Basic Immunology

Lecture *3rd and 4th*

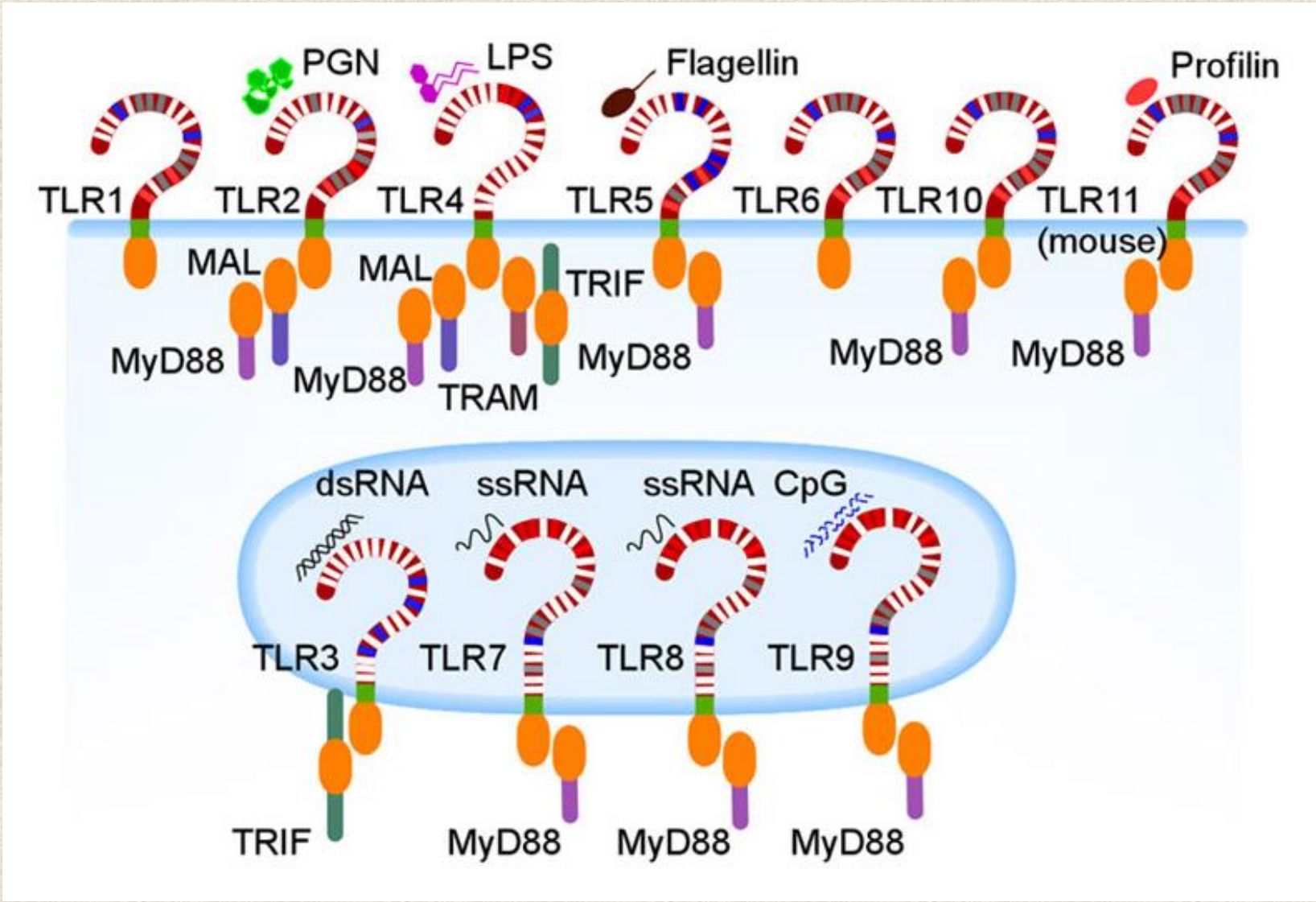
Recognition molecules.

Recognition and antigen presentation by MHC.

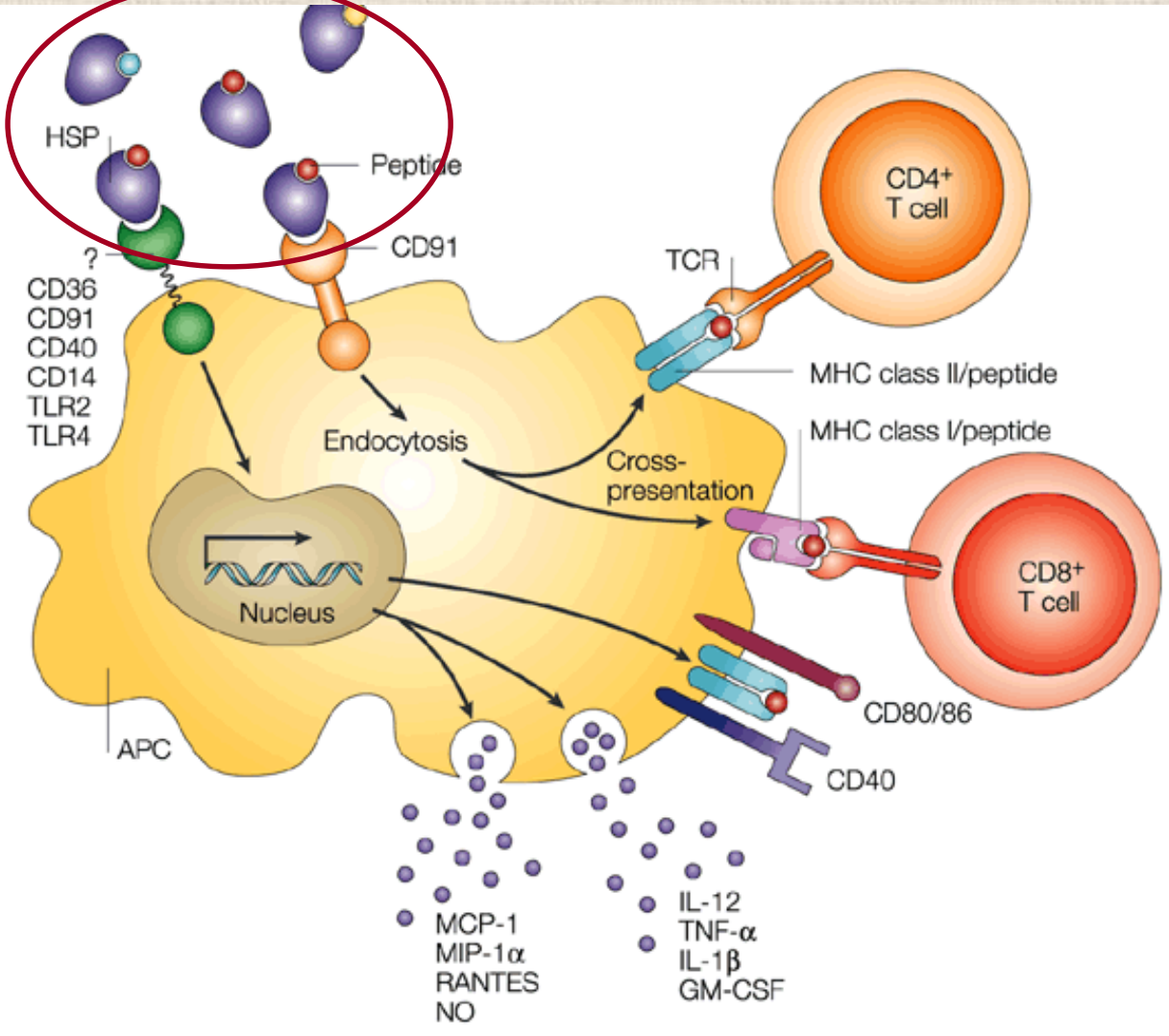
Molecular structure, genetics, classes and their functions of MHC. Antigen presentation and MHC restriction. Superantigens and septicemia.

