Antigen and antigen recognition by lymphocytes

Antigen presentation to T lymphocytes

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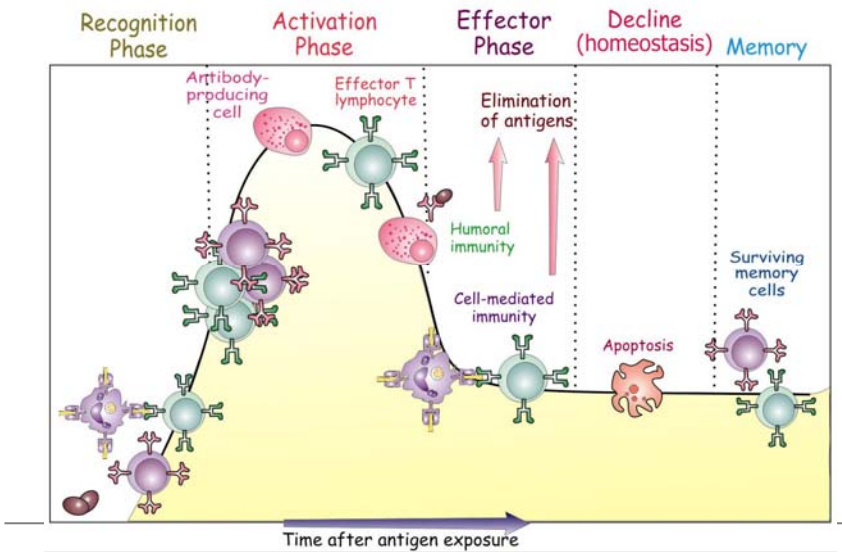
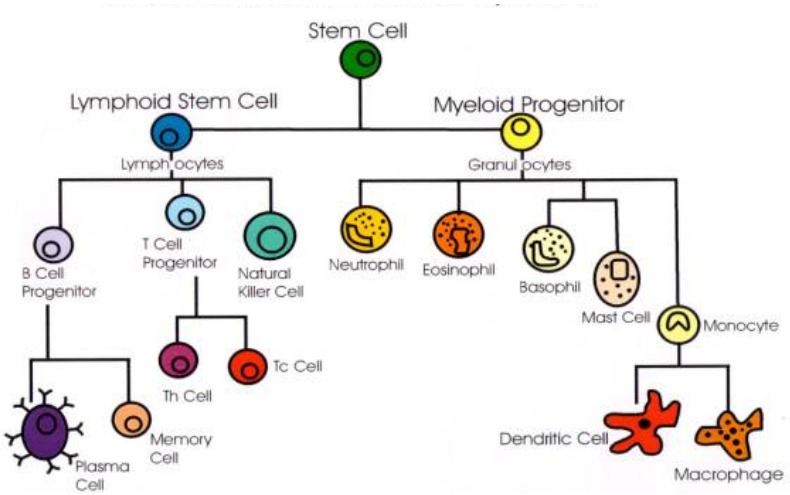
Phase of immune response



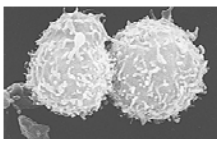
Phase of adaptive immunity

- Recognition phase
  - Antigen recognition
  - Antigen processing and presentation
- Activation phase
  - Lymphocyte activation
  - Proliferation and differentiation of effector cells
- Effector phase

