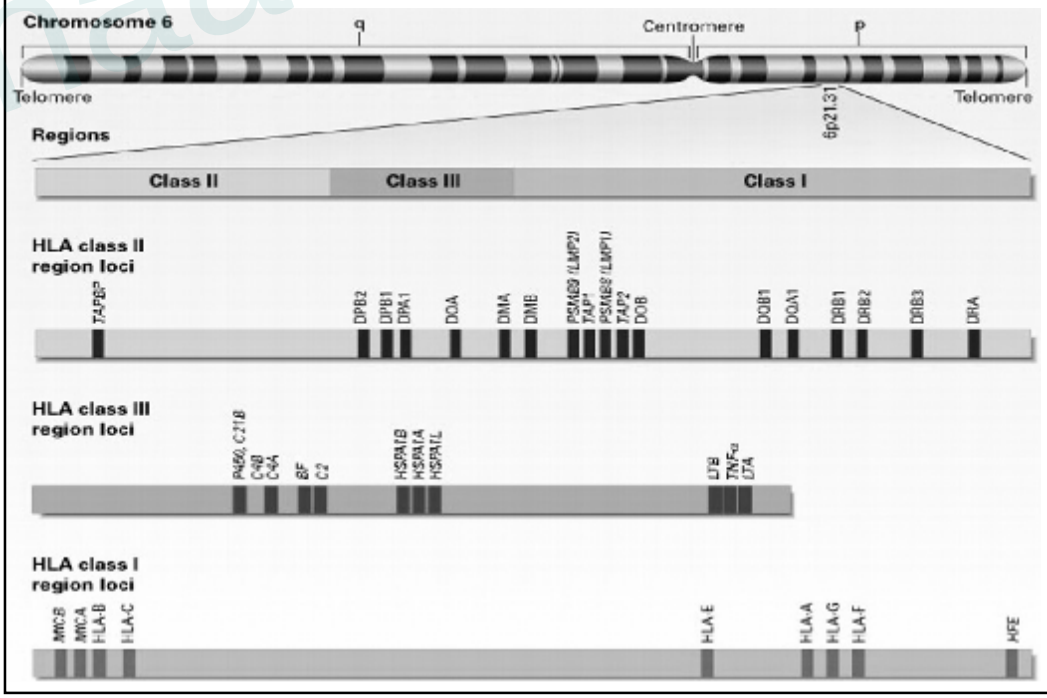
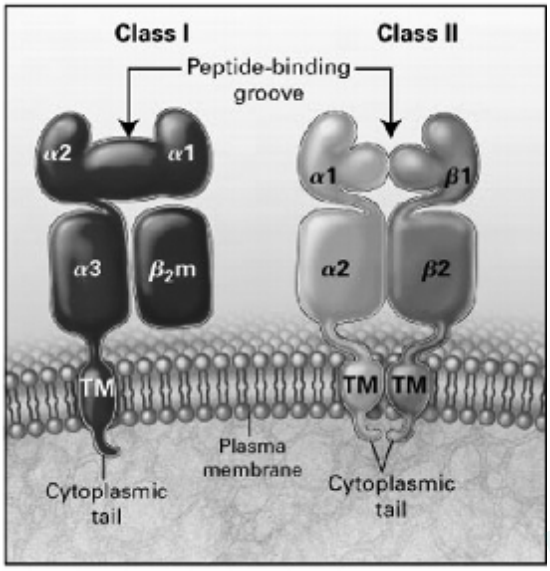
Major histocompatibility complex (MHC)

the HLA Complex on Chromosome 6



Structure of HLA Class I and Class II Molecules



Klein J and Sato A. N Engl J Med 2000;343:702-709

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Structure of MHC class I

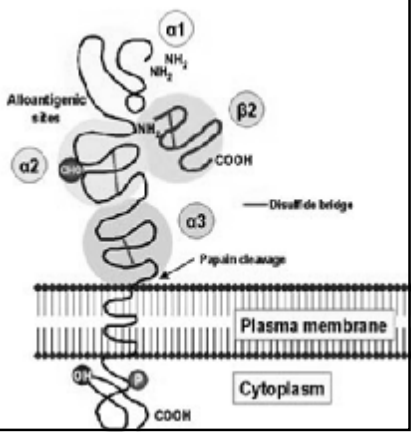
Two polypeptide chain : long α chain short β