Immunological recognition molecules

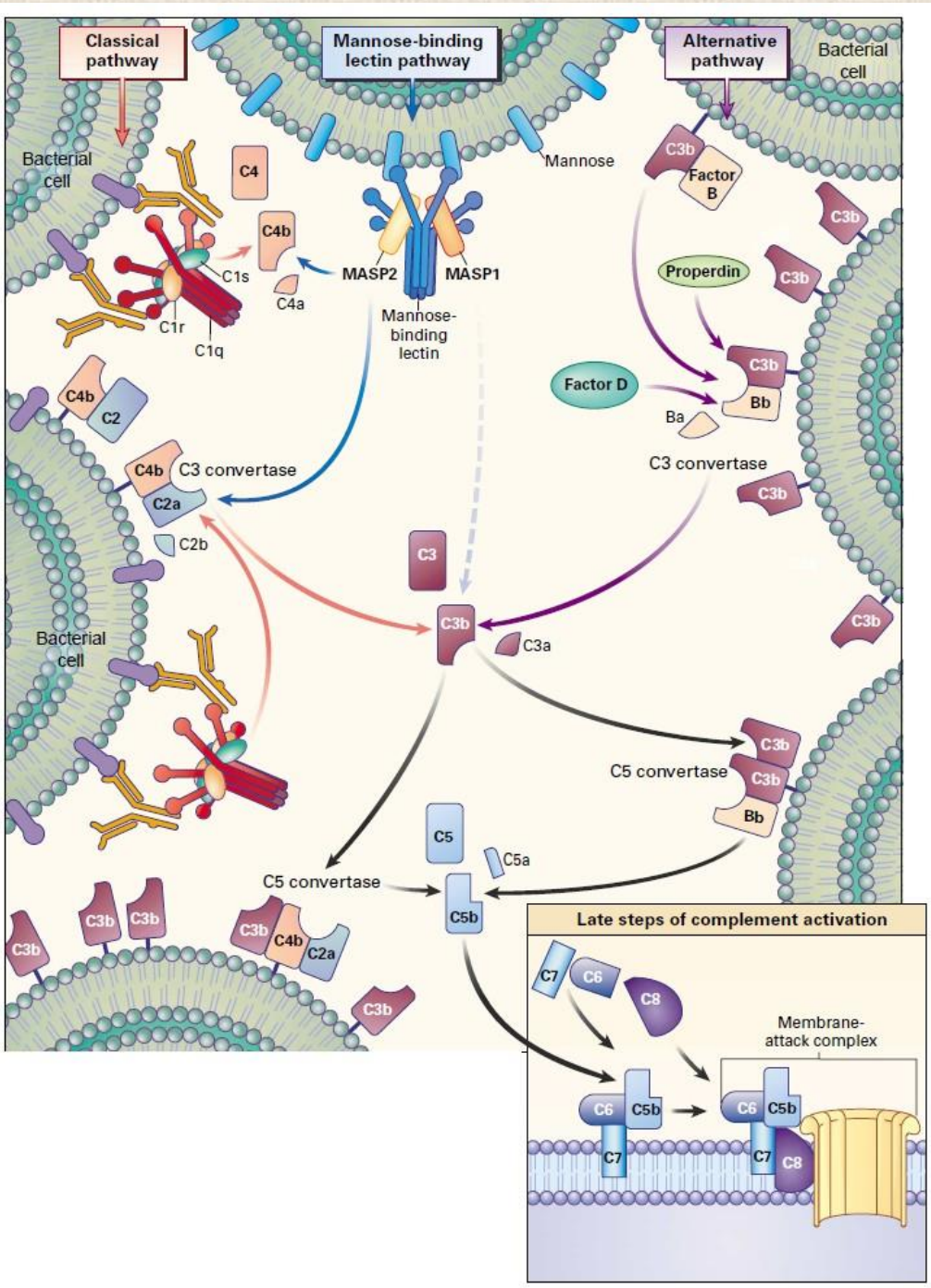
Innate	Natural	Adaptive
TLRs Heat shock proteins Complement	Invariant TcRs (both γδ and αβ) Natural (auto) antibodies	Immunoglobulins BcR TcR MHC I and MHC II



Toll Like Receptors (TLR) recognize molecular patterns associated with a broad range of pathogens, including bacteria, fungi, protozoa and viruses.



Heat shock proteins (Hsp60, 70, 90, gp96) play important role in antigen presentation, activation of macrophages, lymphocytes and dendritic cells. As part of their molecular chaperone functions play role in antigen presentation by MHC molecules.



Complement system

The complement system is a part of the immune system that enhances (complements) the ability of antibodies and phagocytic cells to clear pathogens from an organism. It is part of the innate immune system, which is not adaptable and does not change over the course of an individual's lifetime. However, it can be recruited and brought into action by the adaptive immune system.

Antigen recognition in adaptive immunity

Native antigens are recognized by immunoglobulins or B cell receptors.

T cells can recognize only in denatured (presented) forms of the antigens.

Basic terms

immunogen (fine chemical structure can induce specific immune response)

epitope (antigen determinant) well circumscribed region of the antigen molecule targeted by Ig/BcR or TcR

hapten (small molecular weight antigen can not induce immune reaction itself, but specifically recognized by immunoglobulins)

carrier (indifferent, large molecular weight molecule, hold on the surface hapten molecules; carrier molecules did not participate in the anti-hapten immune reaction only hapten)

Human immunoglobulins

IgG – blood, lymph, make up 80% of Ig only Ig of maternal origin to pass the placenta wall give newborns (Mw 150 kD) neutralize toxins and viruses

IgM – Blood, lymph (cell surface) pentamer structure (Mw 900 kD) first antibodies formed in response to initial infection.

IgA – Mucosal surfaces, blood (active in dimeric or tetrameric form) (Mw 150-600 kD)

IgD – only membrane-bounded form in B-cell surfaces (Mw 150 kD) may function in initiation of antibody-antigen response

IgE – blood, in perifery can bound to basophiles and mast cells (Mw 190 kD) initiation of allergic reactions

Antigen – antibody reactions

- Neutralization (e.g. toxins)
- Precipitation (soluble molecules)
- Agglutination (particles, cells)
- Opsonization (large particles)
- Complement fixation

Antigen Recognition by T Cells

-T cells recognize antigens only displayed on surfaces of the body's own cells as MHC and peptide complexes

Main T cell types:

