Antigen recognition by T and B cells

- T and B cells exhibit fundamental differences in antigen recognition

- B cells recognize antigen free in solution (native antigen).

- T cells recognize antigen after it has been phagocytosed, degraded and small pieces of the antigen have been bound by MHC molecules.

Role of Antigen-Presenting Cells (APC)

- Helper T cells: recognize antigen after processing and presentation by MHC-II on APC (dendritic cells, macrophages, B cells).

- Cytotoxic T cells: recognize antigen when it is presented on MHC-I.

- Since most nucleated cells in the body express class I MHC, most cells in the body can present antigen to cytotoxic T cells. Although they are presenting antigen, these cells are usually not referred to as "antigen-presenting cells". If they are presenting antigen that will cause them to be killed by cytotoxic T cells, they are referred to as "target cells".

Antigen presenting cells

- **Remember: 1) MHC-II, 2) deliver co-stimulatory signals**
- **Professional APC: DC> MΦ > B cells, why?**
- **DC: Always express high levels of MHC-II molecules and co-stimulatory activity (B7 molecule)**
- **MΦ: requires activation to up-regulate MHC-II molecules and co-stimulatory molecules (B7 molecules)**
- **B cells: always express MHC-II molecules but needs to be activated to express co-stimulatory activity (B7 molecule)**

Professional vs Non-Professional APCs

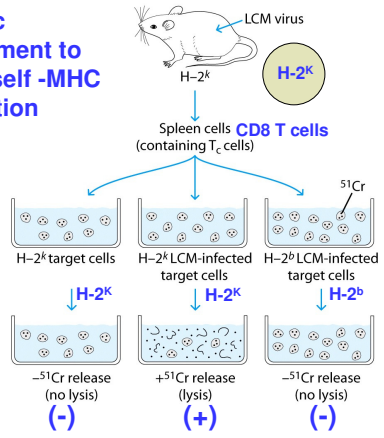
TABLE 8-1 Antigen-presenting cells

Professional antigen-presenting cells	Nonprofessional antigen-presenting cells	
Dendritic cells (several types)	Fibroblasts (skin)	Thymic epithelial cells
Macrophages	Glial cells (brain)	Thyroid epithelial cells
B cells	Pancreatic beta cells	Vascular endothelial cells

Self MHC Restriction

- Both MHC-I and MHC-II molecules can only recognize antigens when presented by SELF-MHC molecules.
- No value for individual to have T cells that recognize foreign antigen associated with foreign MHC
- Self MHC restriction occurs in thymus

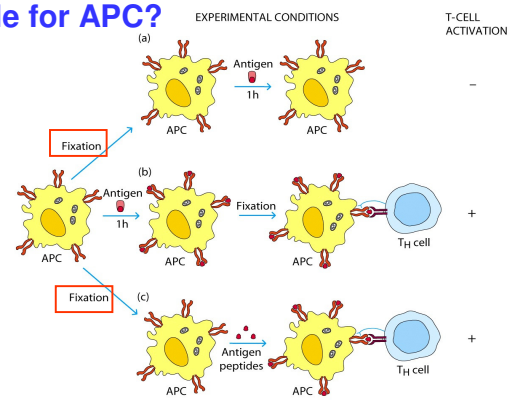
Classic Experiment to show self -MHC restriction



Ag processing is required

- Classical experiment showing that B and T cells have different requirement for antigen recognition.
- Processing is required for Th activation
- Processing is a metabolic active process

Role for APC?



Points Concerning Antigen Processing and Presentation

1. Location of pathogen
- viruses in cytosol, MHC class I pathway, Tc response (**Cytosolic pathway**)
- extracellular bacteria, MHC class II pathway, Th2 response → Ab formation (**Endocytic pathway**)
- intracellular bacteria, MHC class II pathway, Th1 response → cellular response (Endocytic)

Points Concerning Antigen Processing and Presentation

2. Peptides derived from both self and non-self proteins can associate with MHC class I and class II molecules.
3. Chemical nature of MHC groove determines which peptides it will bind.

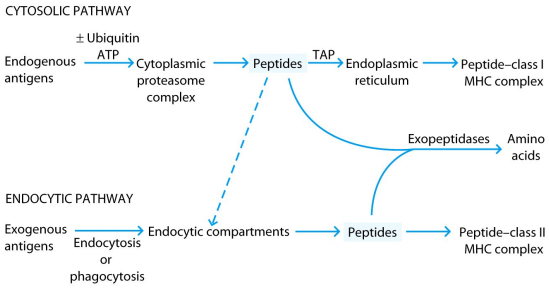
MHC-I and MHC-II associated with peptides processed in different intracellular compartments

A) Class I MHC binds peptides derived from endogenous antigens

B) Class I MHC binds peptides from antigens that have been processed via the cytosolic pathway (derived from the cytoplasm of the cell)

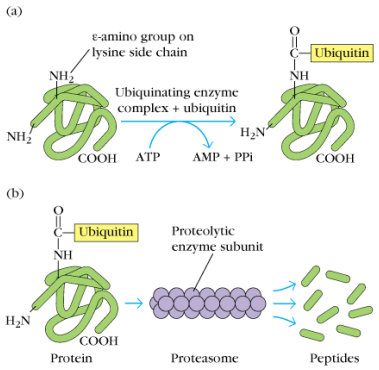
C) Class II MHC molecules bind peptides derived from exogenous antigens. These antigens were internalized by phagocytosis or endocytosis.