- Cytoplasmic contains sites for phosphorylation
- Transmembrane contains hydrophobic AAs
- Highly conserved α3 domain binds CD8
- Highly polymorphic *antigen binding groove* formed by α1 and α2

B2-Microglobulin

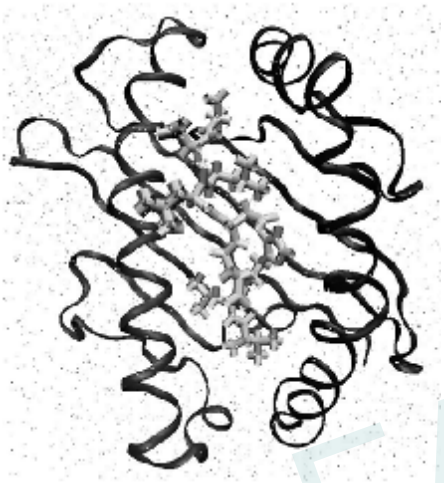
is essential for expression of MHC class I

is non-polymorphic in humans



Structure of MHC class I Ag-binding groove

- Groove composed of
  - α helix on 2 opposite walls
  - Eight β sheets as floor
- Residues lining floor are most polymorphic
- Groove binds peptides 8-10 AA long



Non-classical MHC genes MHC class Ib genes

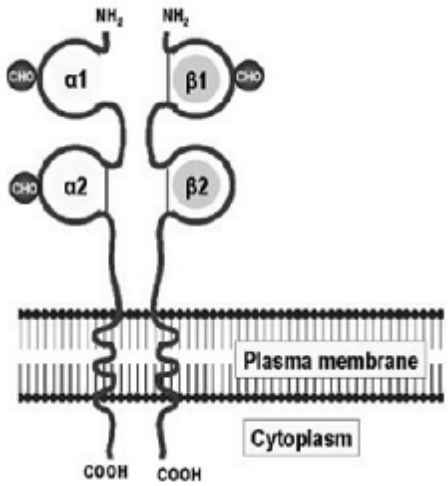
- HLA-E, HLA-F, HLA-G, *and* HLA-H
- They are much less polymorphic than the A, B,C
- HLA-G is expressed on fetus-derived placental cells
- HLA-F is expressed in a variety of tissues
- Involved in recognition by NK cells

CD1

- MHC class 1-like molecules
- is encoded outside the MHC genes
- presents microbial lipids to CD1-restricted T cells.

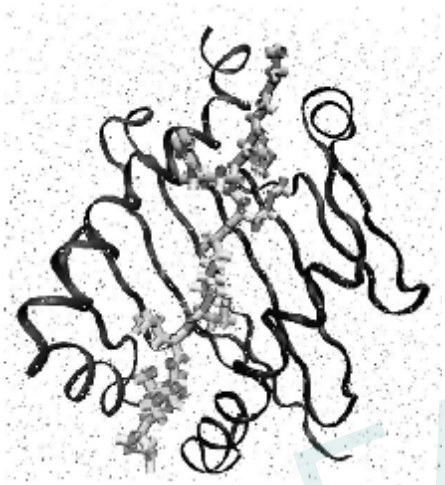
Structure of MHC class II

- Two polypeptide chains α and β
  - approx equal length
  - Cytoplasmic contains sites for phosphorylation and binding to cytoskeleton
  - Transmembrane contains hydrophobic AAs
  - Highly conserved α2 and β2 domains binds CD4
  - Highly polymorphic peptide binding region formed by α1 and β1