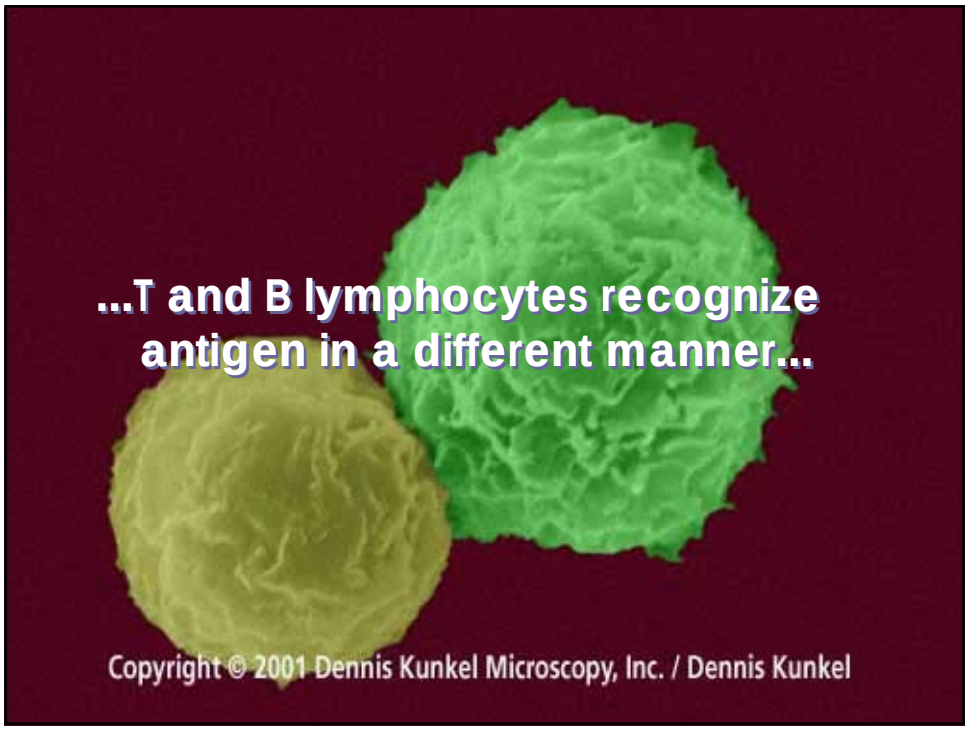
Cells of the immune system



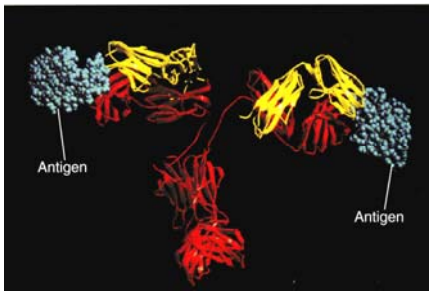
Lymphocyte classes

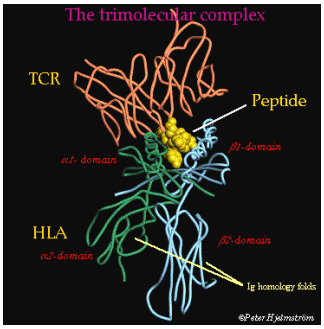


Class	Functions	Receptor	Marker
▪ B lymphocytes	HMI	sIg	FcR, MHC class II CD21, CD19
▪ T lymphocytes			
Helper T cell (Th)	- B cell activation (HMI) - induction& activation of CMI	αβ heterodimers	$CD3^+CD4^+CD8^-$
Cytotoxic T cell(CTL)	- Lysis of tumor/infected cells - Macrophage activation	αβ heterodimers	$CD3^+CD4^-CD8^+$
▪ Natural killer cells	- Lysis of tumor/infected cells - ADCC	Ig superfamily member	CD16 (IgG-FcR)



