Lec.6: ANTIGENS

Definitions

- Immunogen - a substance that induces a specific immune response.
- Antigen (Ag) - a substance that reacts with the products of a specific immune response.
- Hapten - a substance that is nonimmunogenic but which can react with the products of a products of a specific immune response.
- Epitope or Antigenic Determinant - the portion of an antigen that combines with the specific immune response (B- cell receptor or T- cell receptor).
- Haptens are small molecules which could never induce an immune response when administered by themselves but which can when coupled to a carrier molecule. Free haptens, however, can react with products of the immune response after such products have been elicited. Haptens have the property of antigenicity but not immunogenicity.
- Antigenicity is defined as the property of a substance (antigen) that allows it to react with the products of a specific immune response (antibody or T-cell receptor).
- Immunogenicity is defined as the property of a substance (immunogen) that endows it with the capacity to provoke a specific immune response.
- Adjuvant is an agent, distinct from antigen, that enhances T cell activation by promoting the accumulation of APCs at a site of antigen exposure and by enhancing the expression of co-stimulators and cytokines by the APCs.

Factors influencing immunogenicity

Many different substances can induce immune responses. The following characteristics have an important influence in the ability that a substance has to behave as an immunogen:

1-Contribution of the immunogen

A. Foreignness. As a rule, only substances recognized as “non-self” will trigger the immune response. Microbial antigens and heterologous proteins are obviously “non-self” and are strongly immunogenic.

B. Molecular Size. The most potent immunogens are macromolecular proteins [molecular weight (M.W.) > 100,000]. Molecules smaller than 10,000 daltons are weakly immunogenic.

C. Chemical Structure and Complexity. Proteins and polysaccharides are among the most potent immunogens, although relatively small polypeptide chains, nucleic acids, and even lipids can, given the right circumstances, be immunogenic. Some glycolipids and phospholipids can stimulate T cells and produce a cell-mediated immune response.

D- Degradability

For an antigen to be recognized as foreign by an individual’s immune system, sufficient antigens to stimulate an immune response must be present. Foreign molecules are rapidly destroyed and thus cannot provide adequate antigenic exposure. In the case of vaccination, an adequate dose of vaccine at appropriate intervals must be administered for an immune response to be stimulated.

2-Contribution of the Biological System

A-Genetic Constitution of the Animal. Different animal species or different strains of one given species show different degrees of responsiveness to a given antigen. In humans, different individuals can behave as “high responders” or “low responders” to any given antigen. The genetic control of the immune response seems mainly related to the repertoire of MHC molecules, which bind antigen fragments and present them to the immune system. The animal will respond well to those antigens that are processed into peptides or oligopeptides with high affinity for the binding sites of the MHC molecules .

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

3-Method of Antigen Administration.

A-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. For example, high doses of antigen can often be tolerogenic and blunt the immune response.

B--A given dose of antigen may elicit no detectable response when injected intravenously, but may elicit a strong immune response if injected intradermally. This last route of administration results in slow removal from the site of injection and prolonged antigenic stimulation. The presence of dendritic cells in the dermis (where they are known as Langerhans cells) is believed to be a significant factor determining the vigorous immune responses obtained when antigens are injected intradermally. The injected antigen is trapped on the surface of those dendritic cells, which migrate to the lymph node follicles, where the initial stages of the immune response take place.

C. Use of Adjuvants.

Chemical nature of antigens :

Antigens, or immunogens, are usually large organic molecules that are proteins or large polysaccharides and, rarely, if ever, lipids. Antigens, especially cell surface or membrane-bound antigens, can be composed of combinations of biochemical classes (e.g., glycoproteins, glycolipids). For example, histocompatibility HLAs are glycoprotein in nature and are found on the surface membranes of nucleated body cells composed of solid tissue and most circulating blood cells (e.g., granulocytes, monocytes, lymphocytes, thrombocytes).

- Proteins are excellent antigens because of their high molecular weight and structural complexity.
- Lipids are considered inferior antigens because of their relative simplicity and lack of structural stability. However, when lipids are linked to proteins or polysaccharides, they may function as antigens.

- Carbohydrates (polysaccharides) by themselves are considered too small to function as antigens. In the case of erythrocyte blood group antigens, protein or lipid carriers may contribute to the necessary size and the polysaccharides present in the form of side chains confer immunologic specificity.
- Nucleic acids are poor antigens because of relative simplicity, molecular flexibility, and rapid degradation. Anti–nucleic acid antibodies can be produced by artificially stabilizing them and linking them to an immunogenic carrier.