Structure of MHC class II Ag-binding groove

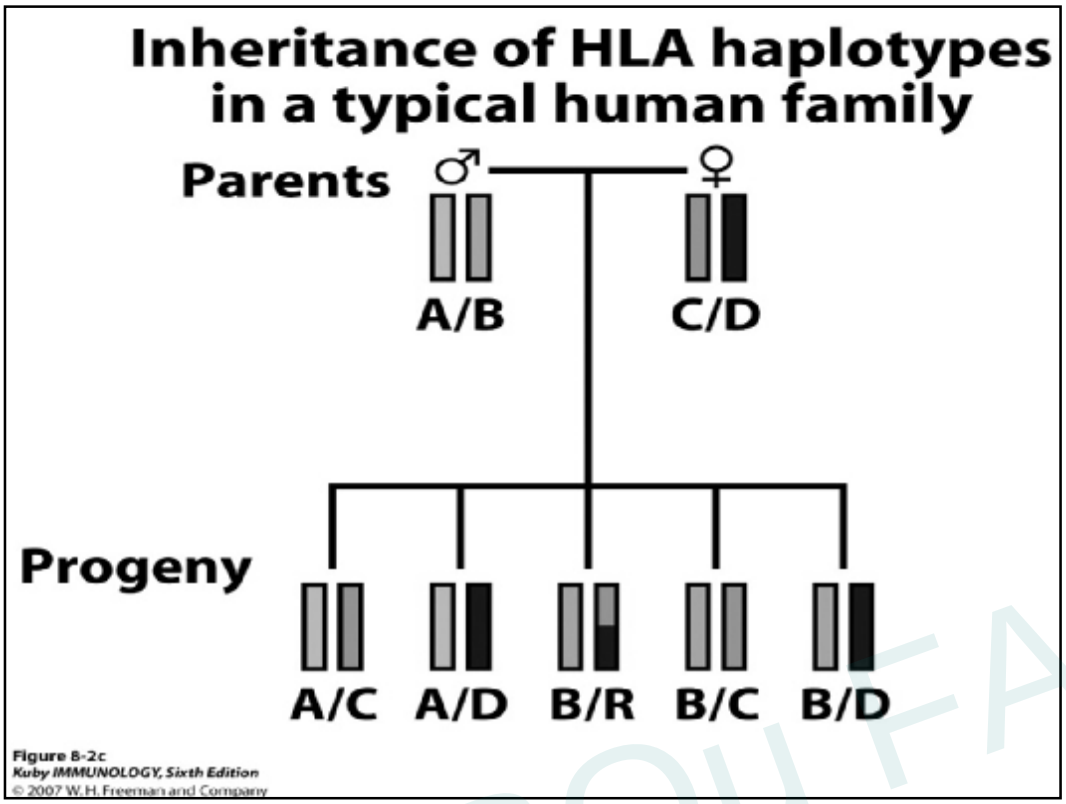
- Groove composed of
  - α helix on 2 opposite walls
  - Eight β sheets as floor
  - Both α1 and β1 make up groove
- Residues lining floor are most polymorphic
- Groove binds peptides 13-25 AA long (some outside groove)