D) These peptides are said to have been processed within the endocytic pathway.



Endogenous Pathway

- Peptides are generated by proteasome degradation
- Peptides are transported from cytosol to the RER
- Peptides loading onto MHC-I is aided by chaperones



Kuby Figure 8-5

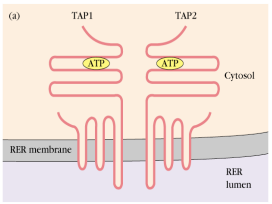
- **Size**
- **Hydrophobicity**

- The cytosolic antigen processing pathway - 2. The role of the **TAP (Transporter associated with Antigenic Processing).**

- Peptides from proteasome degradation of cytoplasmic proteins are transported across the membrane of the rough endoplasmic reticulum by a heterodimeric protein designated as TAP.

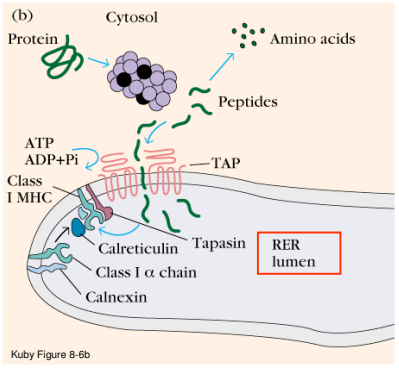
- **TAP** is composed of two subunits - **TAP1 and TAP-2**
- TAP-mediated transport is **ATP-dependent**

The genes for TAP1 and TAP2 are encoded within the MHC.



Kuby Figure 8-6a

The cytosolic antigen processing pathway - 3. Assembly of the class I-peptide complex



Kuby Figure 8-6b

1. The class I alpha chain is stabilized by calnexin.

2. When the alpha chain binds beta-2-microglobulin:
- **calnexin is lost**
- **calreticulin and tapasin bind**

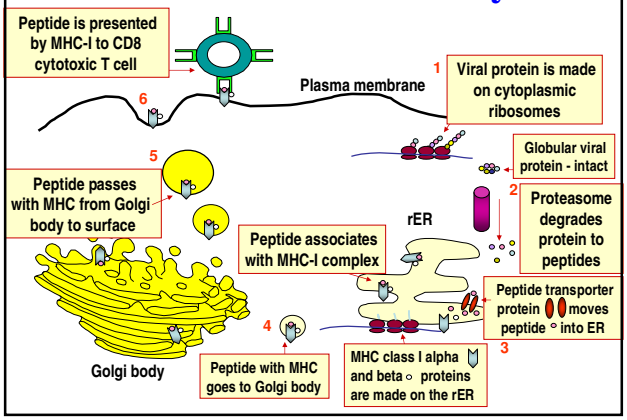
3. Tapasin & calreticulin brings the class I molecules into the vicinity of the TAP.

4. A cytoplasmic peptide transported through the TAP is loaded onto the class I molecule.

5. Class I MHC dissociates from calreticulin and tapasin.

Class I MHC-peptide complex is transported to Golgi and to the cell surface.

Class I MHC Pathway

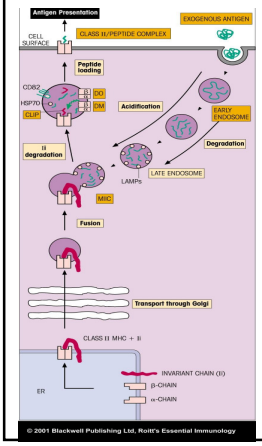


Class II Processing:

- The endocytic antigen processing pathway – processing of externally-derived peptides

- Antigen can be taken into cells by various means: phagocytosis, endocytosis, pinocytosis, receptor-mediated endocytosis

- Antigen taken up in these ways passes through a series of intracellular compartments of increasing acidity - early endosome (pH 6.5-6.0), late endosome (pH 6.0-5.0), phagolysosome (pH <5.0)



The endocytic antigen processing pathway - processing of externally-derived peptides

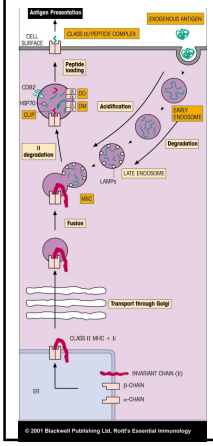
Three major events occur in the endosomal pathway:

1) Degradation of material that was taken in – endosome goes through acidification and fusion with lysosome which contain a wide array of degradative enzymes

2) Loading of peptides from this material on to class II MHC molecules

3) Transport of class II MHC - peptide complexes back to the cell surface

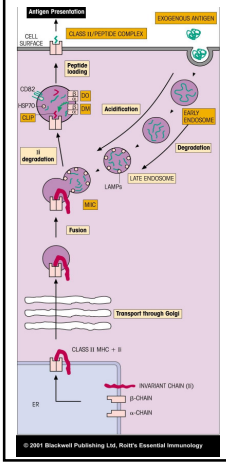
Figure 5-18



The endocytic antigen processing pathway - processing of externally-derived peptides

The endosomal compartment is completely separate from the endoplasmic reticulum ---> So, externally derived peptides are usually not loaded on to MHC-I.

Figure 5-18



The endocytic antigen processing pathway - processing of externally-derived peptides

Class II MHC is synthesized in the ER, but is not loaded with peptides there because it's peptide binding site is blocked by the invariant chain (Ii).

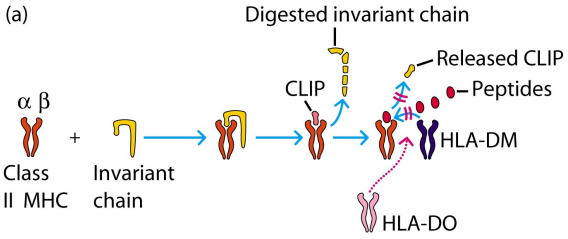
Once class II MHC enters the endosomal compartments, the invariant chain is degraded, leaving a small fragment - CLIP - in the peptide binding site.

CLIP is removed by HLA-DM, which loads a peptide on to class II MHC

HLA-DO inhibits HLA-DM until the cell is activated

Figure 5-18

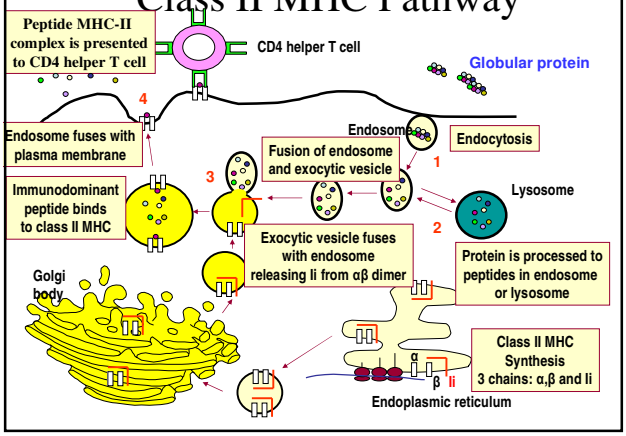
Invariant Chain- guides transport to endocytic Vesicles



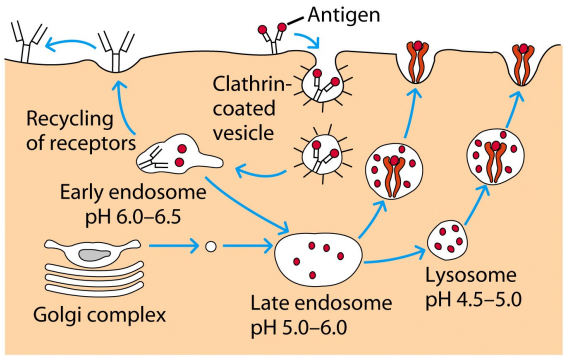
CLIP= Class II-associated invariant chain peptide

HLA-DM – mediates exchange
HLA-DO – inhibits HLA-DM

Class II MHC Pathway

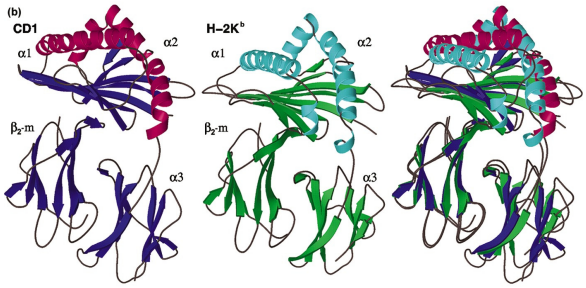


Receptor (Ab)-Mediated Endocytosis



Presentation of Non-Peptide Antigens

- CD1 molecules (CD1a-d)
- Structurally related to MHC-I
- Encoded outside the MHC region
- Present in APC (DC>MØ>B cells)
- Presents peptides of 12-22 aa in size
- Presents to CD4, CD8 and NK cells
- Present LIPIDS and glycolipids



The End!