Antigen recognition by B and T lymphocytes





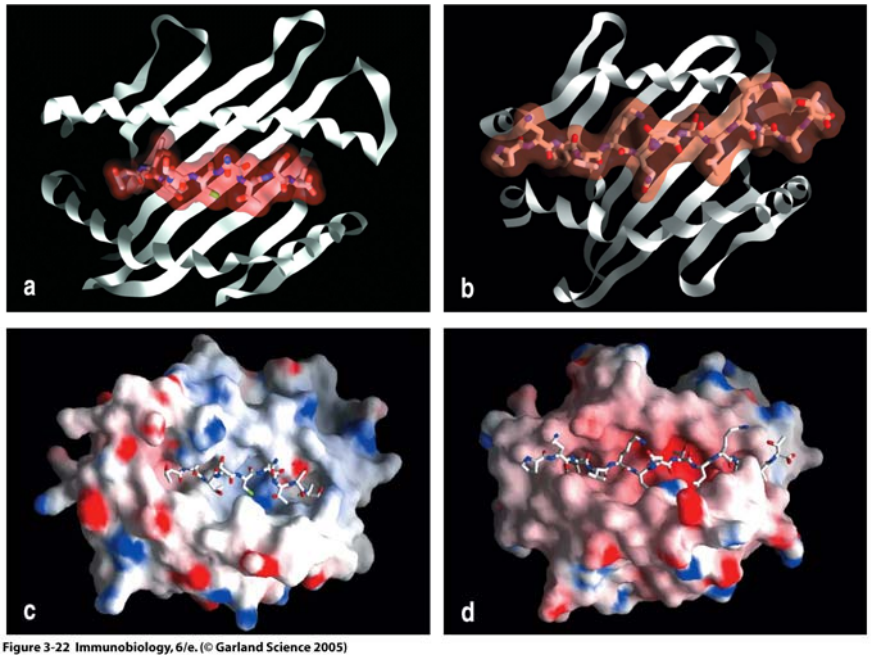
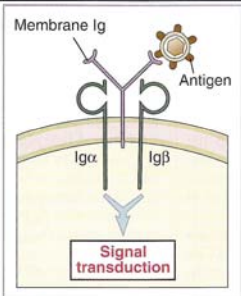
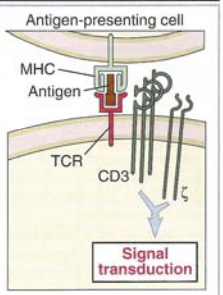
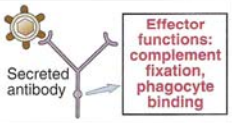
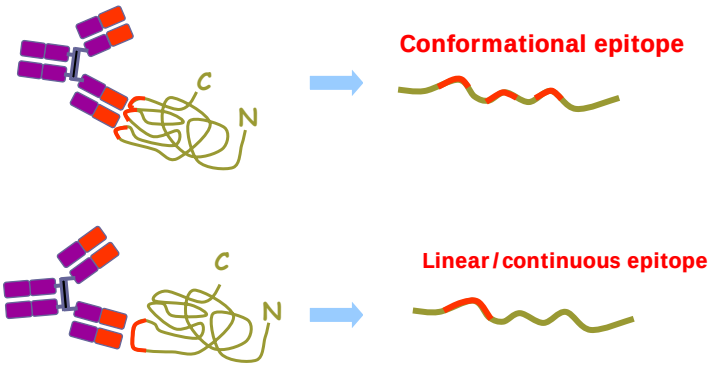


Figure 3-22 Immunobiology, 6/e. (© Garland Science 2005)

Feature or function	Antibody (Immunoglobulin)	T cell receptor (TCR)
		
		
Forms of antigens recognized	Macromolecules (proteins, polysaccharides, lipids, nucleic acids), small chemicals Conformational and linear epitopes	Peptides displayed by MHC molecules on APCs Linear epitopes

Abbas and Lichtman, 2004

Antigenic determinant



Antigen

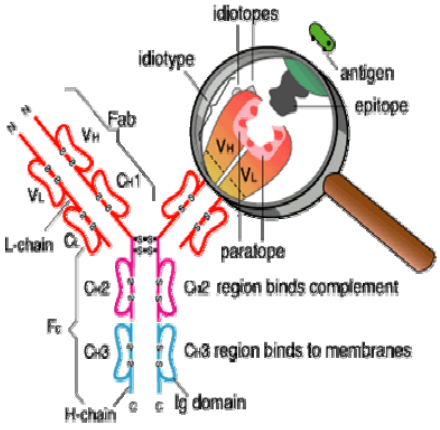
- Antigen: a substance that reacts with the products of specific immune response
- Immunogen: any substance that induces a specific immune response.

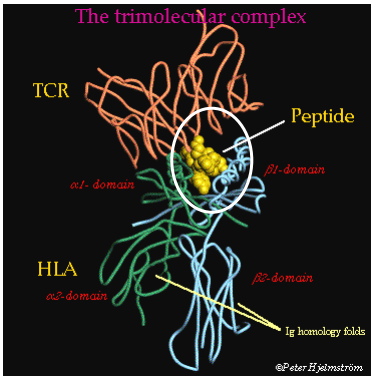
>>>> Not all antigens are immunogenic !! <<<<

Epitope (antigenic determinant)

- a site on an antigen recognized by an antibody or antigen receptor. A single protein antigen can have more than 1 epitopes.
- Immunodominant epitope:
  - A portion of an antigen that is recognized by the majority of the lymphocytes specific for that antigen
  - For T cells, immunodominant epitopes correspond to the peptides generated within APCs that bindmost avidly to MHC molecule and that are most likely to stimulate T cells

