Introduction

Definitions:

• **Antigen** is any substance that causes your immune system to prompt the generation of antibodies

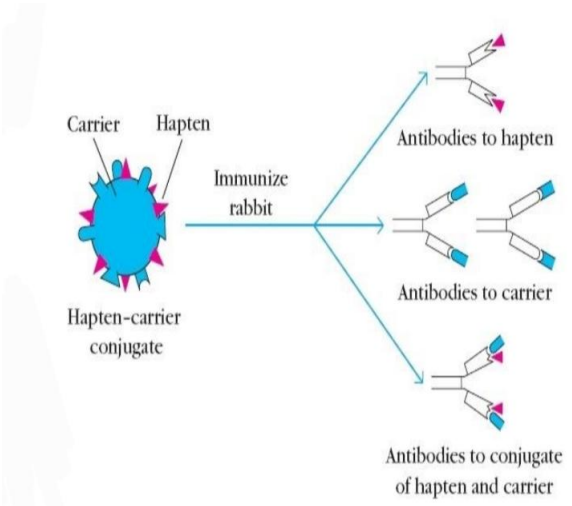
• **Immunogen**: a stimulus that produces a humoral or cell mediated immune response

• **Haptens**: Low molecular weight substances, these substances are not immunogenic by themself, but if coupled to a larger carrier molecule (albumin, globulins), they become immunogenic

• Antigens can be proteins, polysaccharides, conjugates of lipids with proteins (lipoproteins) and glycolipids

• An antigen may be a foreign substance from the environment such as chemicals, bacteria, viruses, or pollen

• An antigen may also be formed within the body, as with bacterial toxins or tissue cells



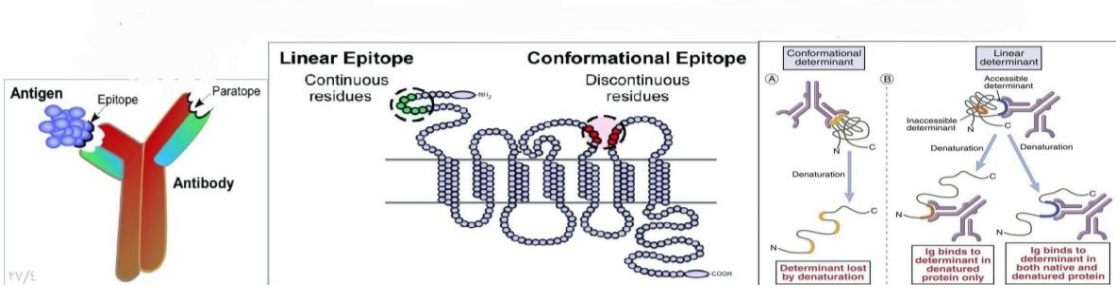
Antigenic Determinants-epitopes

• The body recognizes antigens by the three-dimensional shapes or regions called antigenic determinants or epitopes (Sites on or within antigen with which antibodies react)

• 2 types of antigenic determinants

1. Conformational determinants: amino acid residues that aren't in a sequence but become spatially juxtaposed in the folded protein. They are recognized by B cells or antibody

2. Sequential (or linear) determinants: They are mainly recognized by T cells, but some also can be recognized by B cells



Properties that make molecules more effective antigens include:

1. Foreignness: foreignness means substances that never contact with lymphocytes in embryo period.
2. Stable molecules, ie, molecules that assume and maintain a definite shape
3. Larger molecules with molecular masses between 5000 and 100,000 daltons
4. Molecules that are structurally complex, with distinctive shapes and novel subunit combinations
5. Route of administration: Parenteral routes are more immunogenic than oral route

Types of Antigens

- Exogenous antigens
- Endogenous antigens
- Auto-antigens

1. Exogenous Antigens

- Exogenous antigens are antigens that have entered the body from the outside, for example by inhalation, ingestion, or injection

1. Bacterial antigens:
– Antigens related to bacterial cells: Somatic antigen (O), Capsular antigen, Flagellar Ag (H), etc
– Antigen secreted by bacteria: for ex Exotoxins
2. Viral antigens:
– Protein coat viral antigens
– Soluble antigens (soluble nucleoproteins)

2. Endogenous Antigens

- Endogenous antigens are antigens that have been generated within cells as a result of normal cell metabolism, or because of viral or intracellular bacterial infection
- Human tissue antigens:

1. Blood group antigens: A, B and Rh antigens
2. Histocompatibility antigens: Glycoprotein molecules on all nucleotide cells:
– Major histocompatibility complex antigens (MHC)
– Human leukocyte antigen (HLA)
3. Cells infected with viruses