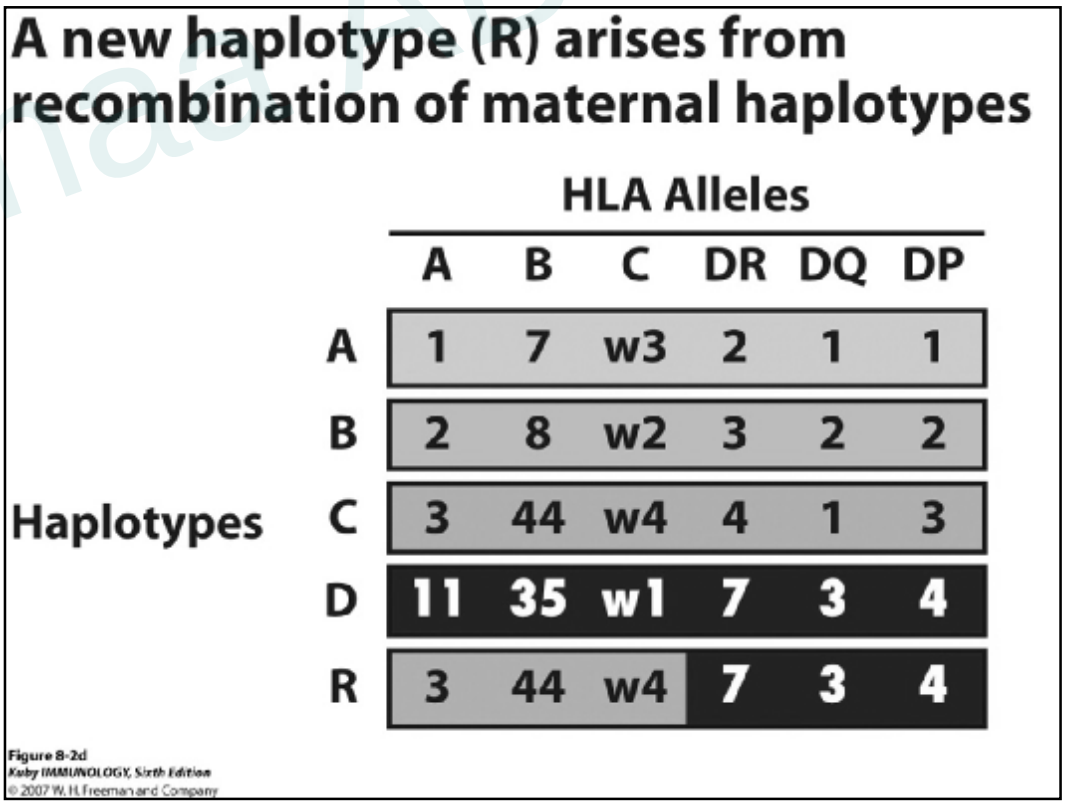


Distribution of MHC Class I and Class II

Tissue/cell	MHC class I	MHC class II
Hematopoietic		
T cells	+++	+*
B cells	+++	+++
Macrophages	+++	++
Dendritic cells	+++	+++
Neutrophils	+++	–
Erythrocytes	–	–
Non-hematopoietic		
Thymic epithelium	+	+++
Liver hepatocytes	+	–
Kidney epithelium	+	–
Brain	+	–†

Figure 5.23 The Immune System, 3ed. (© Garland Science 2009)





Codominant expression

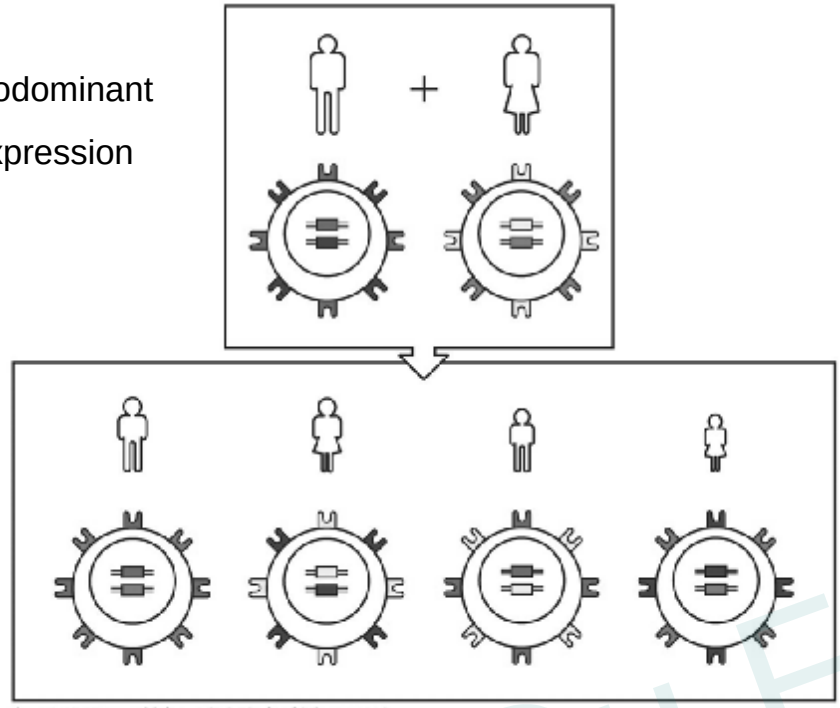


Figure 5-14 Immunobiology, 6/e. (© Garland Science 2005)