Epitope

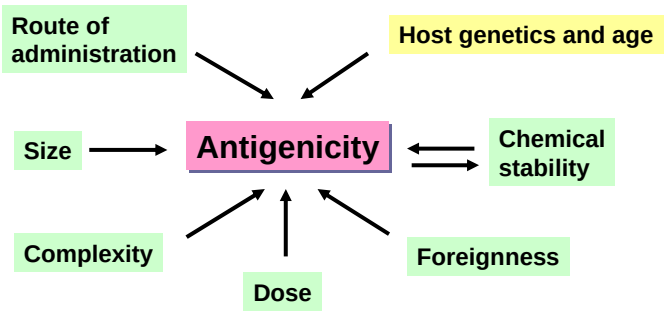




Hapten (Greek: haptein: to grasp, fasten)

- A small molecule (<1000 Da) that is non-immunogenic but which can react with the products of an adaptive immune response.
- Haptens are small molecules which could never induce an immune response when administered by themselves but which can when coupled to an antigenic molecule (carrier). Consequently, free haptens can react with products of the immune response after such products have been elicited.
- Haptens have the property of antigenicity but not immunogenicity.
- Example:
  - **Penicillin** >> Penicilloyl-albumin complex >> allergic response to penicillin
  - **Poison Ivy plant** >> Resin + skin protein >> skin protein attacked by lymphocytes (allergic contact dermatitis)

What makes a good antigen ?



Tizard, 2004

Factors that influence the immunogenicity of proteins

Parameter	↑ Immunogenicity	↓ Immunogenicity
Size	Large	Small (MW<2500)
Dose	Intermediate	High or Low
Route	Subcutaneous > Intraperitoneal > i.v. or intragastric	
Composition	Complex	Simple
Form	Particulate Denatured	Soluble Native
Similarity to self protein	Multiple difference	Few difference
Interaction with host MHC	Effective	Ineffective

Chemical nature of immunogens

- **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.
- **Polysaccharides** - Pure polysaccharides and lipopolysaccharides are good immunogens.
- **Nucleic Acids** - Nucleic acids are usually poorly immunogenic. However they may become immunogenic when they are single stranded or complexed with proteins.
- **Lipids** - In general lipids are non-immunogenic, although they may be haptens. Some glycolipids and phospholipids can stimulate T cells and produce a cell-mediated immune response.

Cross-reaction

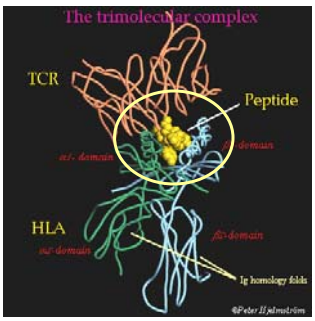
- Identical or similar epitopes may sometimes be found on apparently unrelated molecules. As a result, antibodies directed against one antigen may react unexpectedly with unrelated antigen.
  - Intestinal bacteria antigen A (in gr. O pig) x Blood group A antigen
  - *Yersinia enterocolitica* x *Brucella abortus*
  - TGE virus (pig) x FIP virus (cat)
- The epitopes on the 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 with similar protein in another species.
  - Antisera to bovine serum X sheep serum protein

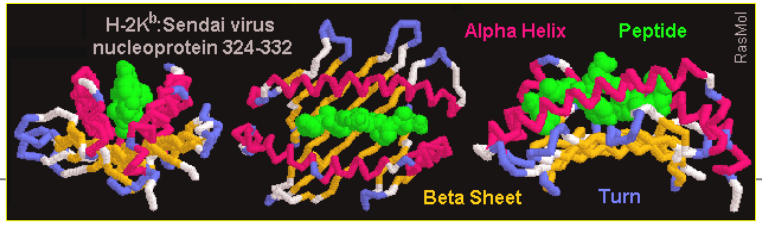
Type of antigens

- **T-independent Antigens (TI):** antigens which can directly stimulate the B cells to produce antibody without the requirement for T cell help.
  - Usually containmultiple identical epitopes that can cross-link antigen receptor of B cells and thereby activate them.
  - In general, polysaccharides are T-independent antigens.
- **T-dependent Antigens (TD):** antigens that do not directly stimulate the production of antibody without the help of T cells.
  - Structurally these antigens are characterized by a few copies of many different antigenic determinants
  - Proteins are T-dependent antigens.