3. Auto-antigens

- 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 under normal conditions, not be targeted 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

Superantigens

• They activate multiple clones of T-lymphocytes
• They are active at very low concentration causing release of large amounts of cytokines
• The massive T-cell activation and release of large amounts of cytokines cause systemic toxicity
• It does not lead to acquired immunity i.e no memory
• Example: Bacterial toxins:
– Staph. aureus toxic shock syndrome toxin (TSST) and enterotoxins
– Strpt. pyogenes pyrogenic toxin A

Requirement of T Cells Response

1. T cells present mainly in lymph and lymphoid organs; however, microbes usually enter through epithelial cells (like skin, respiratory sys, altimetry tract..etc.) where T cells number is very low. Accordingly, microbial antigens needs to be transported to lymph nodes to enhance chances of encounter with T cells
2. T cells can not interact with complex microbial antigen, antigens need to be captured, processed, and then presented for T cells in a specific way in order to allow interactions
3. T cells respond only to protein antigens and not to other types of chemical antigens

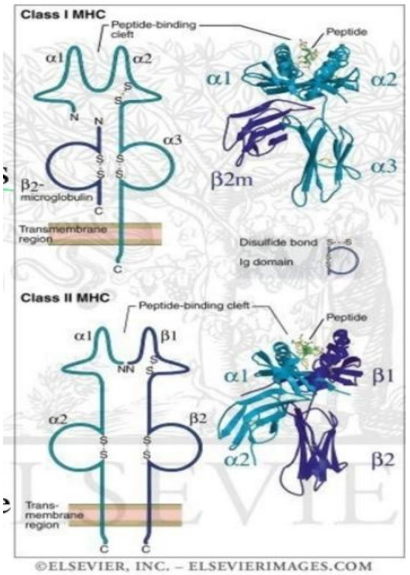
Antigen Presenting Cells

• A group of immune cells, whose role is to take up, process and present antigenic peptides to T cells
• **Professional APC:** Macrophages, dendritic cells, and B cells, which can express MHC class II molecules
• **Non-professional APC**: Other cell type capable of expressing MHC class II molecules eg. Endothelial cells Fibroblasts Activated T cell

Major Histocompatibility Complex (MHC)

• MHC molecules are membrane proteins on APCs that displays peptide antigen for recognition by T cells
• MHC molecules are the principal determinants of acceptance or rejection of tissue graft
• Two main classes of MHC

• **MHC class I:**
– Regulation of immune responses to intracellular parasites (endogenous antigens) such as viruses -all cells can be infected by viruses, therefore all cells express MHC class I
– Structure: α1, α2, α3, and β2 microglobulin
– Contain a peptide binding cleft that accommodate 8-11 aa
– Necessary for CD8+ T cells activation



• **MHC class II:**

– Regulation of immune responses to exogenous antigens, few cells are specialized to take up extracellular antigens, and so the distribution of MHC class II expression is restricted to APCs

– Structure: 2α chains (α1, α2) and 2 β (β1, β2)

– Contain peptides binding cleft of 10-30 residues

– Important for binding and activation of CD4+ T cells

Features of Peptides Binding to MHC Molecules

• Each MHC molecule display one peptide at a time

• Peptides are acquired during intracellular assembly

• Low affinity and broad specificity binding so many different peptides can bind to the same MHC molecule, and even can bind self peptides

• Very low off rate: MHC display bound peptides long enough to be located by T cells

• Stable expression of MHC molecules require peptides displaying

• MHC molecules bind only to peptides (protein antigen) so T cells can only respond to protein antigens

Steps in Antigen Preparation for T cells

• Antigens must be prepared in order to be recognized by T cells

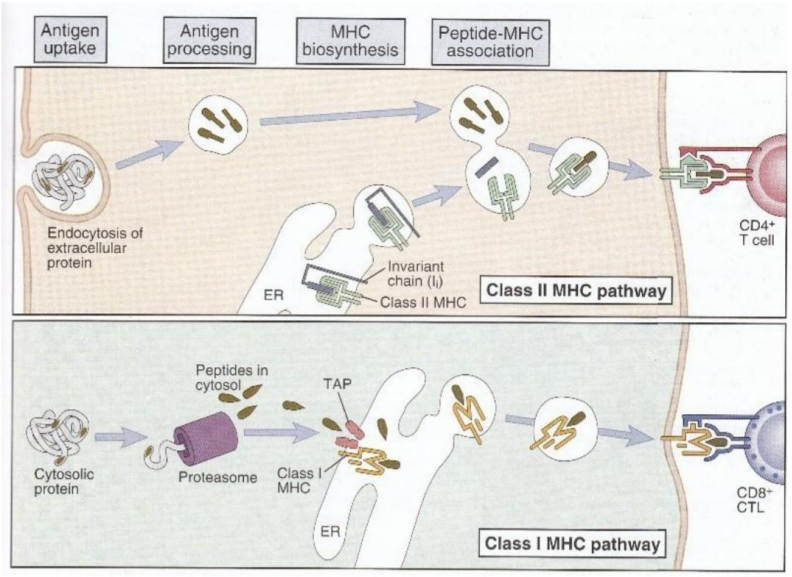
1. TRANSPORT: Antigen must be transported to lymph node for proper interaction with T cells