Important aspects of MHC

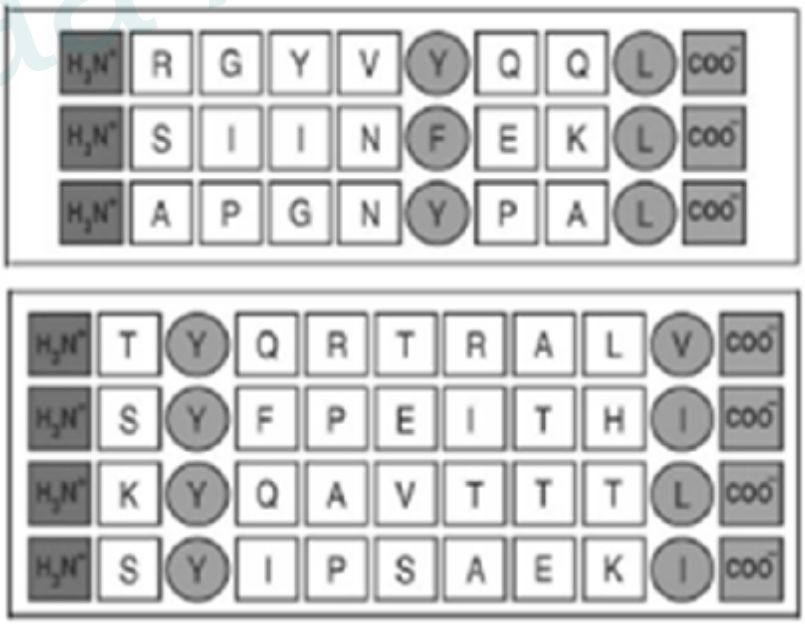
- Each MHC has <u>ONE</u> peptide binding site
  - But each MHC can bind many different peptides
  - Only one at a time
- MHC polymorphism is determined in germline
  - <u>NO</u> recombination mechanisms for creating diversity in MHC
- Peptide must bind with individual's MHC to induce immune response

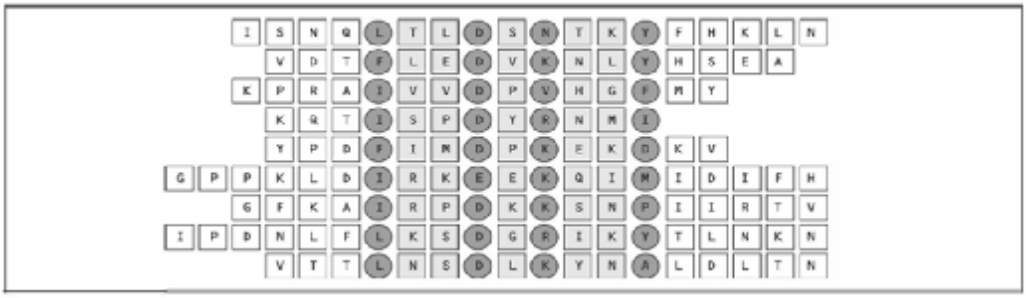
PEPTIDES AND MHC

Peptides are stably bound to MHC molecules, stabilize the MHC molecule on the cell surface.

a wide variety of pathogens, whose proteins will not generally have peptide sequences in common.

If T cells are to be alerted to all possible infections, the MHC molecules on each cell (both class I and class II) must be able to bind stably to many different peptides.





Peptides that bind MHC class II molecules are variable in length

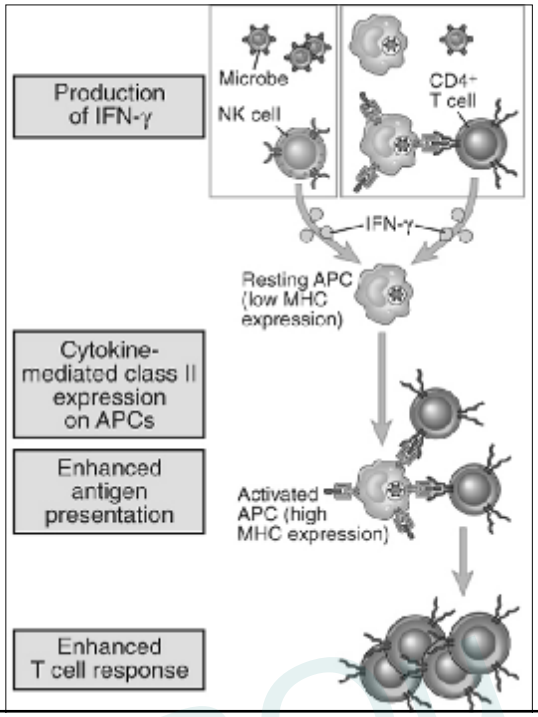
Anchor residues lie at various distances from the ends of the peptide..

All contain the same core sequence (shaded) but differ in length.