Antigen recognition by T lymphocytes

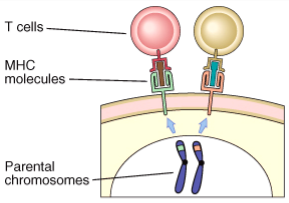
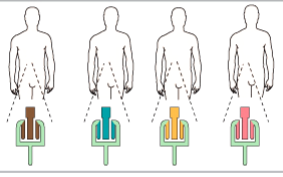
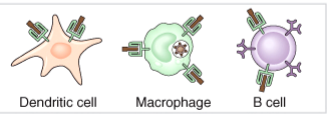
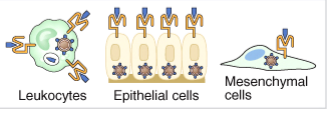
- T cells recognize "peptide" antigen presented in the context of Major Histocompatibility Complex (MHC) molecule on the cellular surface.





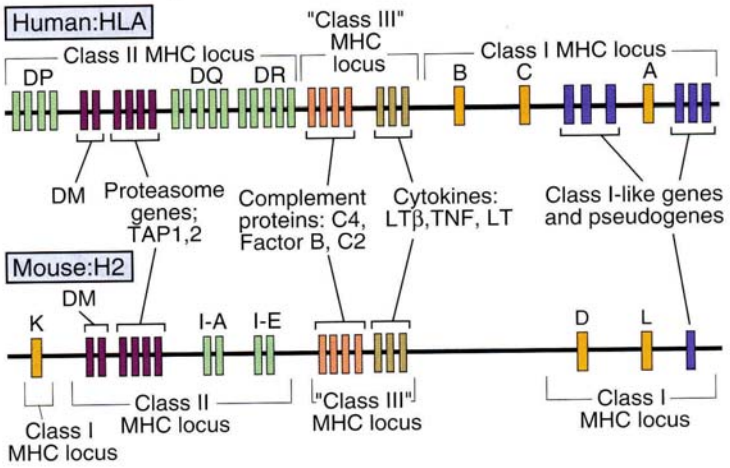
The major histocompatibility complex

- MHC = gene complex (Ir gene)
- Product = MHC molecules (surface glycoprotein)
- Highly polymorphic (several alleles/population)
- Co-dominant expression

Feature	Significance	
Co-dominant expression: Both parental alleles of each MHC gene are expressed	Increases number of different MHC molecules that can present peptides to T cells	
Polymorphic genes: Many different alleles are present in the population	Ensures that different individuals are able to present and respond to different microbial peptides	
MHC-expressing cell types: Class II: Professional APCs, macrophages, B cells	CD4+ helper T lymphocytes interact with dendritic cells, macrophages, B lymphocytes	
Class I: All nucleated cells	CD8+ CTLs can kill any virus-infected cell	

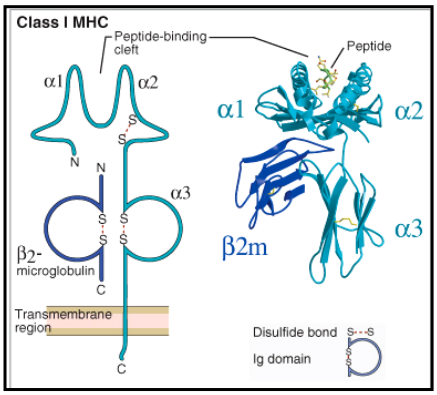
MHC complex

Haplotype: Combination of MHC alleles found on human chromosome

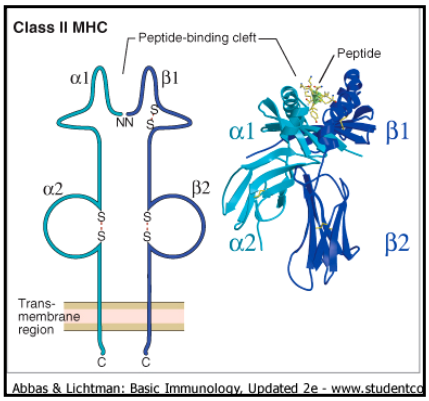


Abbas & Lichtman, 2004

MHC molecules

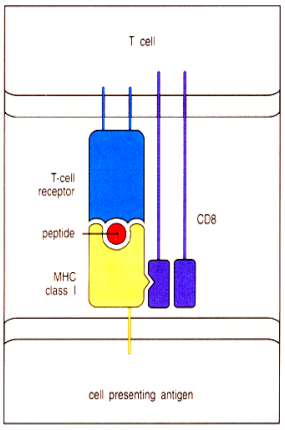


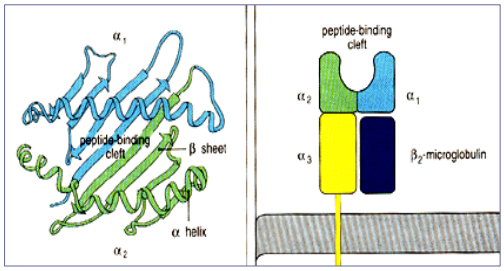
- peptide length = 8-10 amino acids with anchor residues



