the production of antibodies, which neutralize the target microbes and eliminates from the body by several effector mechanisms.**
  - ***Cellular immunity:*** **Produced by T- lymphocytes and mediated by production of effector cytokines which activate macrophages to kill microbes in phagocytes and cytotoxic T cells kill the infected cell to eliminate infection.**

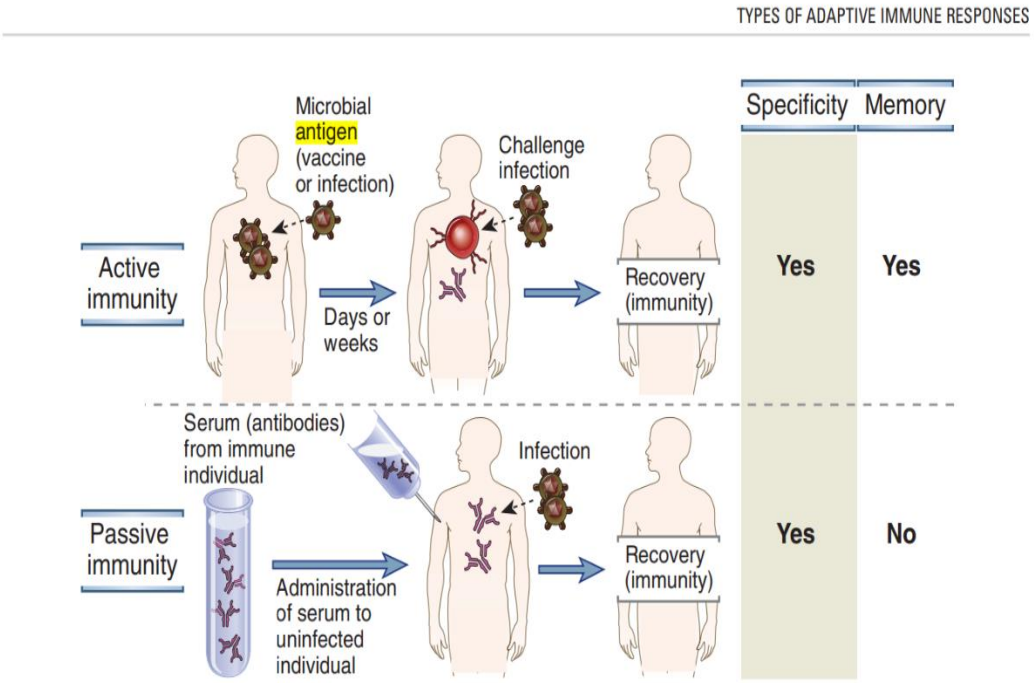
Adaptive immunity can be acquired by two ways

- **Active immunity**
- **Passive immunity.**

- ***Active immunity:*** **<u>When the host's body in response to foreign antigen produces antibody, the immunity develops slowly and persists for a long time</u>. Active immunity may be**
  - ***Natural:*** **When produced due to natural infection by infectious organisms.**
  - ***Artificial:*** **This is produced by the host's body in response to inoculation of an antigen e.g., vaccination**
- **Passive immunity : <u>The antibody is prepared elsewhere and then introduced into host's body. The immunity is rapidly established but persists for short duration.</u>**

Passive immunity may be of two types

- **Natural**
  - **Maternal antibody from mother to foetus (Tran placental transfer)**
  - **Colostrum antibody through milk from mother to neonates.**
- **Artificial**
  - **By injection of immune serum in case of tetanus**
  - **Transfer of lymphocyte or immune cells.**



FEATURE

S OF AD APTIVE IMMUNE RESPONSES

Both humoral and cell mediated immune responses to antigens have a number of fundamental properties

Specificity
Diversity
Memory
Non reactivity to self

1. **Specificity**

The specificity of the immune system is due to the fact that both lymphocytes and antibodies only recognize one epitope or antigenic determinant.(Epitopes are some specific areas or chemical groupings on the surface of antigen molecules. Epitopes are also called antigenic determinants). The immune system can recognize thousands of millions of different antigens, but for each determinant, a specific lymphocyte will be induced.

2. **Diversity:**

The lymphocyte repertoire (stock)is very large in an individual. It is due to an extreme variability(change) in the structure of antigen-binding sites of lymphocytes. Therefore, body can respond to an extremely large number of antigens. This is known as diversity of immune system.