-CD8+ (cytotoxic) T-cells

MHC Class I - peptide complex

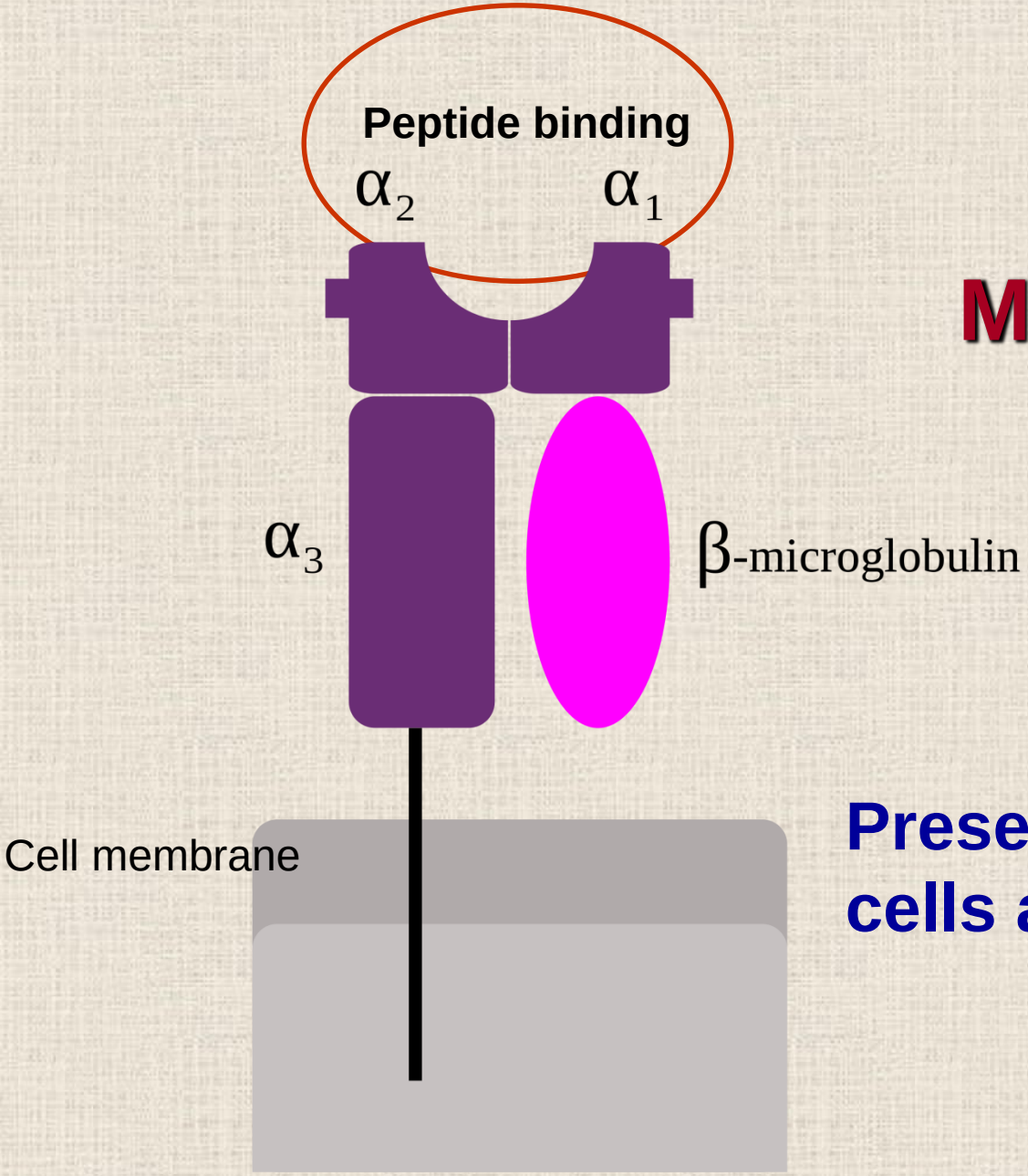
-CD4+ (helper) T-cells

MHC Class II - peptide complex

Major Histocompatibility Complex

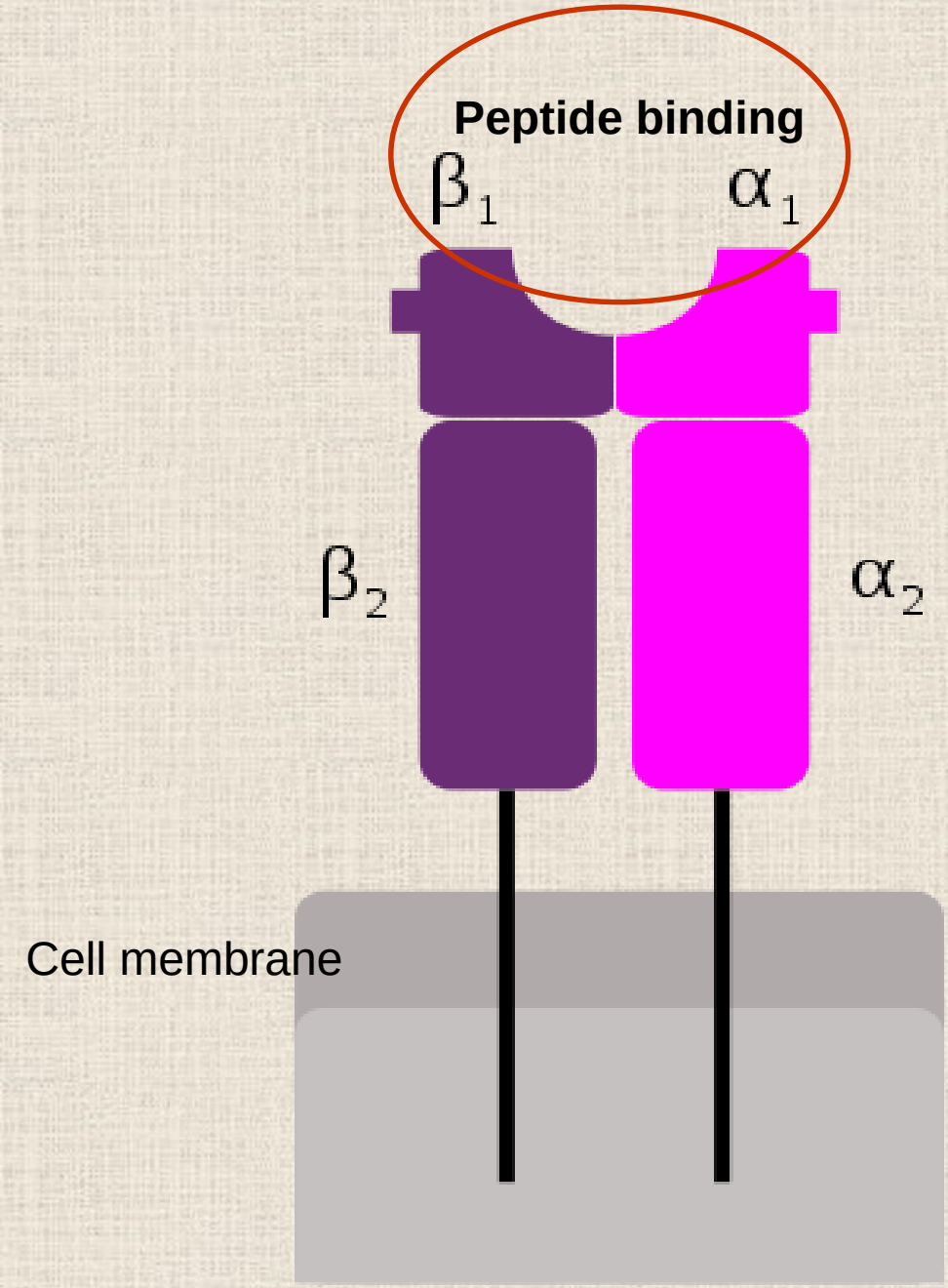
Self and foreign antigens are presented on the cell surface by specialized host-cell glycoproteins encoded in a large cluster of genes that were first identified by their effects on the immune response to transplanted tissues. For that reason, the gene complex was termed the Major Histocompatibility Complex (MHC). The antigen binding glycoproteins are called MHC molecules/antigens. (MHC vs. HLA, H2, BoLA, ChLA etc.)

Inbred strains of mice



MHC Class I

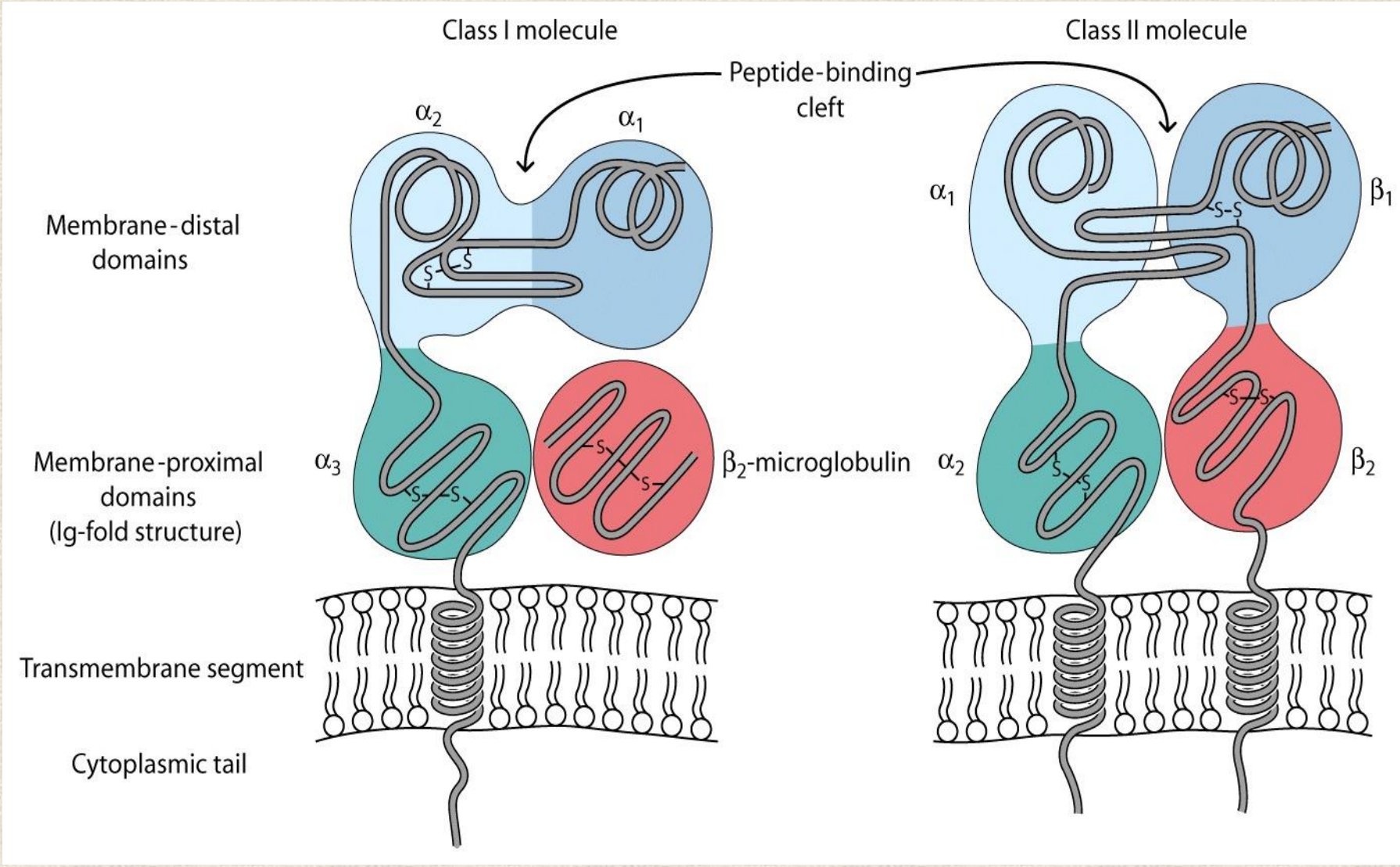
Present in all nucleated cells and platelets



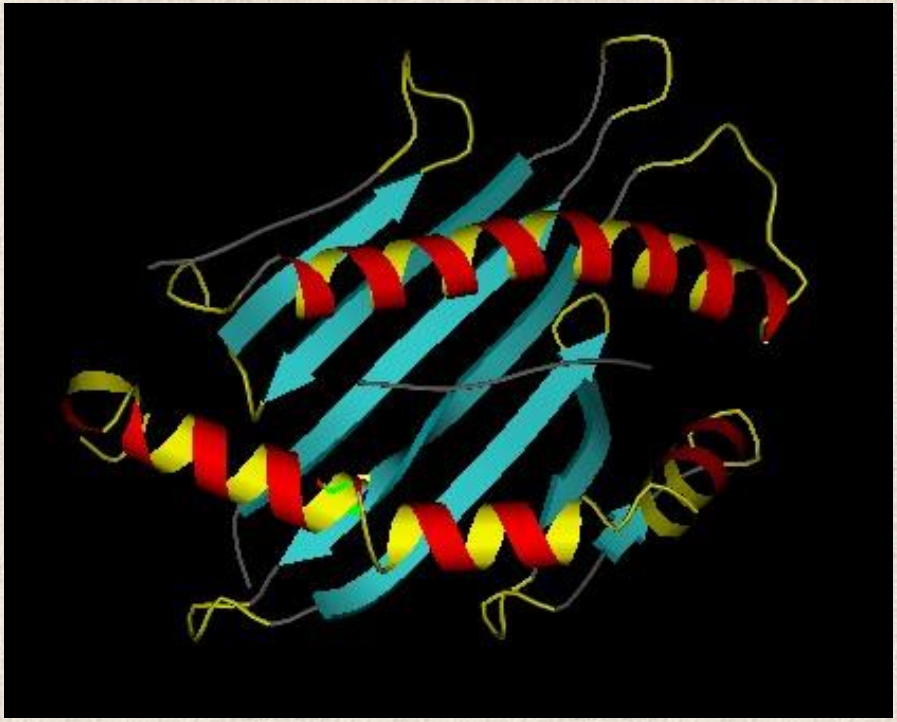
MHC Class II

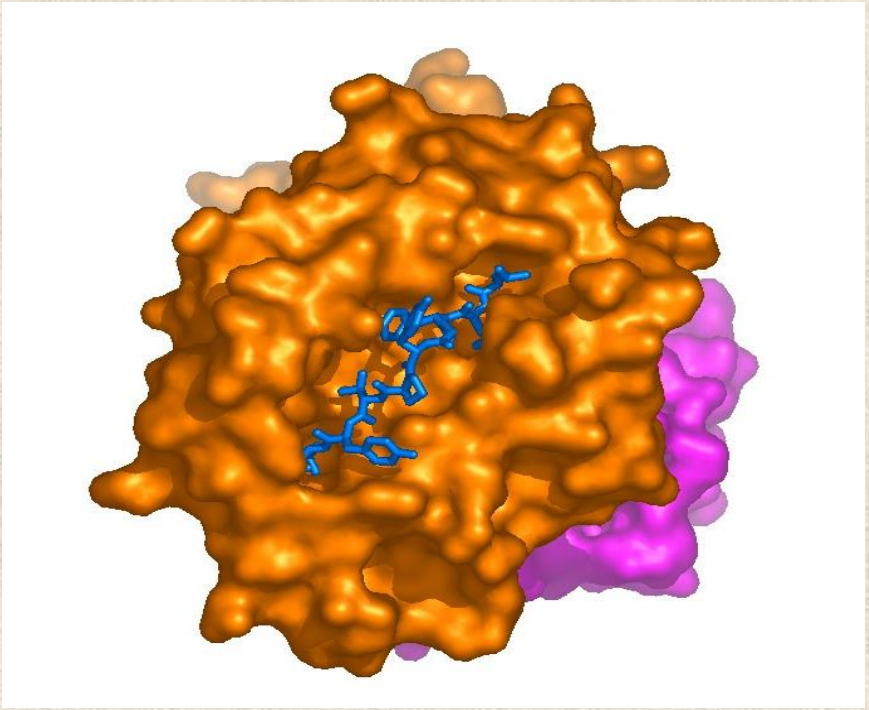
Present in professional or facultative antigen presenting cells (APC)