- varied peptide length 13-17 amino acids

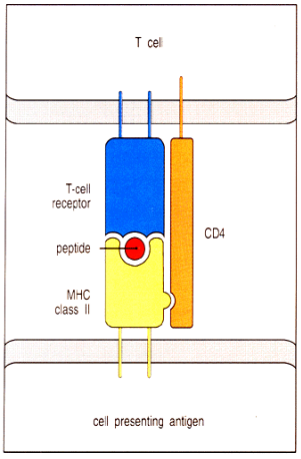
MHC class I molecule

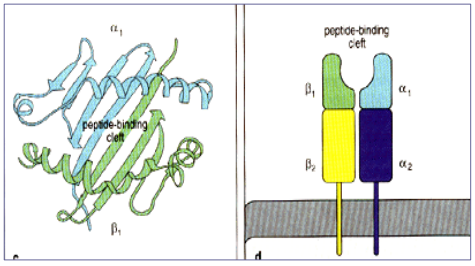




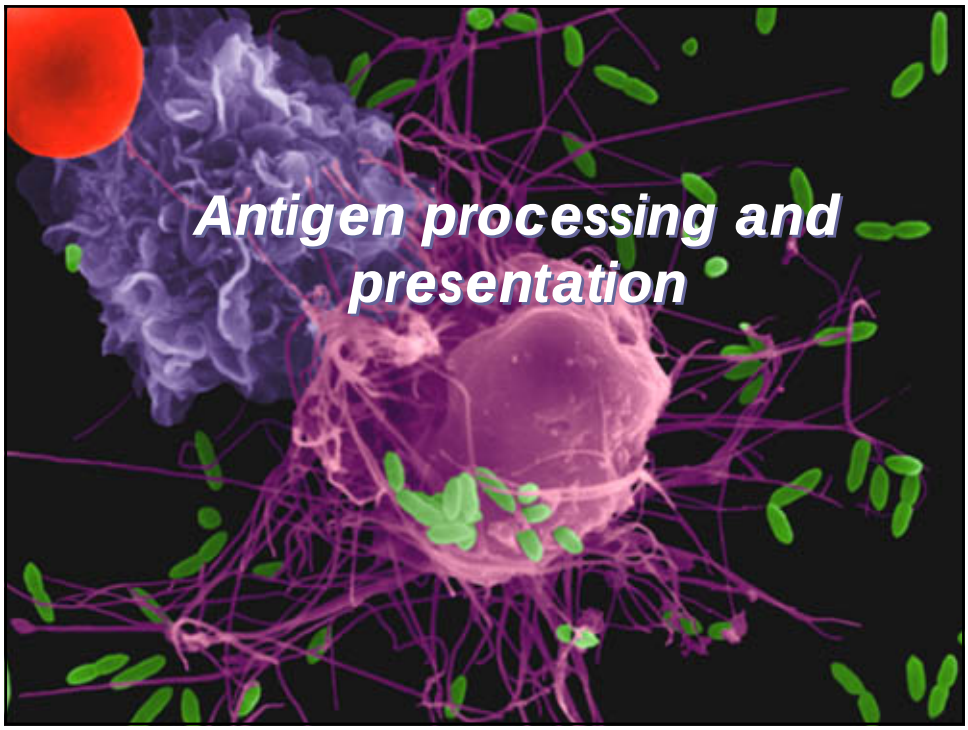
- α-chain + β_2-microglobulin
- peptide length = 8-10 amino acids with anchor residues