3. **Memory**

Secondary response occurs after re-exposure to the same antigen. This property of immune system is known as immunologic memory. Each exposure to an antigen expands the progeny of a particular antigen responsive lymphocyte, i.e. it expands the clone(copy) of a lymphocyte specific for a particular antigen. These memory cells survive for long periods. The immune response of memory cells is rapid, larger and more efficient compared to the previous exposure

4. **Non-reactivity to Self-tolerance**

The specific immune system discriminates between 'self' and 'non-self' (foreign) and responds to only foreign materials to the host, which is antigenic. Abnormalities in the induction of immune response against self -antigen (autogenous antigen) results in disorder called autoimmune disorder

5. **Clonal expansion.**

Lymphocytes specific for an antigen undergo considerable proliferation after exposure to that antigen. The term clonal expansion refers to an increase in the number of cells that express identical receptors for the antigen and thus belong

to a clone. This increase in antigen-specific cells enables the adaptive immune response to keep pace with rapidly dividing infectious pathogens.

6. Contraction and homeostasis.

All normal immune responses decline with time after antigen stimulation, thus returning the immune system to its resting basal state, a state that is called homeostasis .

This contraction of immune responses occurs largely because responses that are triggered by antigens function to eliminate the antigens, thus eliminating an essential stimulus for lymphocyte survival and activation. Lymphocytes, other than memory cells, that are deprived of these stimuli die by apoptosis

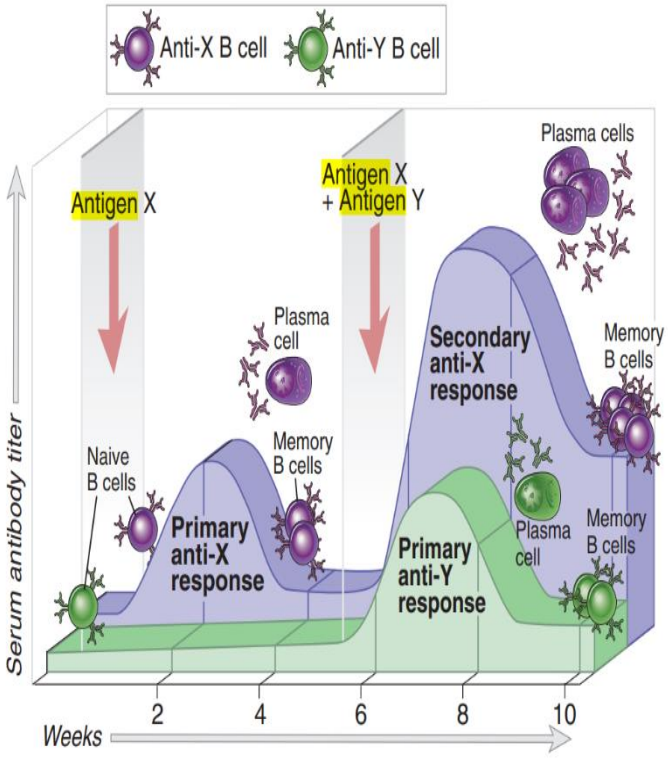


TABLE 1–3 Cardinal Features of Adaptive Immune Responses

Feature	Functional Significance
Specificity	Ensures that the immune response to a microbe (or nonmicrobial antigen) is targeted to that microbe (or antigen)
Diversity	Enables immune system to respond to a large variety of antigens
Memory	Increases ability to combat repeat infections by the same microbe
Clonal expansion	Increases number of antigen-specific lymphocytes to keep pace with microbes
Specialization	Generates responses that are optimal for defense against different types of microbes
Contraction and homeostasis	Allows immune system to recover from one response so that it can effectively respond to newly encountered antigens
Nonreactivity to self	Prevents injury to host during responses to foreign antigens

CELLULAR COMPONENTS OF ADAPTIVE IMMUNE SYSTEM

The principal cells of the immune systems are lymphocytes, antigen presenting cells (APCs) and effector cells. Lymphocytes specially recognize foreign antigen and respond in two different ways

Humoral immunity

Cell mediated immunity

- **B lymphocytes when recognize antigens (extra cellular), they are differentiated in to antibody secreting cells and function as the mediators of humoral immunity.**
- **T- lymphocytes recognize, intracellular antigen and destroy the microbes or infected cells. They do not produce antibody. T lymphocytes do not respond to soluble antigens but they recognize peptide antigen attached to host proteins and produce different lymphokines to eliminate the antigen.**

For specific immune response, the antigen must be captured and presented to specific lymphocytes. The cells, which perform this function, are called antigen-presenting cells (APCs). They are mostly dendritic cells.