Important aspects of MHC

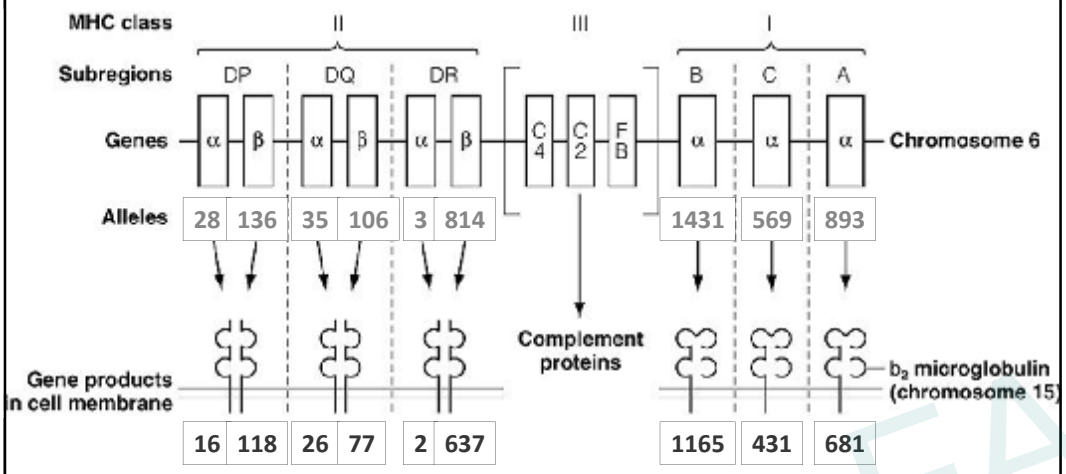
- MHC molecules are membrane-bound
  - Recognition by T requires cell-cell contact
- Mature T must have TCR that recognizes particular MHC
- Cytokines (especially IFN-γ) increase expression of MHC

Enhancement of class II MHC expression by IFN-γ



Why so much polymorphism?

Polymorphism of the Major Histocompatibility Complex



MHC polymorphism ensures that all individuals in a species are not equally susceptible to an infection

Antigen process and presentation

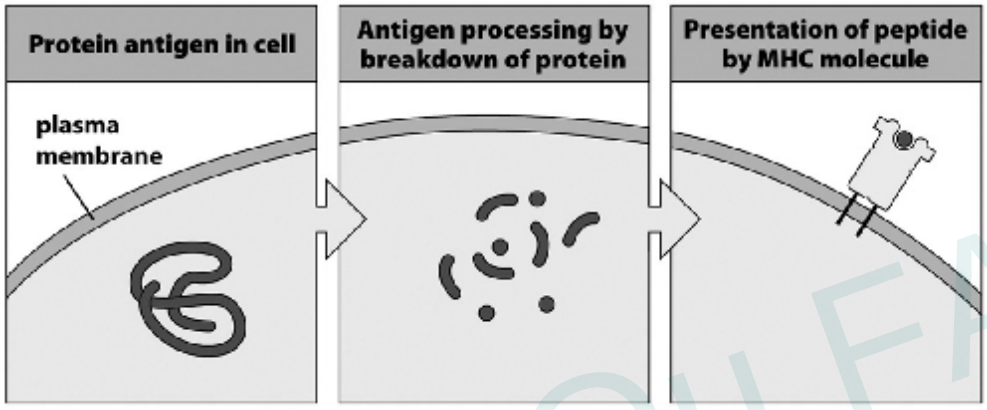
Ag processing and presentation

- **Ag processing**
  - Ability of APC to breakdown Ag into peptides and associate them with MHC.
- **Ag presentation**
  - Process of displaying peptide Ag in context of MHC to T cell

Antigen processing and presentation

- Produces peptides suitable for presentation by Class I and Class II

  - ❑Virus and tumor peptides -> Class I presentation -> T-cytotoxic cells
  - ❑“extracellular” antigens -> Class II presentation -> T-helper cells