Exogenous and Endogenous Antigens

According to source of antigens, antigens are divided into:

• Xenoantigen

• Alloantigen

• Autoantigen

• Heterophile antigen

A. Most of the antigens to which we react are of exogenous origin, and include microbial antigens, environmental antigens (such as pollens and pollutants), and medications. The objective of the immune response is the elimination of foreign antigens, but, in some instances, the immune response itself may have a deleterious effect (hypersensitivity states). This type of antigens are called **xenoantigen.**

B. **Alloantigens**,is an antigenic determinants that distinguish one individual from another within the same species, are unique exogenous antigens. These are alleles of highly polymorphic systems, which define the antigenic makeup of the cells and tissues of an individual. A classic example is the A, B, O blood group antigens: some individuals carry the A specificity, some are B positive, some are AB positive, and some express neither A nor B (O). Other alloantigenic systems are the histocompatibility (MHC or in the human, HLA) antigens of nucleated cells and

tissues, the platelet (P1) antigens, and the immunoglobulin allotypes. Examples of sensitization to exogenous alloantigens include:

1. Women who may become sensitized to fetal red cell antigens or immunoglobulin alloantigens during pregnancy.

2. Repeated blood transfusions that can induce sensitization against cellular or immunoglobulin alloantigens from the donor(s).

3. Organ transplantation that usually results in sensitization against histocompatibility alloantigens expressed in the transplanted organ.

C. **Endogenous antigens**, by definition, are part of self, and the immune system should not react against them. The response to self antigens can be the cause of severe pathological situations (autoimmune diseases), although it may also have an important role in normal catabolic processes (i.e., antibodies to denatured IgG may help in eliminating antigen-antibody complexes from circulation; antibodies to oxidized LDL may help in eliminating a potentially toxic lipid). This type of antigens are called autooantigen

D-**Heterophile Antigens** :Common Ags shared by different species (between human andanimal or microbes, between different species of microbe) eg; M protein of streptococus bears common antigen determinant with basement membrane of kidney (This common between bacteria and human being can causes poststreptococcal glomerulonephritis).

T-Dependent and T-Independent Antigens

According to whether need the help of T cells when B cells produce antibodies , there are two types of antigens:

1. For most antigens, including complex proteins, heterologous cells, and viruses, a measurable antibody response was only observed in animals reconstituted with

mixtures of T and B lymphocytes. Since T lymphocytes do not synthesize antibody, their role must be one of assisting the proliferation and/or differentiation of B lymphocytes. The antigens that can elicit antibody responses exclusively in animals reconstituted with both T and B cells are known as T-dependent antigens. Structurally, T-dependent antigens are usually complex proteins with large numbers of different antigenic determinants with little repetition among themselves.

2. Other antigens, particularly polysaccharides, can induce antibody synthesis in animals depleted of T lymphocytes, and are known as T-independent antigens.

TABLE 6.4. Features of B-cell and T-cell epitopes

Feature	*B-cell epitopes*	*T-cell epitopes*
Location on native protein molecules	Located on surface	Internally located
Accessibility to receptors/antibodies	Freely accessible	Not accessible
Amino acids making up the epitope (protein antigens)	Hydrophilic	Hydrophobic (predominantly)
Sequential or nonsequential epitopes	Both	Only sequential
Need for association with MHC molecules for recognition	No	Obligatory
Need for antigen processing by proteolysis	No	Obligatory
Contribution of primary, secondary, tertiary and quaternary structures of protein molecules	All of them contribute to epitope function	Only primary structure contributes to epitope function

Hapten :