Class I and class II MHC Molecules

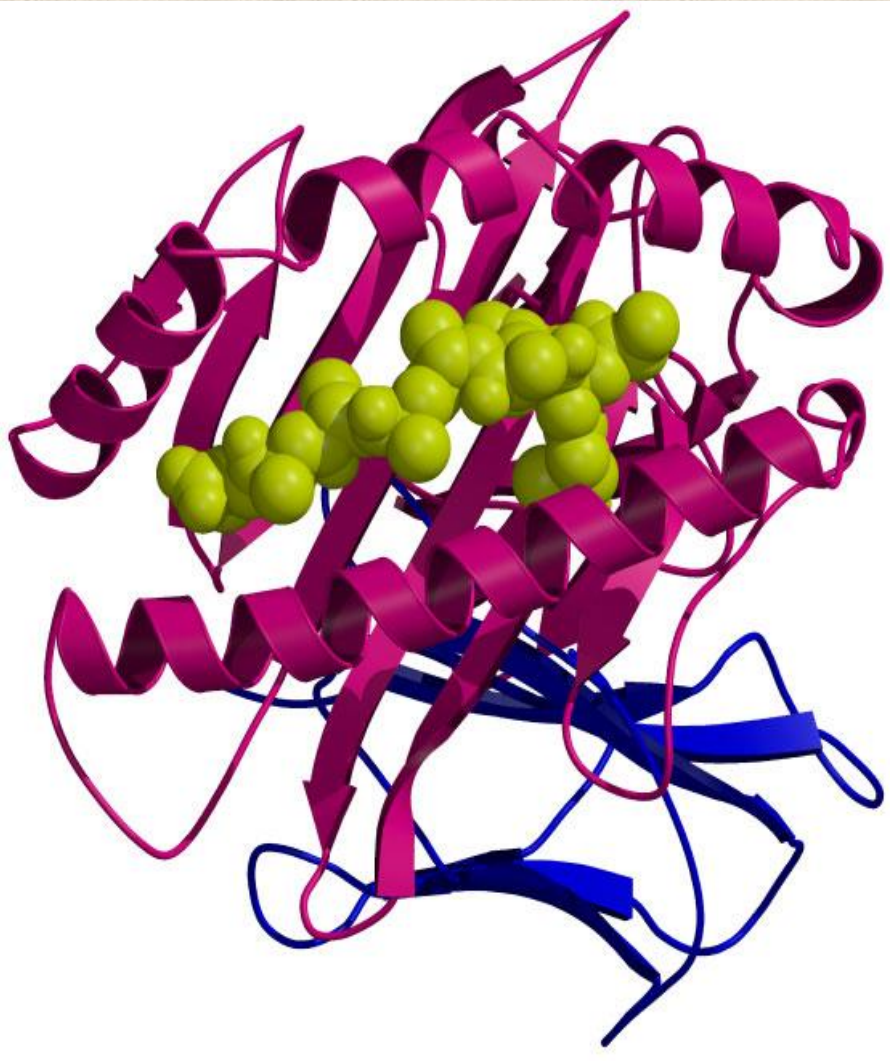


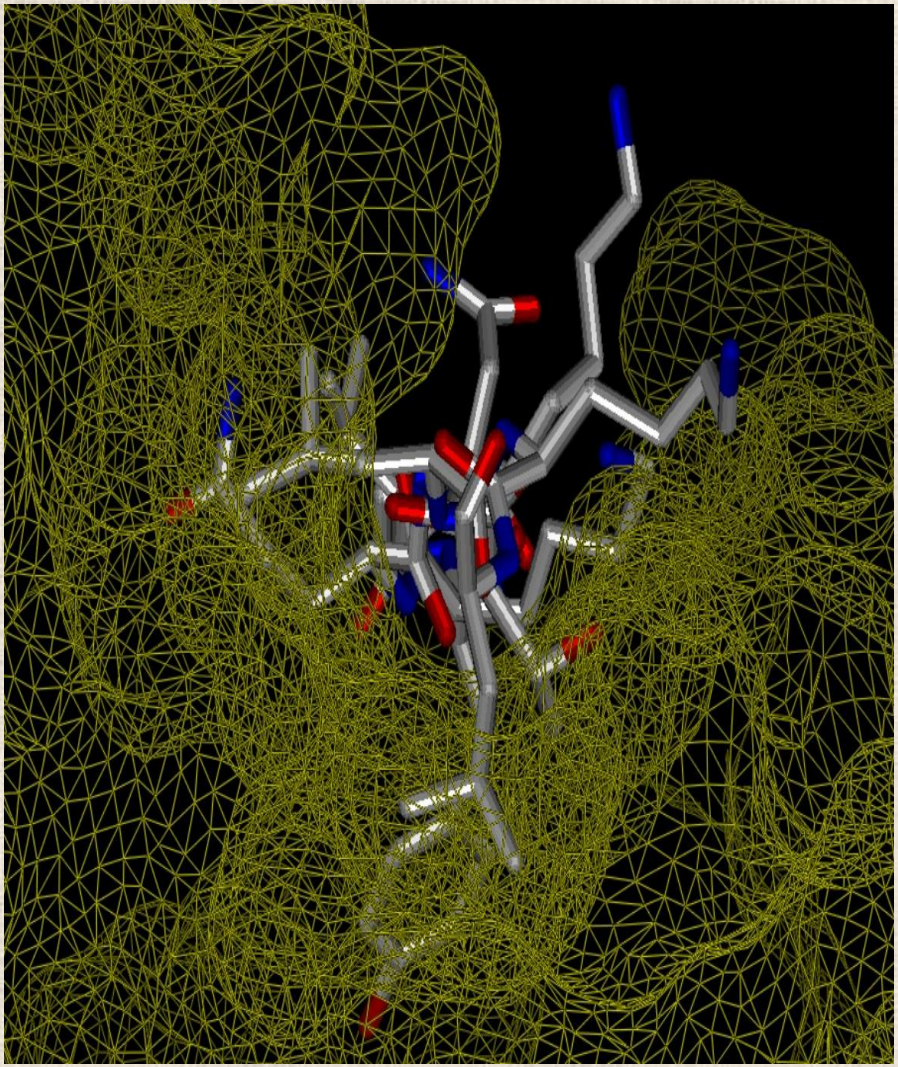
Antigen binding site of MHC class I



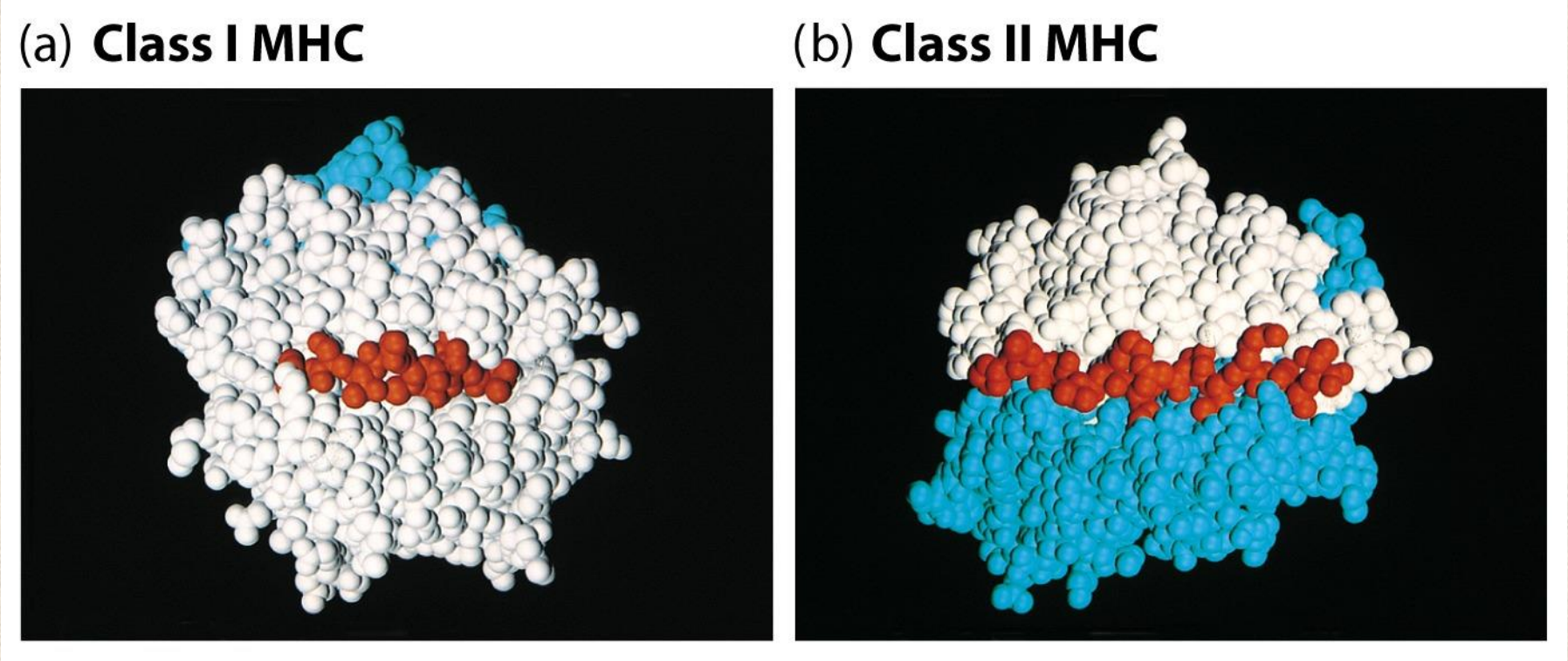


Antigen binding site of MHC class II

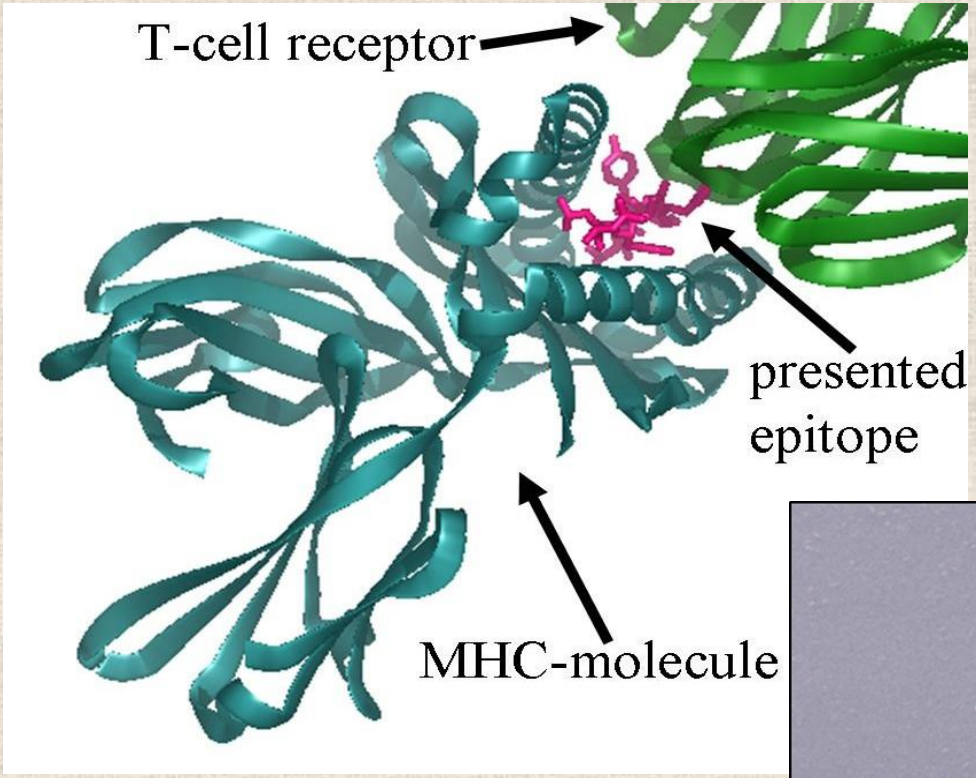


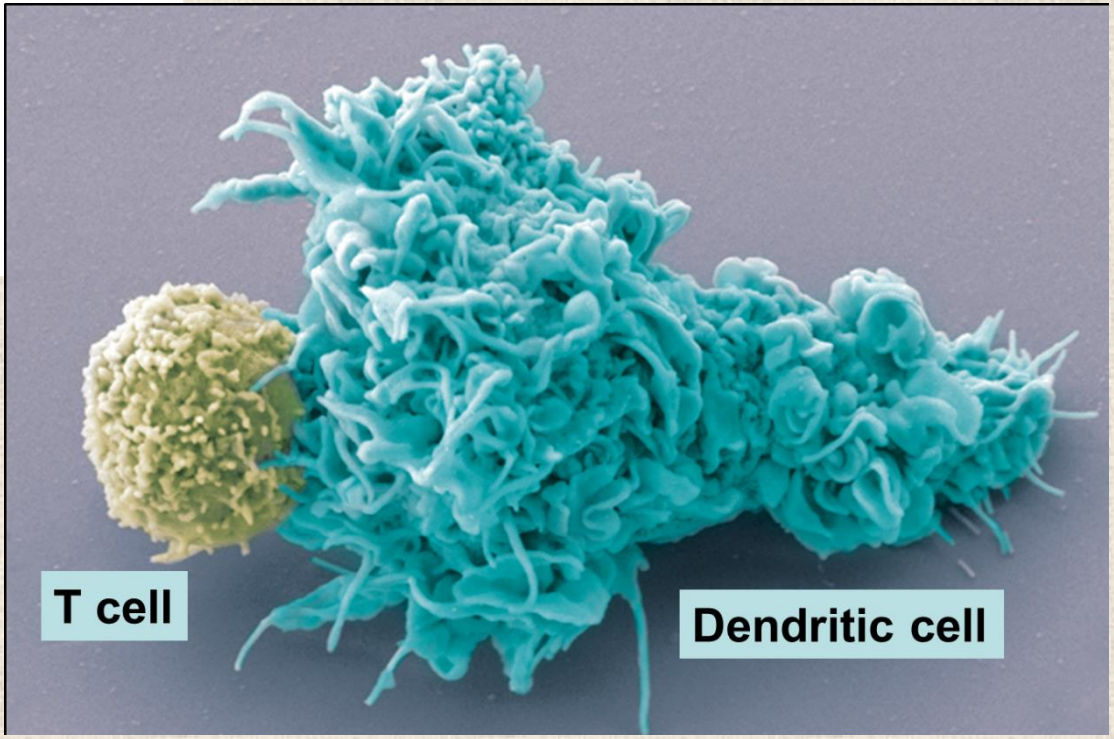


MHC class I and class II molecules with bound peptides

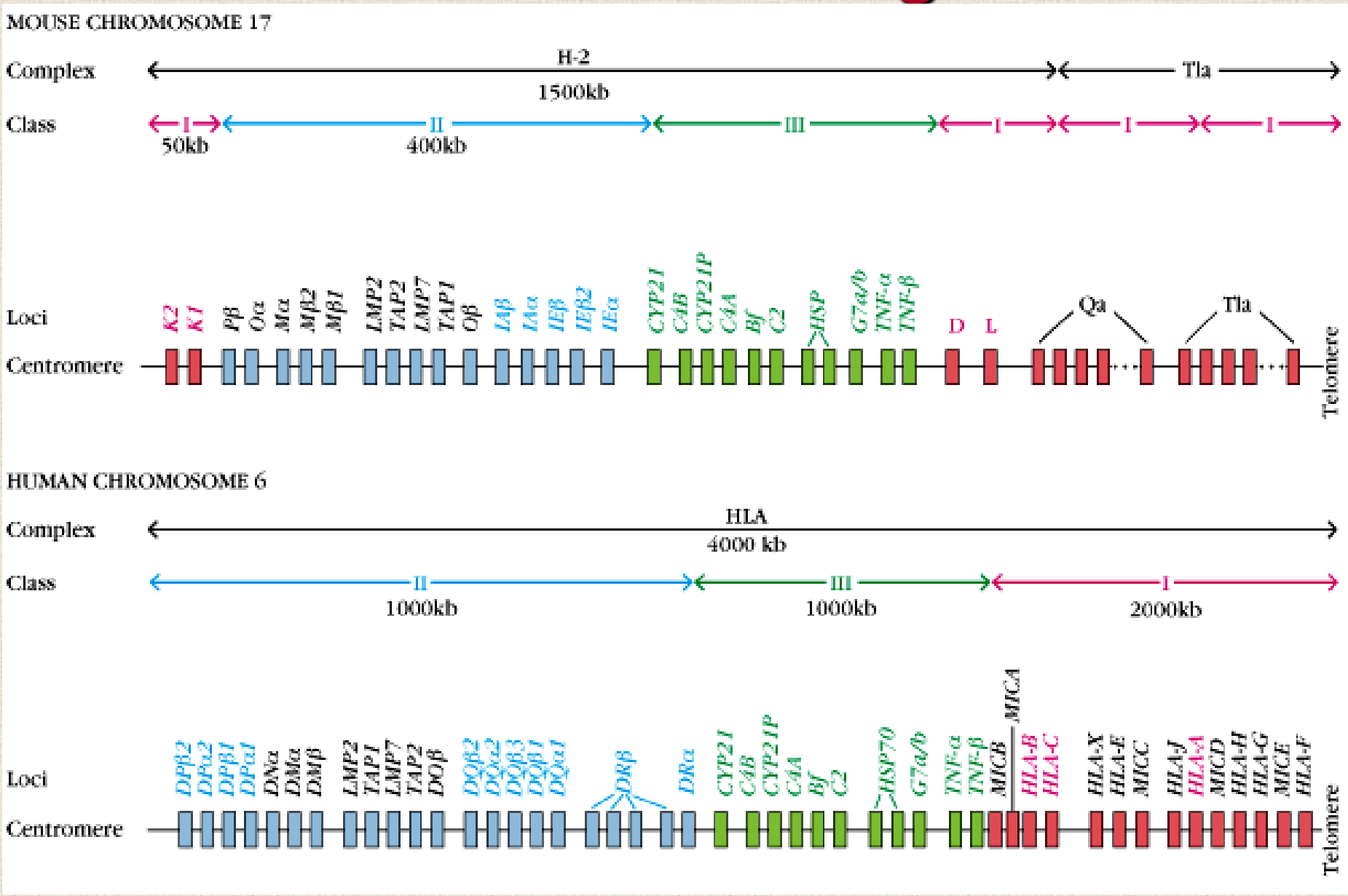


MHC presents antigen for T cell

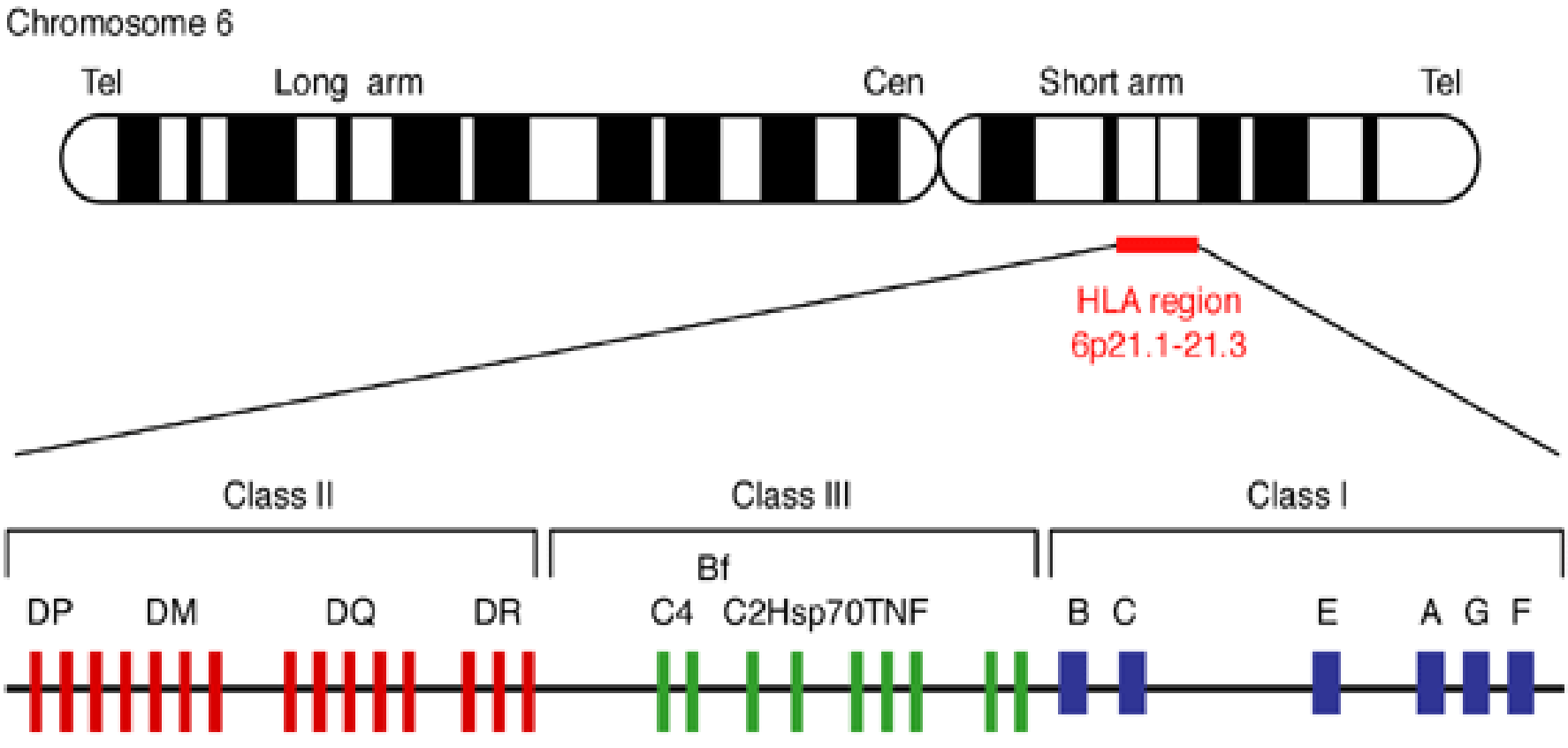




Structure of MHC genes



HLA map