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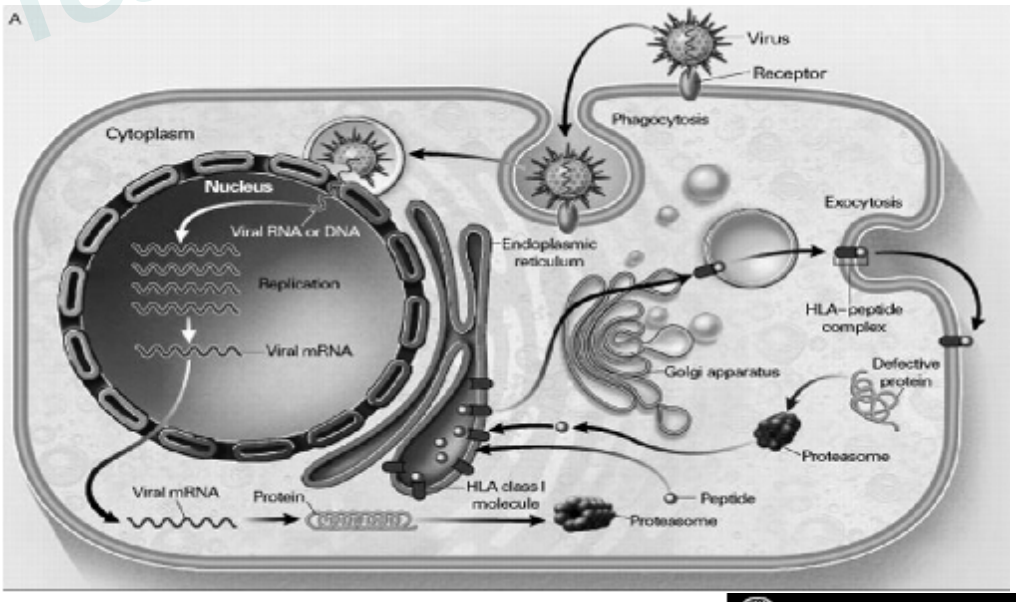
Antigen Processing
MHC class I



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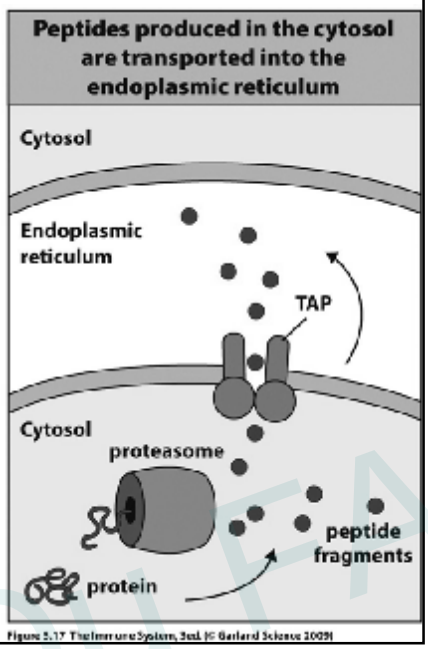
Peptides are moved into ER through TAP

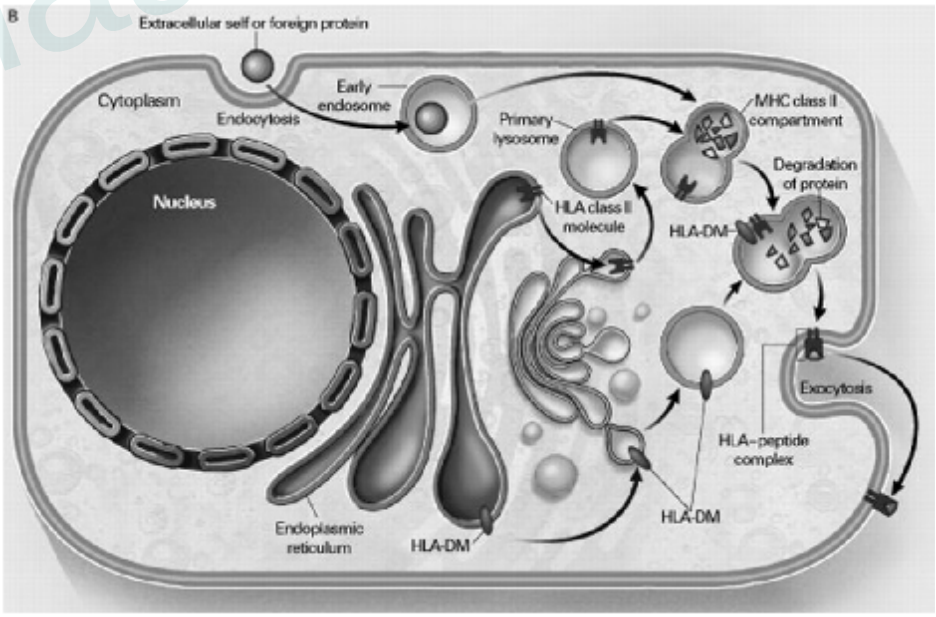
Protein degradation into MHC Class I peptides