Effector cells perform numerous functions to eliminate the antigen. Activated T lymphocytes, mononuclear phagocytes and other leukocytes function as effector cells in different immune responses

Characteristics	Humoral immunity	Cell mediated immunity
Antigen	Extra cellular antigen	Intracellular antigen
Responding lymphocytes	B-lymphocytes	T-lymphocytes
Effector function	Antibody mediated elimination	Lymphokines mediated elimination or lysis of infected cells or antigen
Passive transfer	Through serum	Through T-cells

Lect. 6 part 2

Antigen

This Lecture Deals With:

- **Antigen**
- **Factors determining antigenicity**
- **Types of antigen**

Antigen

The adaptive immune system, uses receptors that can bind and respond to almost all the foreign macromolecules present in an invading microorganism. These foreign macromolecules are called antigens .

- **Antigen is a substance which when introduced into the tissues of a susceptible animal, it stimulates the formation of specific neutralizing substances or antibody which it reacts specifically in some observable way or produced lymphokines or both antibody and lymphokines.**
- **The ability of a material to induce an immune response is referred to as immunogenicity and such material is called as immunogen.**
- ***Immunogenicity* is the ability to induce a humoral and/cell mediated immune response.**
- ***Antigenicity* is the ability of a molecule to be recognized by an antibody or lymphocyte.**
- **All molecules possessing the property of immunogenicity also possess antigenicity but the reverse is not true.**
- **Molecules vary in their ability to act as antigens and stimulate immune response.**

What Makes a Good Antigen?

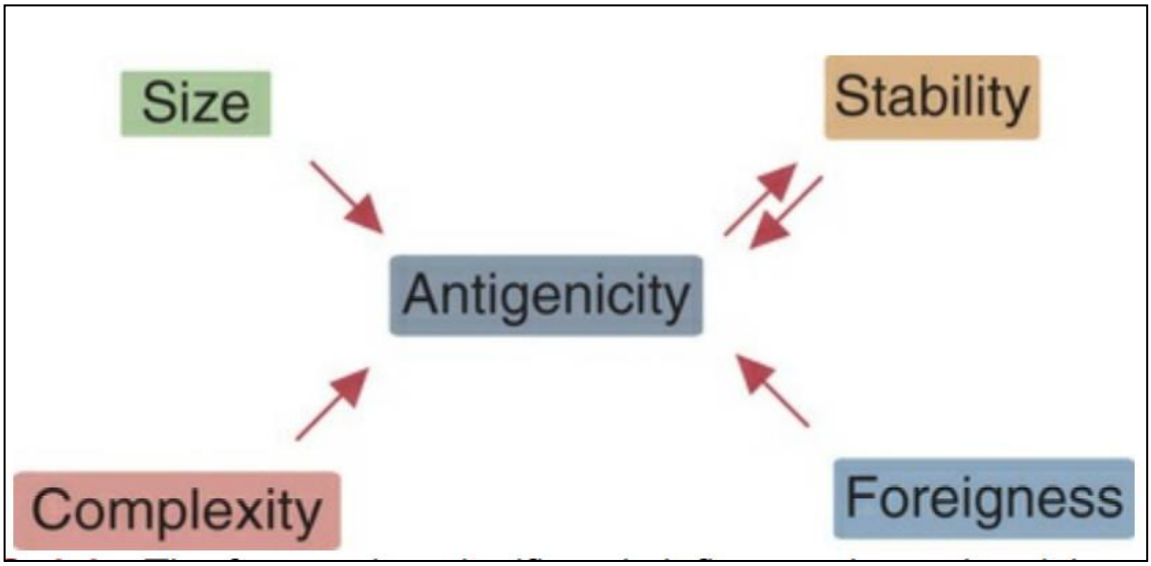
- **Molecules vary in their ability to act as antigens (their antigenicity) .**
- **The best antigens are large, complex, and foreign. However, their ability to stimulate an immune response is also determined by their route of administration, by the amount of antigen administered, and by the genetic makeup of the immunized animal.**
- **Simple polysaccharides, such as starch or glycogen, are not good antigens simply because they are often degraded before the immune system has time to respond to them.**
- **Lipids tend to be poor antigens because of their wide distribution, relative simplicity, structural instability, and rapid metabolism.**
- **Mammalian nucleic acids are very poor antigens because of their relative simplicity and flexibility, and because they are very rapidly degraded. Microbial nucleic acids, on the other hand, have a structure very different**

from that found in eukaryotes As a result, they can stimulate potent immune responses.