Gene map of the human leukocyte antigen (HLA) region

The MHC is **polygenic** (there are ***several*** different class I and class II ***genes*** encoding proteins with different specificities) and highly **polymorphic** (there are ***multiple alleles of each gene***) that most individuals are likely to be heterozygous at each locus. Alleles are expressed from both MHC haplotypes in any one individual (**co-dominant**), and the products of all alleles are found on all expressing cells.

In human there are three classical class I molecules (**HLA-A, B, C**) and three classical class II molecules (**HLA-DR, DP, DQ**). The HLA-A has more than 20, B has more 50, and C more than 10 alleles. HLA-DR has 20, HLA-DQ has 9, and HLA-DP has 6 alleles.

What type of cells express MHC Class I and MHC Class II?

MHC I Any cell type with nucleus and the platelets

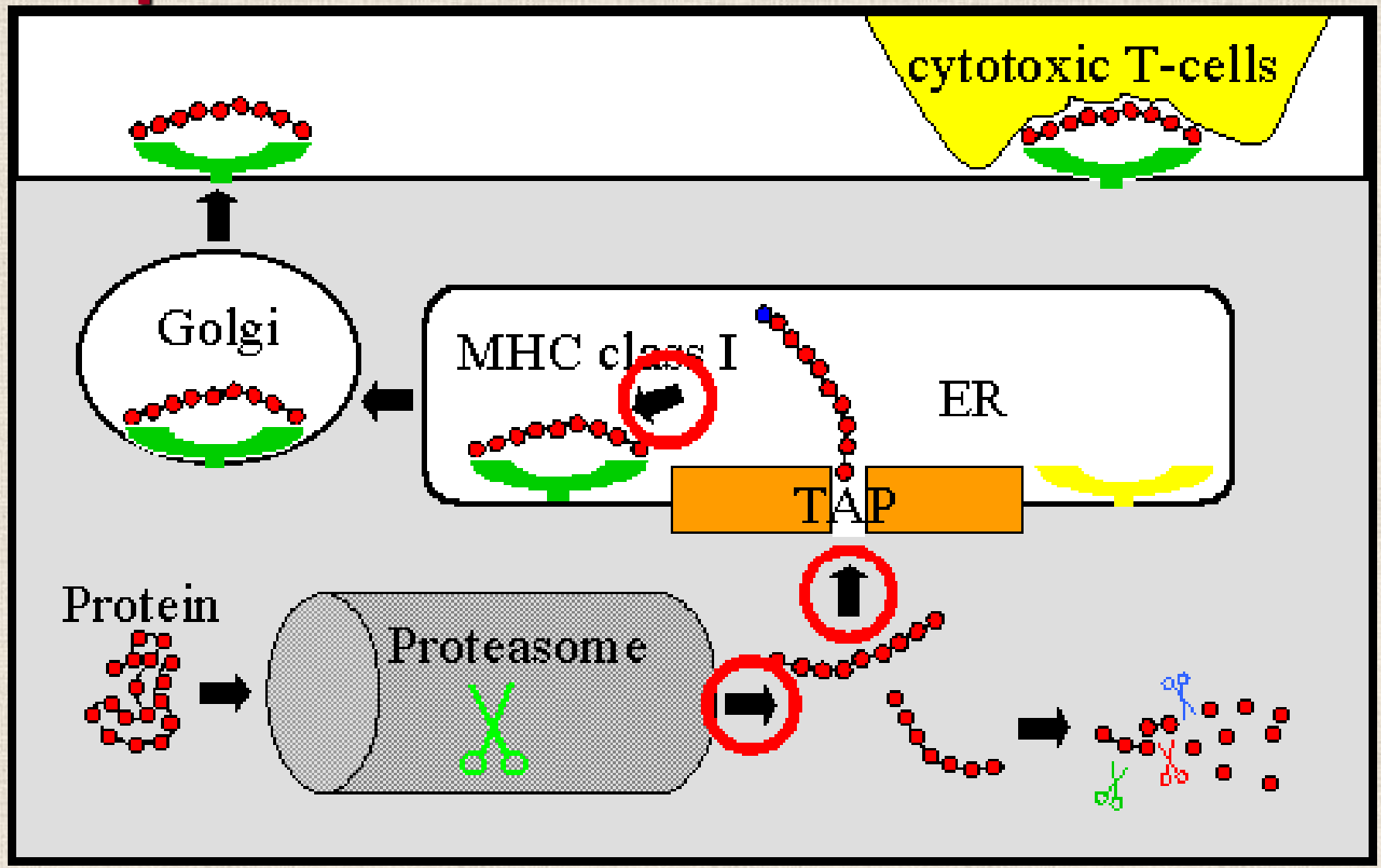
MHC II Mainly professional antigen presenting cells

- Dendritic cells
- B cells
- Macrophages, monocytes
- (Thymic epithelial cells)

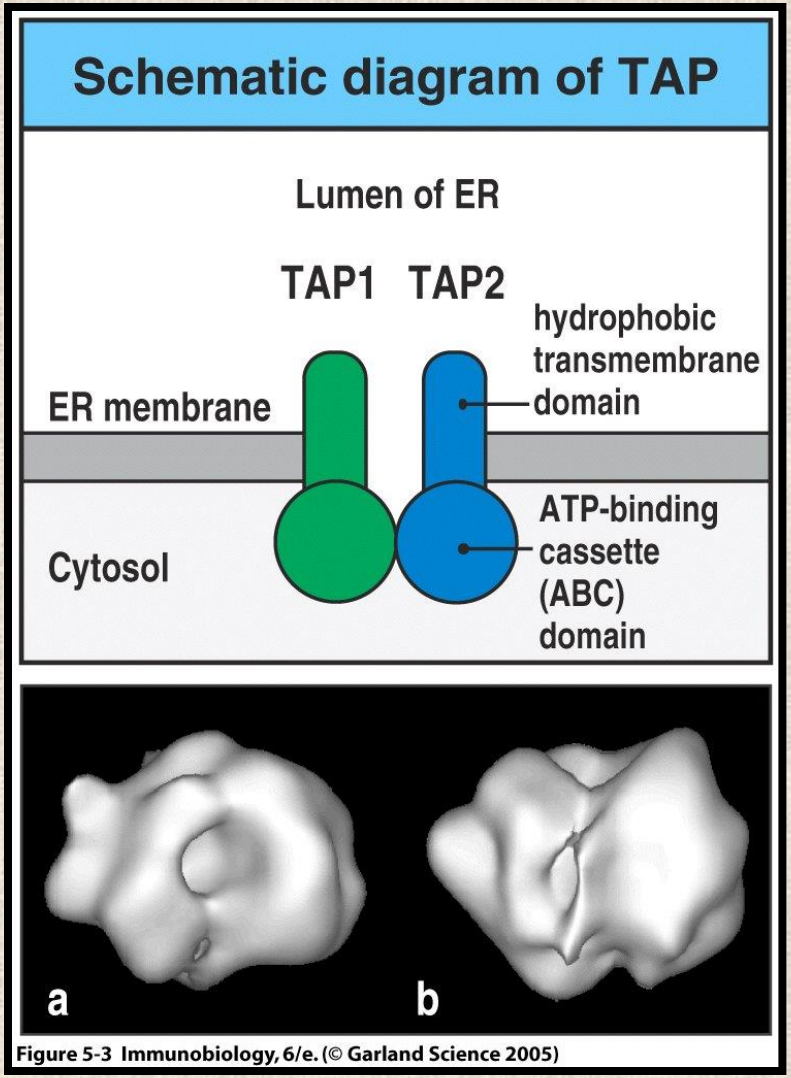
Facultative antigen presenting cells in pathologic conditions