- (**T**ransporter associated with **a**ntigen **p**rocessing)
- TAP favors transport of peptides
- suitable for Class I



- **Non-functional TAP**
  - No MHC Class I presentation
  - No stimulation of T-cytotoxic cells

Antigen Processing
MHC class II



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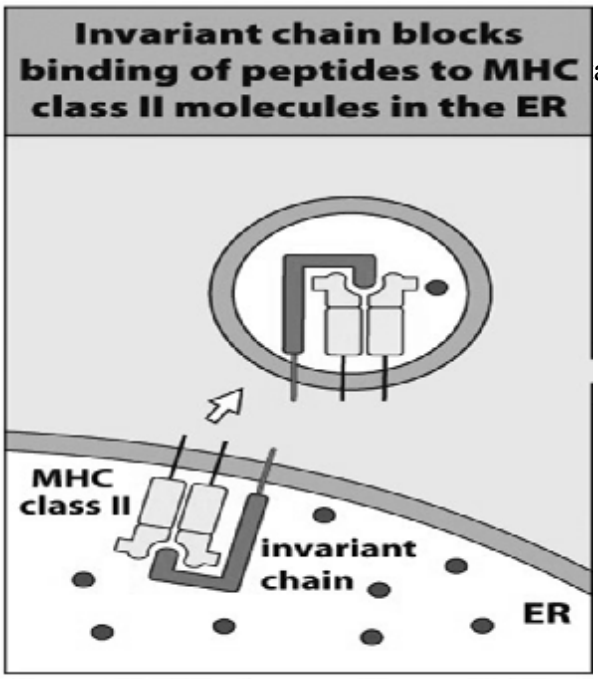

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Figure 5.21 The Immune System, 3ed. (© G

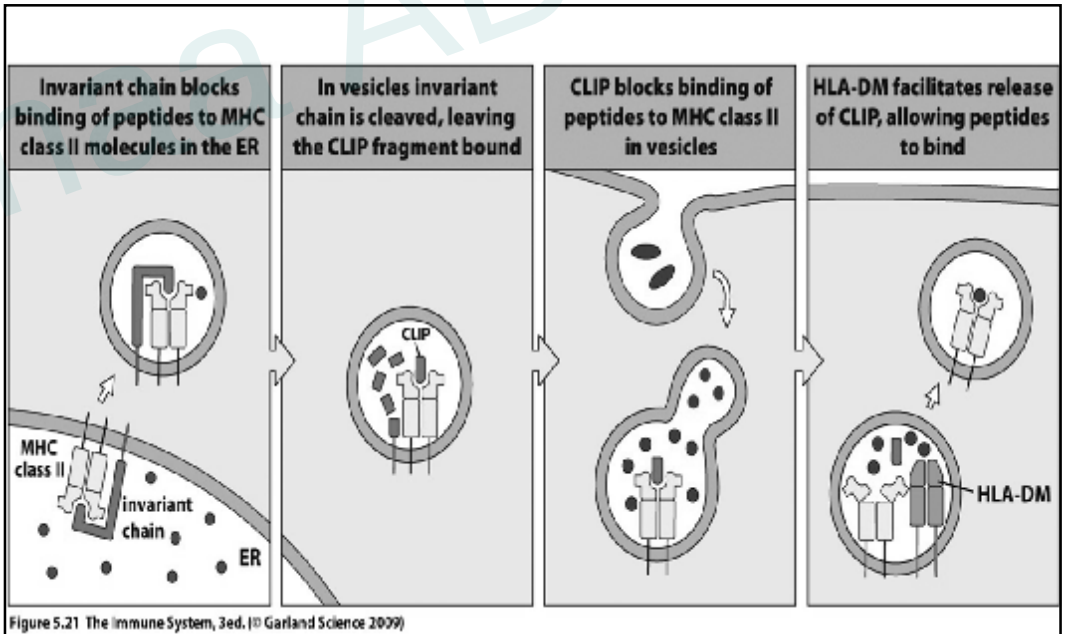

Figure 5.21 The Immune System, 3ed. (© Garland Science 2009)

CLIP – class II invariant chain peptide