2. UPTAKE: Access of native antigens and pathogens to intracellular pathways of degradation

3. DEGRADATION: Limited proteolysis of antigens to peptides

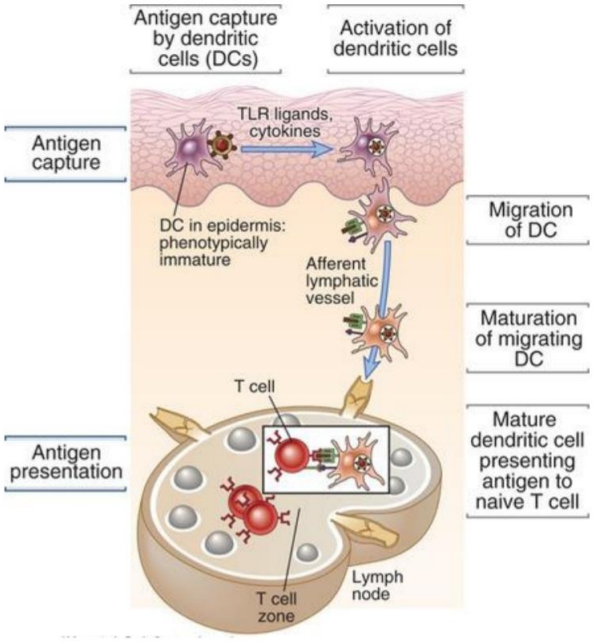
4. ANTIGEN-MHC COMPLEX FORMATION: Loading of peptides onto MHC molecules

5. ANTIGEN PRESENTATION: Transport and expression of peptide-MHC complexes on the surface of cells for recognition by T cells



1. **Antigen Capture and Transport to Lymph Node**

• Immature DCs in the epithelium capture microbial antigens and leave the epithelium
• The DCs migrate to draining lymph nodes being attracted by chemokines produced in the nodes
• During their migration the DCs mature
• Once at the lymph nodes the DCs start the processing of presenting the antigen to T cells
• DCs at their maturation express different membrane proteins, for example immature DCs express surface receptors essential for microbial binding and capture, while mature DCs express MHC molecule



2. **Uptake of Antigen**

• The process of entering the antigens into the cells (mainly APCs) this is important for exogenous antigen processing, while endogenous antigens are already inside the cells

• Uptake by immature DCs

– Pinocytosis: Liquid or small granule

– Receptor-mediated endocytosis

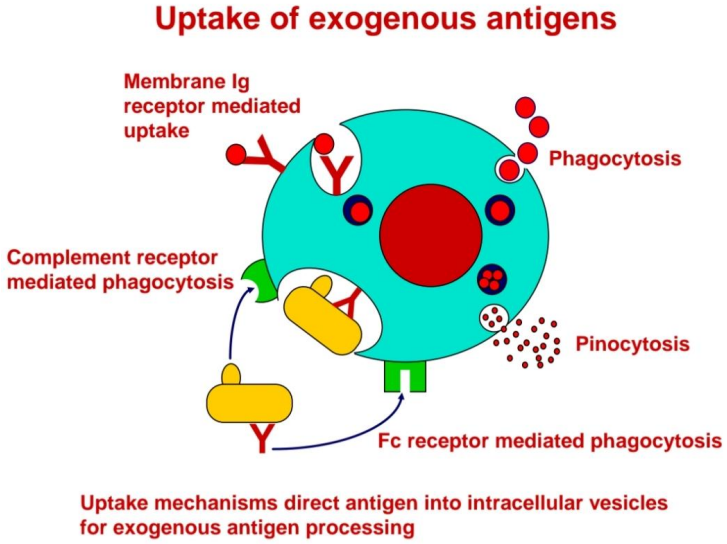
– Phagocytosis: Large molecular or microbe