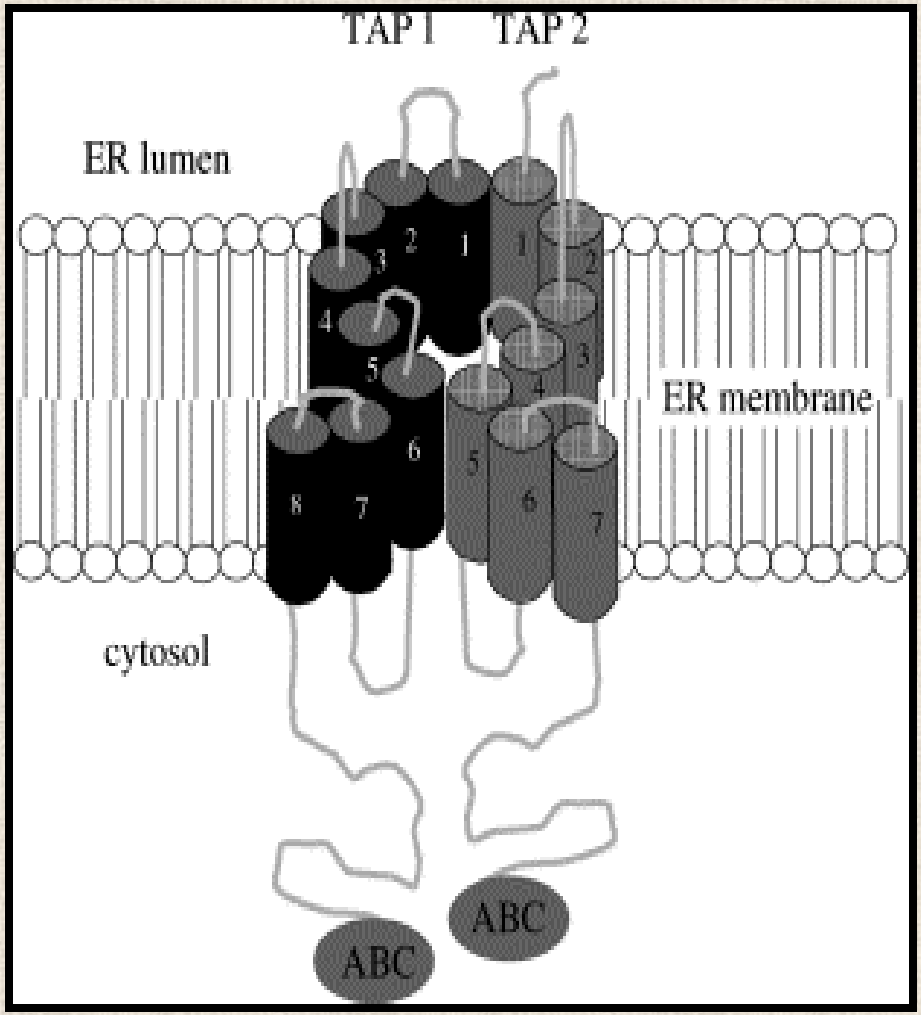
- Inflammatory epithel and endothel

Antigen processing and presentation on MHC Class I



Transporter Associated with Antigen Processing





Molecular Immunol. 2002

Chaperons in the MHC Class I antigen presentation

Calnexin, calreticulin, Erp57, tapasin

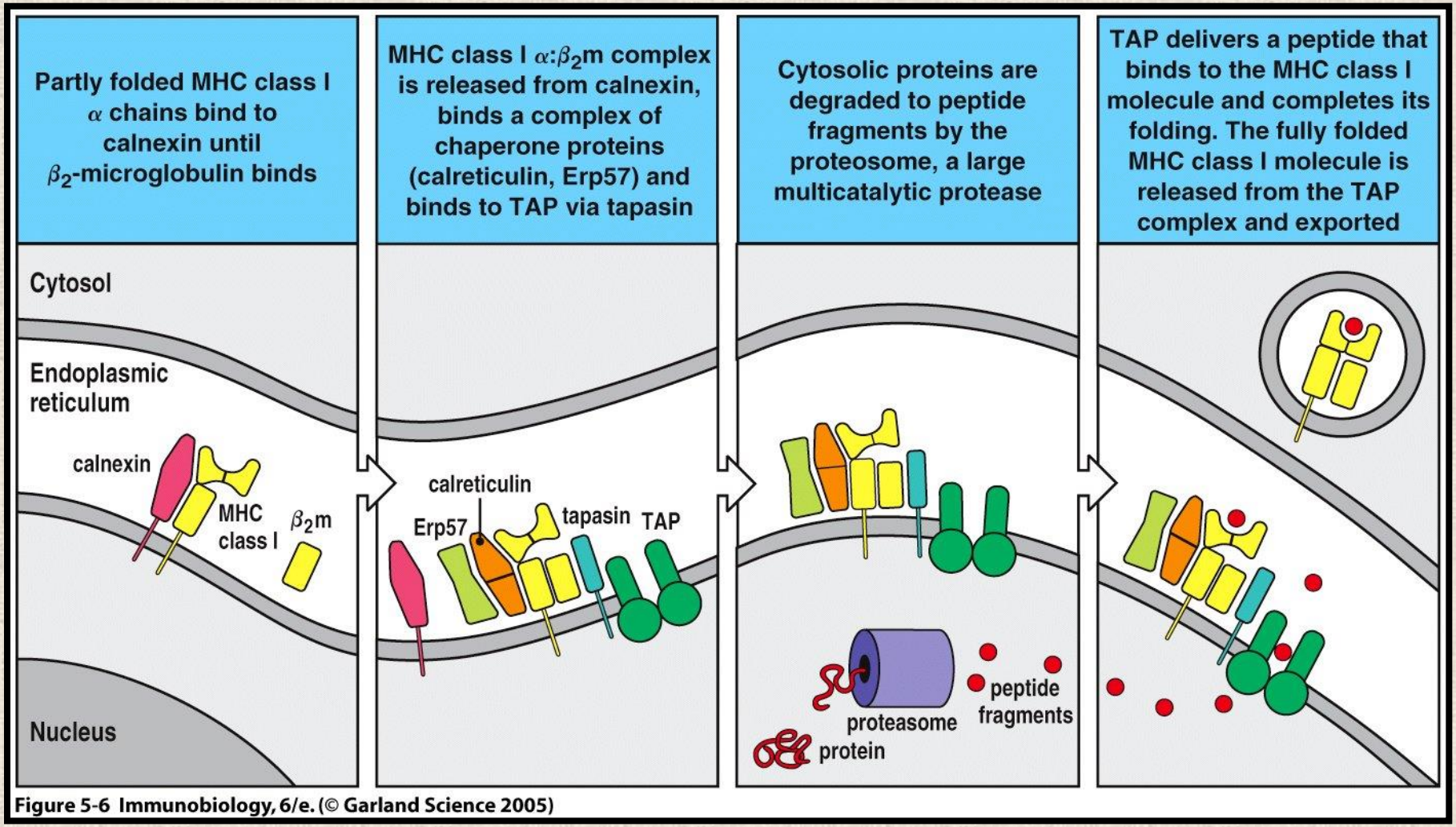


Figure 5-6 Immunobiology, 6/e. (© Garland Science 2005)

Antigen presentation on MHC I

- Cytosolic, mainly normal or viral/modified proteins
- Proteasomal degradation
- Peptide transfer to the ER (TAP1&2)
- MHC I chains produced into ER by ribosomes
- Chaperons: calnexin, calreticulin, Erp57
- Tapasin and TAP1&2
- MHC I & peptide binding within the ER

Generation of antigenic peptides in the endocytic pathway for presentation by MHC II