MHC class II molecule





- α-chain + β-chain
- varied peptide length = 13-17 amino acids



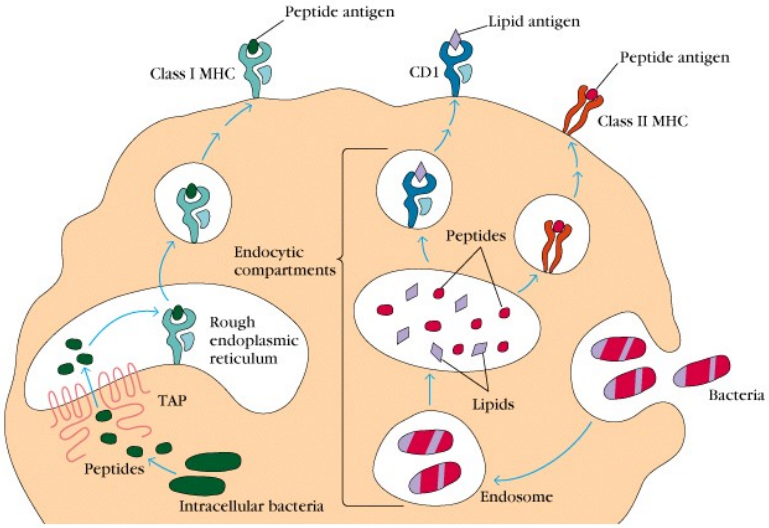
MHC molecule and Ag presentation

TYPE	Expression	Antigen	T cell
class I	All nucleated cells	endogenous antigen	$CD8^+$ Tcell
class II	- APC - Thymic epithelial cells	exogenous antigen	$CD4^+$ Tcell

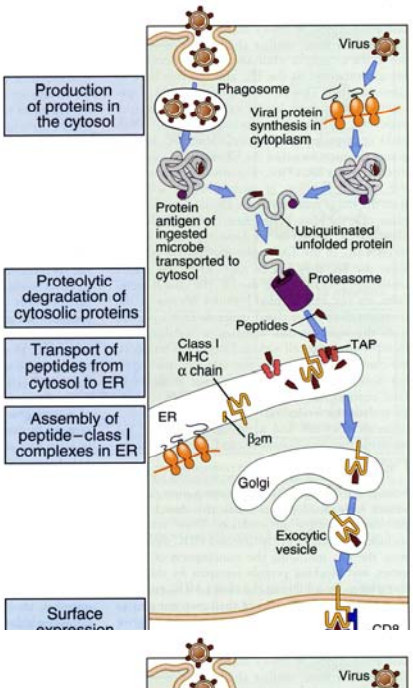
Tissue	MHC class I	MHC class II
Lymphoid tissues		
T cells	+ + +	+*
B cells	+ + +	+ + +
Macrophages	+ + +	+ +
Other antigen-presenting cells (eg Langerhans' cells)	+ + +	+ + +
Epithelial cells of the thymus	+	+ + +
Other nucleated cells		
Neutrophils	+ + +	–
Hepatocytes	+	–
Kidney	+	–
Brain	+	–†
Non-nucleated cells		
Red blood cells	–	–

Figure 3-19 Immunobiology, 6/e. (© Garland Science 2005)

Overview of antigen processing and presentation



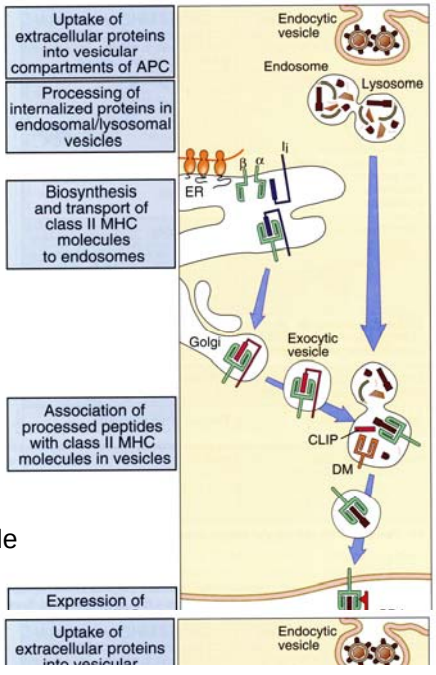
Processing of endogenously produced Ag



TAP: Transporter associated with antigen processing

Abbas & Lichtman, 2004

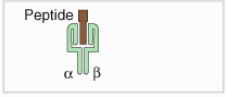
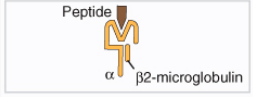
Processing and presentation of exogenously produced Ag by MHC class II molecule