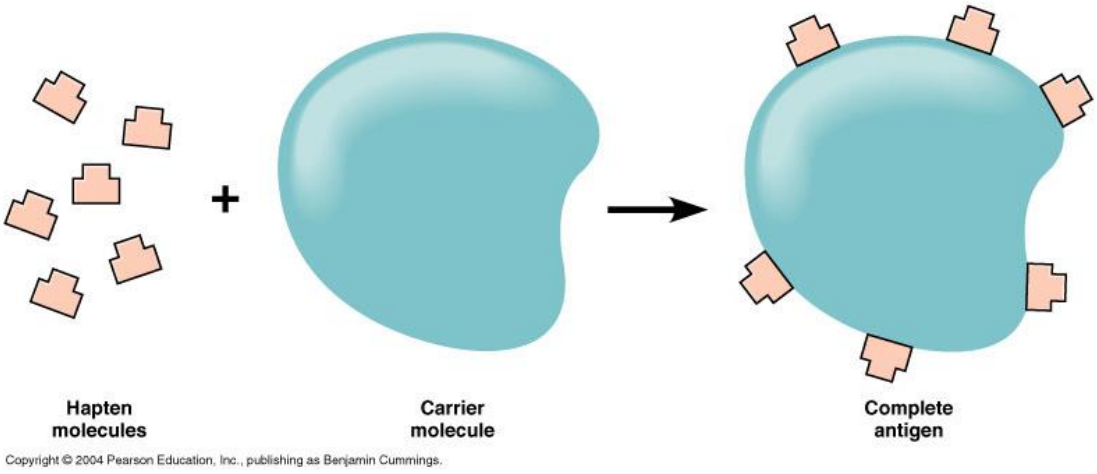
Certain low molecular weight substances, known as haptens, are unable to induce an immune response by themselves. However, if haptens are coupled to an immunogenic carrier molecule, the immune system will recognize them as separate epitopes and produce antihapten antibodies that react with soluble hapten molecules, free of carrier protein. Thus, a hapten is an antigen, but not an immunogen.

Incomplete antigen (hapten): substances only with immunoreactivity

Hapten +carrier complete antigen (immunogens)

Hapten: Only possess immunoreactivity

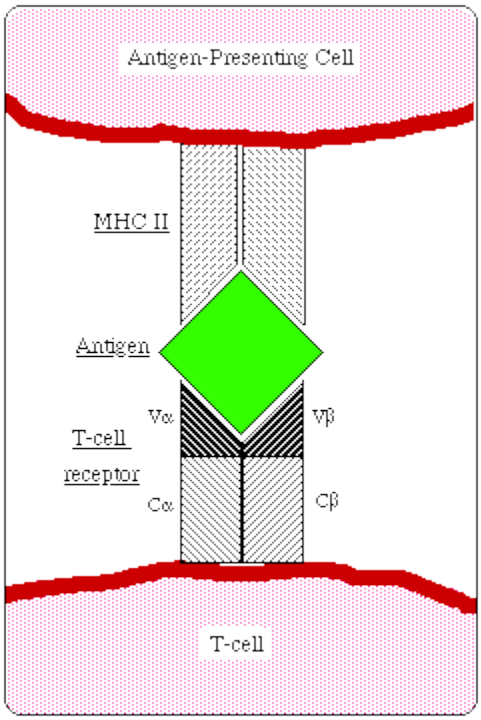
Carrier: Make hapten obtain the immunogenicity



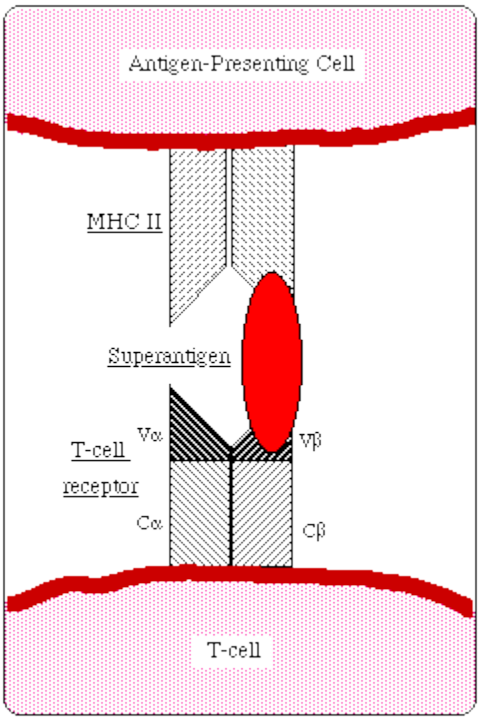
Superantigens

Superantigens are molecules which short-circuit the immune system, resulting in massive activation of T-cells rather than the usual, carefully controlled response to foreign antigens. It is believed that they do this by binding to both the variable region of the beta-chain of the T-cell receptor (V-beta) and to MHC II molecules, cross-linking them in a non-specific way.

This results in polyclonal T-cell activation rather than the usual situation where only the few clones of T-cells responsive to a particular antigen presented by the MHC II molecule are activated. The over-response of the immune system produced results in autoimmunity, as rare clones of T-cells which recognise self antigens are activated, and immune suppression, as the activated cells subsequently die or are killed by other activated T-cells. It is possible that such superantigens might also induce **apoptosis**, or 'programmed cell killing' .



Normal Antigen Presentation



Superantigen