- **Proteins are the most effective antigens because they have properties that best trigger an immune response**

  The best antigens are large, complex, and foreign. However, their ability to stimulate an immune response is also determined by their route of administration, by the amount of antigen administered, and by the genetic makeup of the immunized animal.

FACTORS DETERMINING ANTIGENICITY



1. **Foreignness**

The immunogenicity of a molecule also depends on its degree of foreignness The cells that respond to antigens (antigen-sensitive cells) are lymphocytes that have been selected so that their receptors do not normally bind to molecules originating within an animal (self- antigens) but can bind foreign molecules. These are sufficient to protect animals against almost all potential pathogens. The greater in the difference in molecular structure between a foreign antigen

and an animal's own antigens, the greater will be the intensity or strength of the immune response.

2. **COMPLEXITY**

Good antigens have complex structure. Large complex molecules can be readily taken up by macrophages. Complex proteins are good immunogen containing many different amino acids, especially aromatic ones, are better antigens than large. Repeating polymers, such as lipids, carbohydrates, and nucleic acids are poor antigens, but complex bacterial lipopolysaccharides are good.

3. **STABILITY**

Structural stability is an important feature of good antigens, especially those that trigger antibody responses. Antigen molecule must be stable and rigid. For example, gelatin, a protein known for its instability is a poor antigen but they become stable when amino acid residue like tyrosine or tryptophan are incorporated which cross link the peptide chain.

4. MOLECULAR SIZE

Foreign proteins make the best antigens, especially if they are big (greater than 1000 Da is best). In general, the larger the molecular weight, the better are their antigenic properties. For example, ovalbumin (mol. wt. 40,000 Da). But there are some exceptions e.g. natural protein glucagon (2600 Da) is a good antigen. Many of the major antigens of microorganisms such as the clostridial toxins, bacterial flagella, virus capsids, and protozoan cell membranes are large proteins.