• Uptake by Macrophage:

– Phagocytosis: Large solid or molecular complex

– Pinocytosis: Receptor-mediated endocytosis

– Endocytosis: Low levels of particulate or soluble antigens



3. **Antigen Processing**

• Antigens must be processed in order to be recognized by T cells, require 2 main steps

– Degradation of externally- or internally- derived antigen into short peptide sequences

– Association of the peptide with MHC molecule

Two antigen-processing pathways

	MHC class I	MHC class II
Major antigen sources	endogenous antigen	exogenous antigen
Processing machinery	proteasome	lysosomal enzymes
Cell type where active	all nucleated cells	professional APCs
Site of antigen-MHC binding	endoplasmic reticulum	lysosome and endosome
MHC utilized	MHC class I	MHC class II
Presents to	CD8+ T cell (Tc)	CD4+ T cells (Th)

4. **Antigen Presentation**

• The activation of T cells via T cell receptors, which specifically recognize antigenic peptide in association with either MHC class I or II molecules on the surface of APC.

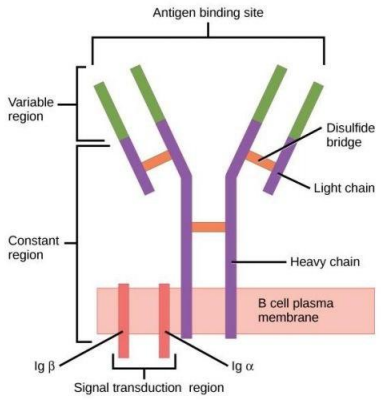
5. **Antigen Recognition**

• Antigens are recognized by and bind to:

1. B-cell receptors (BCR) :

BCR The B lymphocyte antigen receptor is a transmembrane antibody molecule (2 heavy and 2 light chains) associated with two signaling chains called Igα and Igβ

- There is also hinge region, transmembrane part



2. T-cell receptors (TCR)

αß TCR

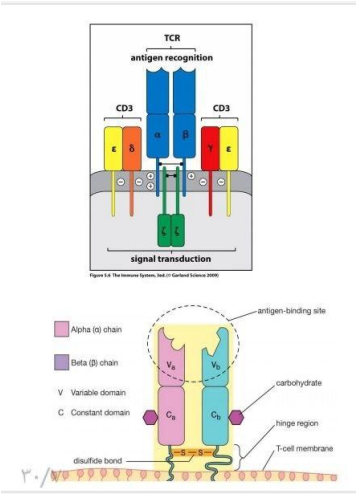
• TCR complex is the αß receptor plus the ζ chain and two CD3 signaling proteins

• Each chain constitute of one variable, one constant, hinge, transmembrane and cytoplasmic tail

• covalently linked to each other by a disulfide bridge between extracellular cysteine residues

• TCR that specifically recognizes peptide-MHC complexes

• Hypervariable regions on both Vα and Vß are the same as those of antibody located on Ag Binding Site



DONE BY:Dr.mohammed farhoud

1. You are a laboratory worker involved in vaccine development for a specific pathogen. Success would be demonstrated when you can show that the candidate vaccine elicits an immune response in vaccinated individuals such that infection cannot be established when the individual is subsequently exposed to the pathogen. It is known that there are neutralizing antibodies directed against a particular surface molecule in individuals who have recovered from infection with the pathogen under study. However, when that molecule was isolated and injected into rabbits as an antigen, it failed to elicit an immune response. The goal of your project is to modify the antigen to do which of the following?

a. to become an immunogen.

b. to overcome tolerance.

c. to overcome autoimmunity.

d. to ensure that it can bind to T cells as well as antibody.

e. to become a carrier.

2. In order to elicit an immune response, a carbohydrate must be which of the following?

a. degraded.
b. bound to a protein carrier.
c. administered intranasally.
d. made of polysaccharides.

3. Patients suffering from toxic shock syndrome are found to have which of the following
as the causative mechanism?

A. High levels of bacterial toxins.
B. Excessive levels of bacterial-specific antibodies.
C. Antigen-antibody complex formation.
D. Generation of bacterial-specific cytotoxic T cells.
E. Massive stimulation of helper T cells irrespective of antigenic specificity.

4. Which of the following explains a polyclonal immune response against a pathogen?
A. The pathogen is composed of a single antigenic determinant.
B. The pathogen contains multiple epitopes.
C. T cells produce cytokines.
D. Macrophages and neutrophils participate in the immune response.
E. The pathogen illicit T-cell dependent response.