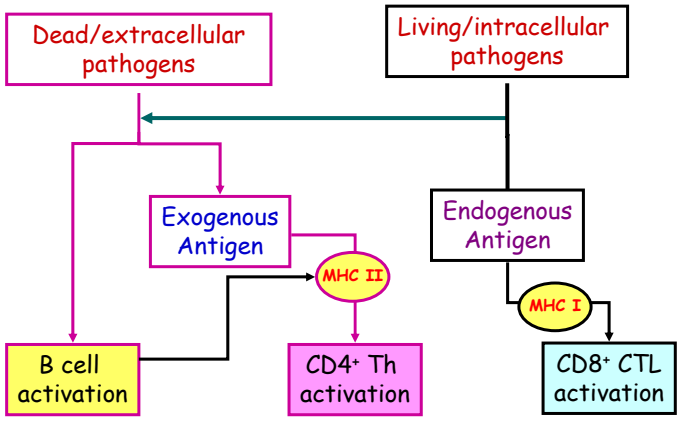
Ii: Invariant chain

CLIP: Class II invariant chain peptide

Abbas & Lichtman, 2004

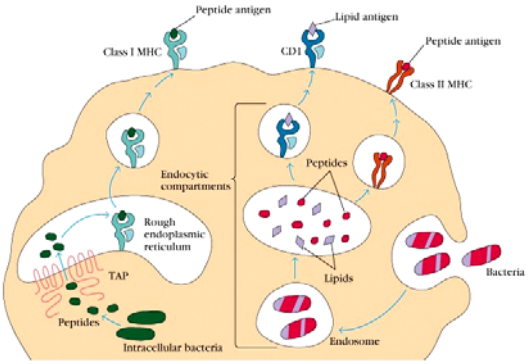
Feature	Class II MHC Pathway	Class I MHC pathway
Composition of stable peptide-MHC complex	Polymorphic α and β chains, peptide 	Polymorphic α chain, β2-microglobulin, peptide 
Types of APCs	Dendritic cells, mononuclear phagocytes, B lymphocytes; endothelial cells, thymic epithelium	All nucleated cells
Responsive T cells	$CD4^+$ T cells (mostly helper T cells) 	$CD8^+$ T cells 
Source of protein antigens	Endosomal/lysosomal proteins (mostly internalized from extracellular environment)	Cytosolic proteins (mostly synthesized in the cell; may enter cytosol from phagosomes)
Enzymes responsible for peptide generation	Endosomal and lysosomal proteases (e.g., cathepsins)	Cytosolic proteasome
Site of peptide loading of MHC	Specialized vesicular compartment	Endoplasmic reticulum
Molecules involved in transport of peptides and loading of MHC molecules	Invariant chain, DM	TAP

Type of immune responses depends on the nature of the antigen.



Antigen processing and presentation

- Th recognizes peptide on MHC class II molecule.
- CTL recognizes peptide on MHC class I molecules.
- Each MHC molecules has different pathway of antigen processing and presentation.
- Endogenous Ag >> Class I
- Exogenous Ag >> Class II



Cross presentation

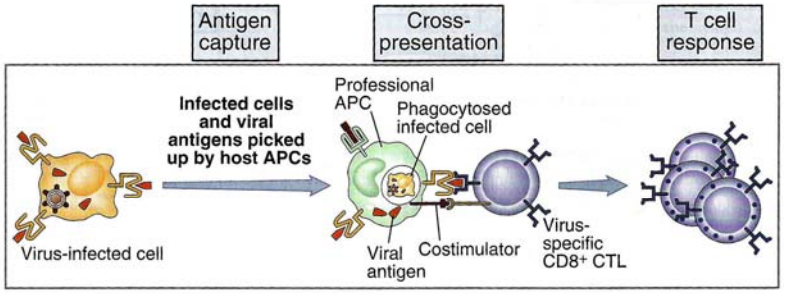


Figure 3–5 Cross-presentation of microbial antigens from infected cells by professional APCs. Cells infected with intracellular microbes, such as viruses, are ingested (captured) by professional APCs, and the antigens of the infectious microbes are broken down and presented in association with the MHC molecules of the APCs. T cells recognize the microbial antigens and costimulators expressed on the APCs, and the T cells are activated. In this example, we show CD8+ T cells (CTL) recognizing class I MHC–associated antigens; the same cross-presenting APC may display class II MHC–associated antigens from the microbe for recognition by CD4+ helper T cells.

Cross presentation of exogenous antigen to CTL by professional APCs.
- Recycle antigen from apoptotic cells
- Antigen delivery via some PRRs, Bacterial endotoxin, heat shock proteins