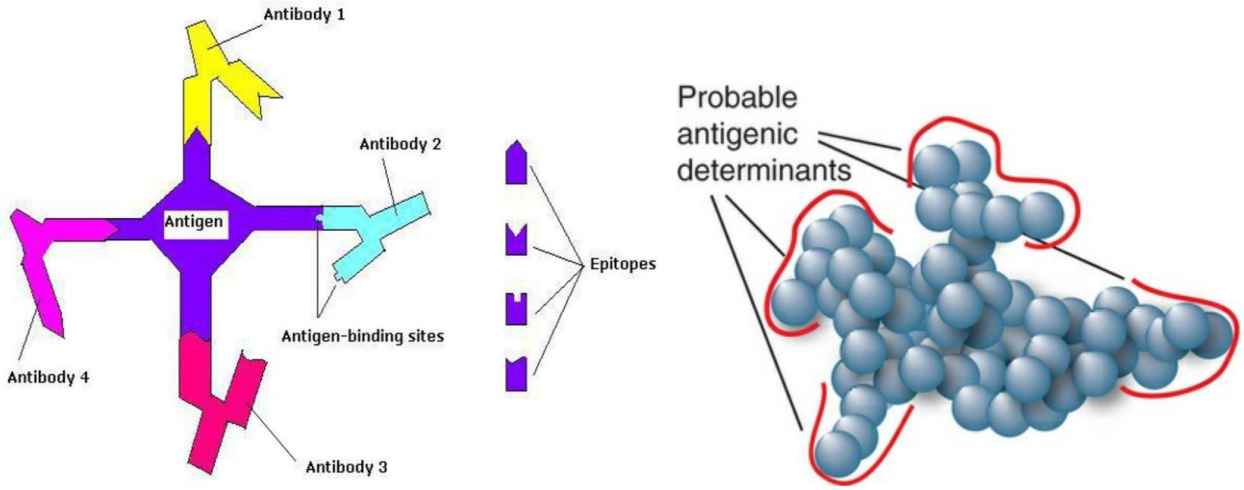
5. Others factor

1. **EPITOPES**

- **Large molecules have regions on their surface that bind to lymphocyte antigen receptors and against which immune responses are therefore directed. These regions, usually on the surface of the molecule, are called epitopes, or antigenic determinants. In a large, complex protein molecule, many different epitopes may be recognized by lymphocytes, but some are much more immunogenic than others. Thus animals may respond to a few favored or ideal**

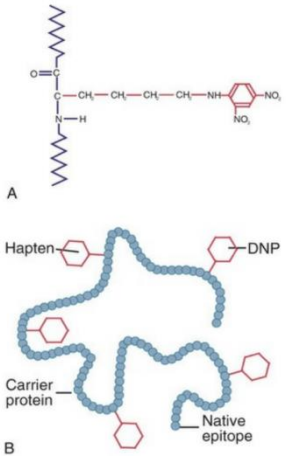
epitopes, and the remainder of the molecule may be ignored. Such favored epitopes are <u>said to be immunodominant.</u>

- **Macromolecules, such as proteins, polysaccharides, and nucleic acids, are usually much bigger than the antigen-binding region of an antibody molecule . Therefore, any antibody binds to only a portion of the macromolecule, which is called a determinant or an epitope.**
- **Macromolecules typically contain multiple determinants, some of which may be repeated and each of which, by definition, can be bound by an antibody. The presence of multiple identical determinants in an antigen is referred to as polyvalency or multivalency.**
- **Most globular proteins do not contain multiple identical epitopes and are not polyvalent, unless they are in aggregates. In the case of polysaccharides and nucleic acids, many identical epitopes may be regularly spaced, and the molecules are said to be polyvalent.**
- **Cell surfaces, including microbes, often display polyvalent arrays of protein or carbohydrate antigenic determinants. <u>Polyvalent antigens can induce clustering of the B cell receptor and thus initiate the process of B cell activation.</u>**



2. Haptens

- **Small molecules, such as many drugs or hormones of less than 1000 Da, are far too small to be appropriately processed and presented to the immune system. As a result, they are not immunogenic. If, however, these small molecules are chemically linked to a large protein molecule, they will form new epitopes on the surface of the larger molecule.**
- **If this complex molecule is injected into an animal, immune responses will be triggered against all its epitopes.**
- **Some of the antibodies made in response to the complex will be directed against new epitopes formed by the small molecule.**
- **Small molecules that can function as epitopes only when bound to other larger molecules are called haptens (in Greek, haptein means "to grasp or fasten").**
- **Typical hapten; in this case, dinitrophenol attached to a lysine side chain. When several haptens are attached to a peptide chain, they serve as new epitopes and will stimulate immune responses.**



- **The antigenic molecule to which the haptens are attached is called the carrier. Many drug allergies occur because the drug molecules, although small, can bind covalently to normal body proteins and so act as haptens.**

- **The antibiotic penicillin is a small nonimmunogenic molecule. Once degraded within the body, however, it forms a very reactive "penicilloyl" group, which can bind to serum proteins such as albumin to form penicilloyl-albumin complexes). The penicilloyl hapten can be recognized as a foreign**
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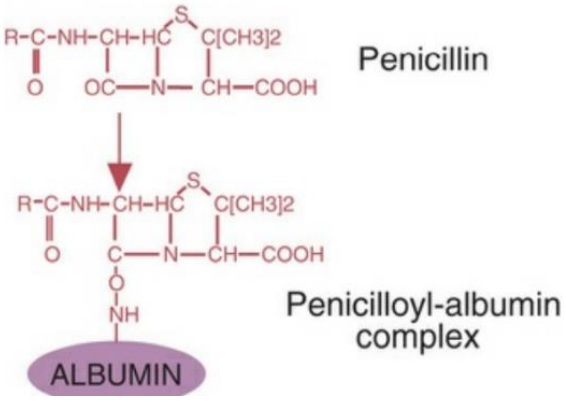


- **epitope in some individuals and so provokes an immune response, resulting in penicillin allergy.**

3. **Cross-reactivity**

Cross-reactivity between antigens occurs when an antibody directed against one specific antigen is successful in binding with another, different antigen. Identical or similar epitopes may sometimes be found on apparently unrelated molecules. As a result, antibodies directed against one antigen may react unexpectedly with an unrelated antigen. In another situation, the epitopes on a protein may differ in only minor respects from those on the same protein obtained from an animal of a related species.

Consequently, antibodies directed against a protein in one species may also react in a detectable manner with the homologous or similar protein in another species. Both phenomena are called cross-reactions. An example of a cross-reaction of the first type is seen when blood typing. Many bacteria possess cell wall glycoproteins with carbohydrate side chains that are identical to those found on mammalian red blood cell glycoproteins. For example, some of the intestinal microbiota possess glycoproteins with A or B side chains on their cell wall. These glycoproteins are absorbed through the intestinal wall and trigger an antibody response. B

Types of Antigens

1. Autoantigens

In some situations (and not always abnormal ones), an animal may display immune responses against normal body components. These are called autoimmune responses. Antigens that induce autoimmunity are called autoantigens. They can include hormones, such as thyroglobulin; structural components, such as basement membranes; complex lipids, such as myelin; intracellular components, such as the mitochondrial proteins, nucleic acids, or nucleoproteins; and cell surface proteins, such as hormone receptors.

2. Microbial antigens:

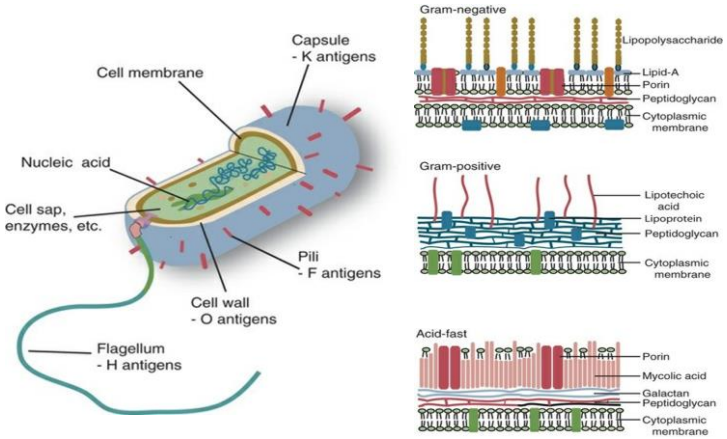
1) **Cellular antigens:**

- **The major components of the bacterial surface include the cell wall and its associated protein structures, the capsule, the pili, and the flagella**
- **The cell wall of Gram-positive organisms compose of peptidoglycan and also contain lipoteichoic acids (Fig.2). lipoteichoic acids has antigenic properties being able to stimulate specific immune response**
- **Most of the antigenicity of Gram-negative bacteria is associated with the lipopolysaccharide. This consists of an oligosaccharide attached to a lipid (lipid A) and to a series of repeating trisaccharides. The structure of these trisaccharides determines the antigenicity of the organism. These polysaccharide antigens are called O antigens.**
- **These antigens serve as pathogen-associated molecular patterns and are recognized by pattern-recognition receptors such as the Toll-like**

receptors. (The major cells expressing TLRs are antigen-presenting cells (APCs). Activation of TLRs in APCs can affect maturation of these cells and T helper 1 (Th1) cell differentiation for processing more specific immune mechanisms).

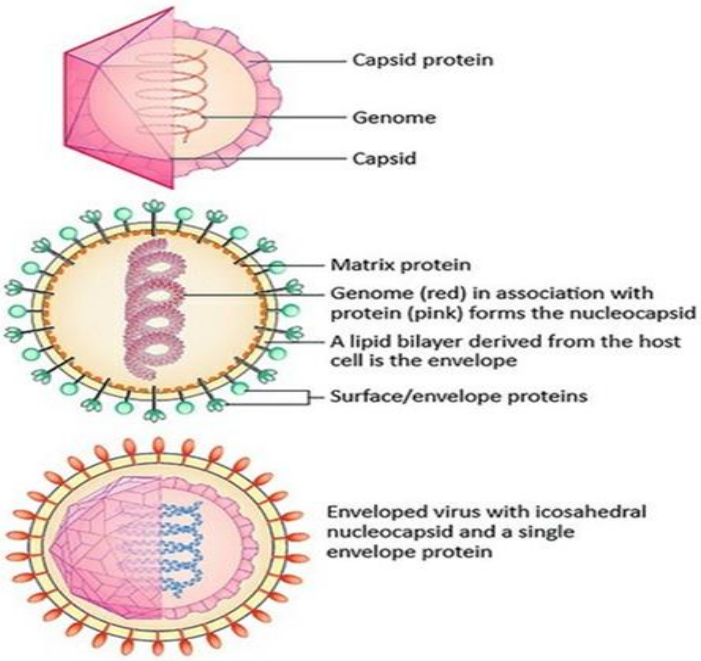
- **Bacterial capsules consist mainly of polysaccharides that are usually good antigens are called K antigens. Pili and fimbriae they are classified as F or K antigens. also ,Flagellar antigens are collectively called H antigens.**

2) **Soluble antigens Some soluble substances produced by the bacteria, which are excreted into the environment. For example, the exotoxins such as Clostridium tetani toxin.**



3. **Viral Antigens**

Viruses are very small structures that grow only inside living cells. They are thus "obligate," intracellular parasites. Viruses usually have a relatively simple structure consisting of a nucleic acid core covered by a protein layer . This protein layer is termed the capsid, and consists of multiple subunits called capsomeres. Capsid protein and envelope (consists of lipoprotein and glycoprotein) are good antigens. Capsid proteins, well capable of stimulating antibody responses. When a virus infects an animal, its proteins are processed, recognized, and trigger adaptive immune responses. Examples, HN protein (glycoprotein) of Newcastle disease virus



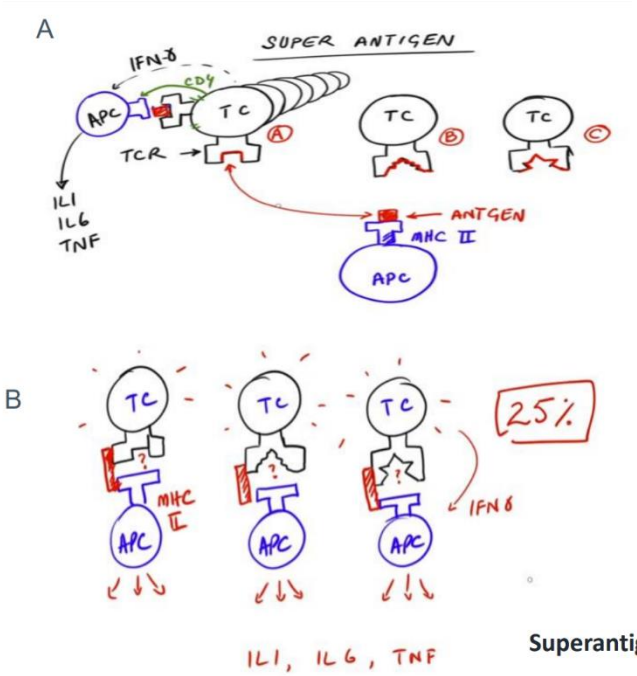
The structure of some viruses. The antigenic proteins include the capsids and envelope proteins. (Courtesy Dr. S. Payne.)

4. **Other Microbial Antigens** **In addition to bacteria and viruses, animals may be invaded by fungi, protozoan parasites, arthropods, and even parasitic worms (helminths). Each of these organisms consists of many different structures composed of proteins, carbohydrates, lipids, and nucleic acids. Many of these molecules can serve as antigens and trigger adaptive immunity. However, their antigenicity does vary, and the adaptive responses triggered by these organisms are not always successful in protecting an animal or eliminating the invader.**

C. Super antigen

Fewer than 1 in 10,000 T cells can bind and respond to any specific foreign antigen. However, some microbial molecules called superantigens are unique in that they may stimulate as many as one in five T cells. These molecules are not simply nonspecific mitogens. All superantigens come from microbial sources such as streptococci, staphylococci, and mycoplasma, and from viruses such as rabies. they bind the T cell and the antigen presenting cell together.

Because of this strong binding, superantigens trigger a powerful T cell response. Some superantigens may stimulate the secretion of so many cytokines that they trigger a <u>toxic shock syndrome</u>



A normal antigen ;

B superantigens

Superantigens cause toxic shock syndrome