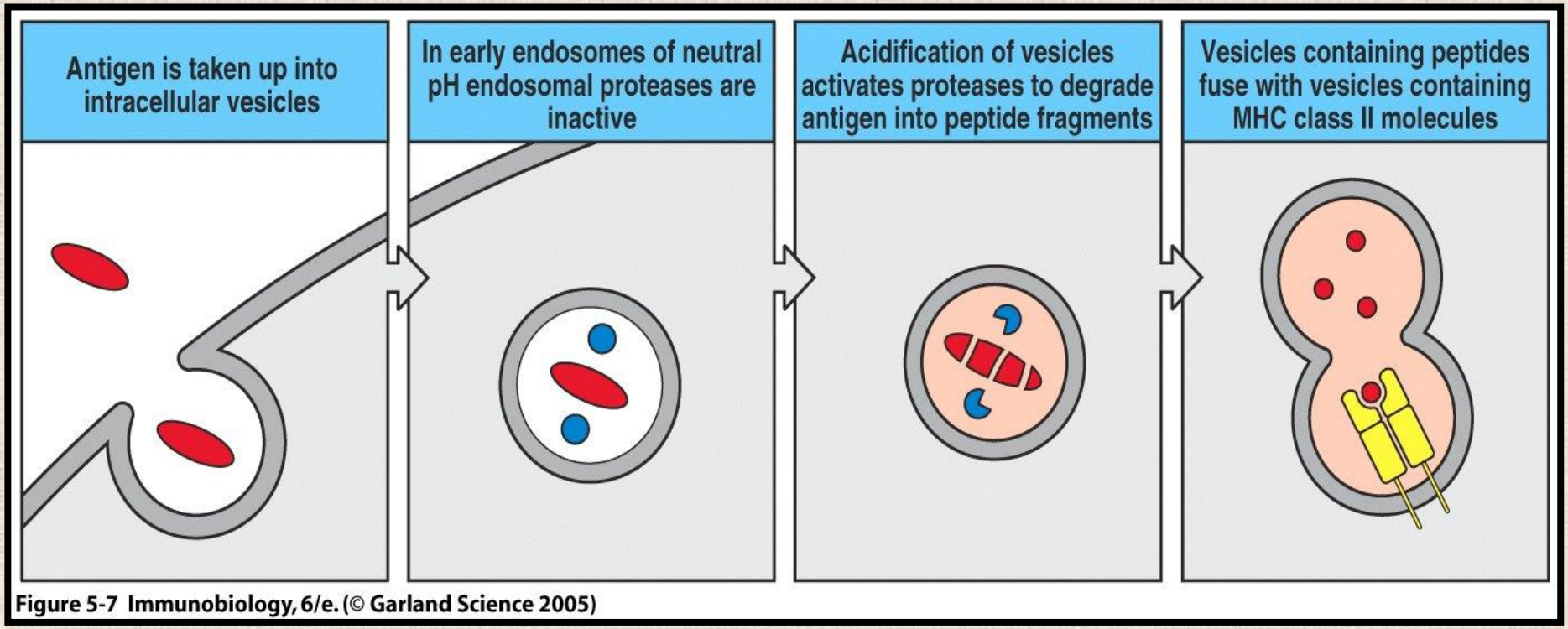


Figure 5-7 Immunobiology, 6/e. (© Garland Science 2005)

Peptide loading of MHC Class II molecules

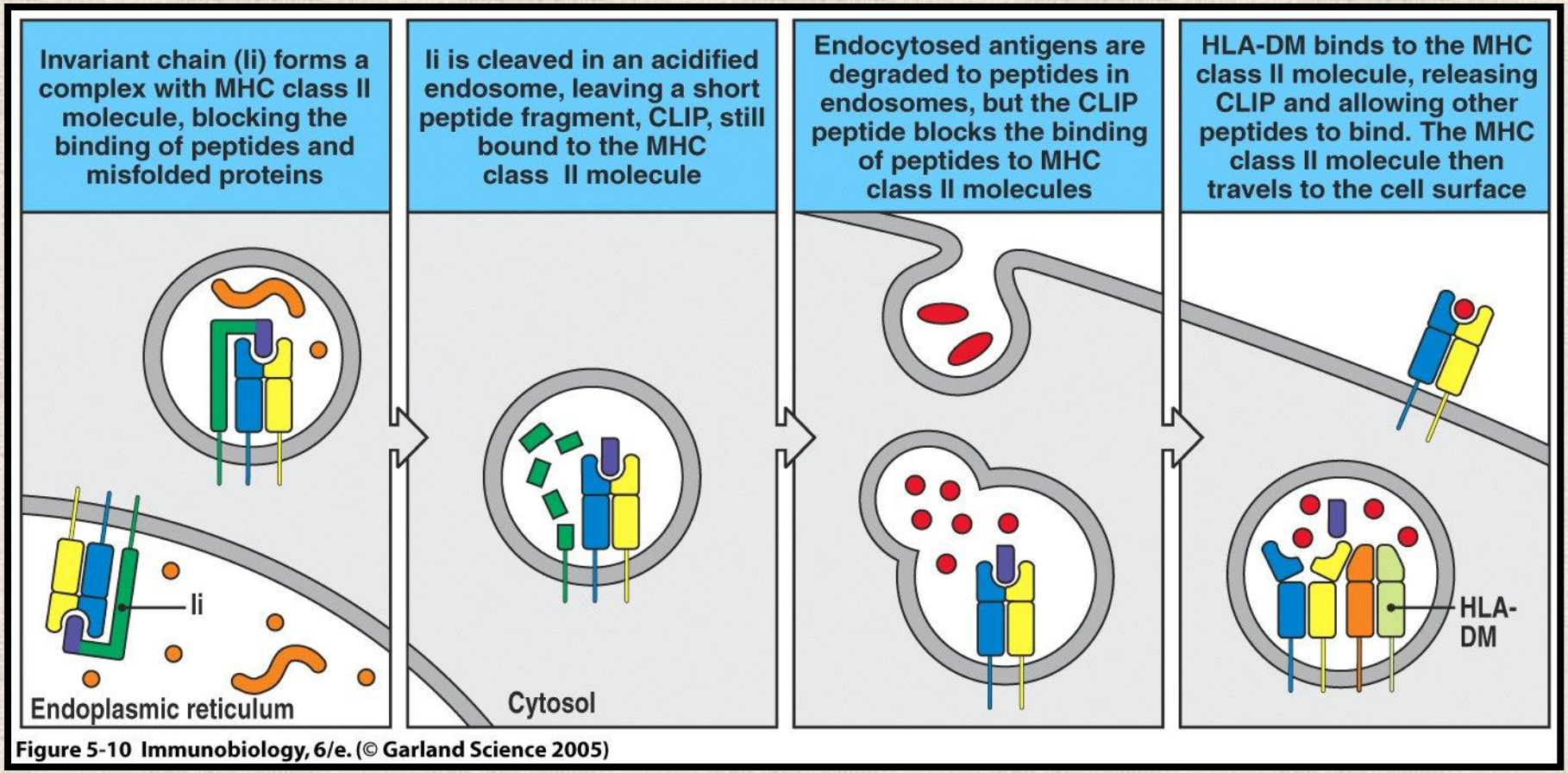


Figure 5-10 Immunobiology, 6/e. (© Garland Science 2005)

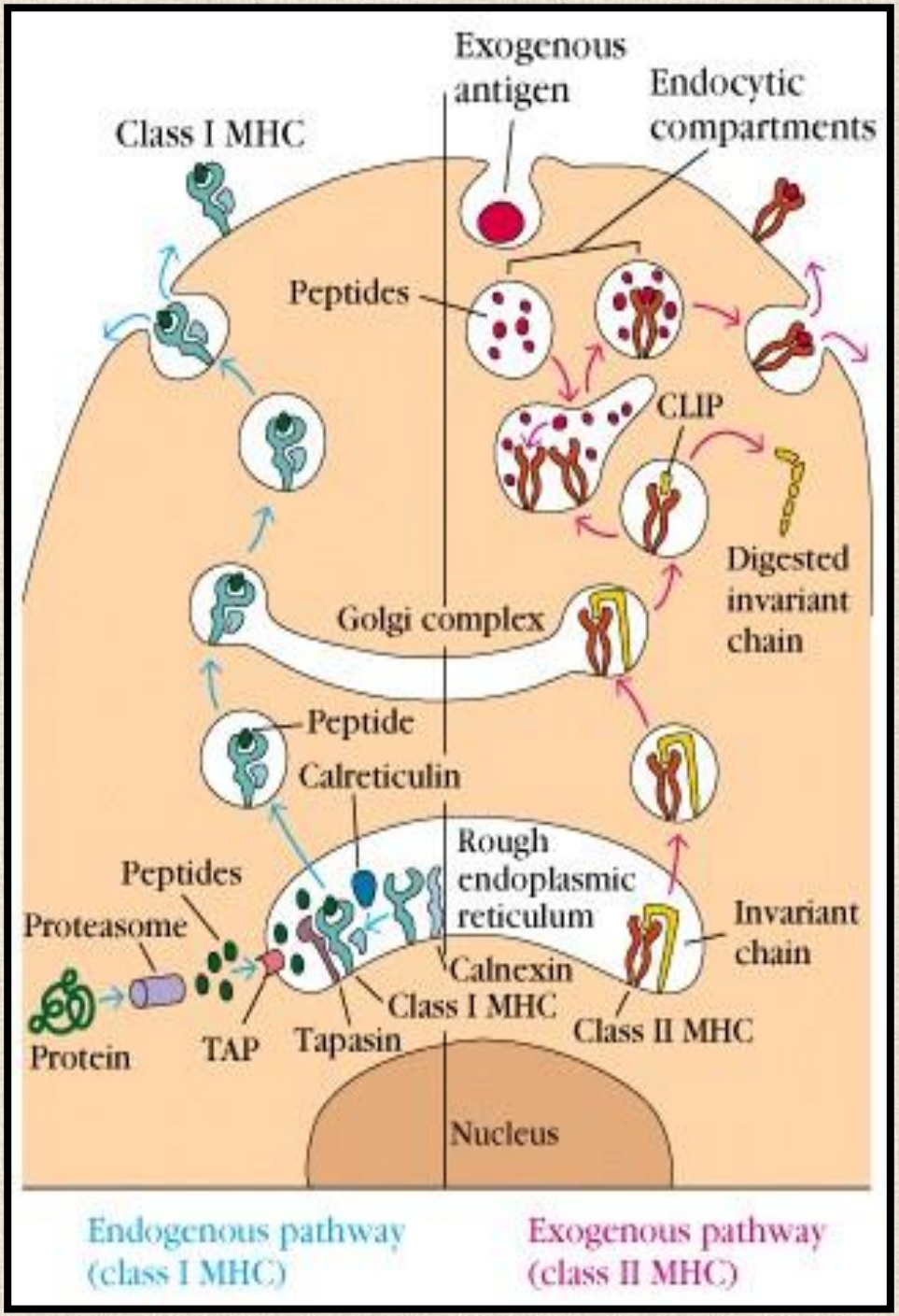
HLA-DM: MHCII chaperon

CLIP=class II associated invariant chain peptide

Antigen presentation on MHC II

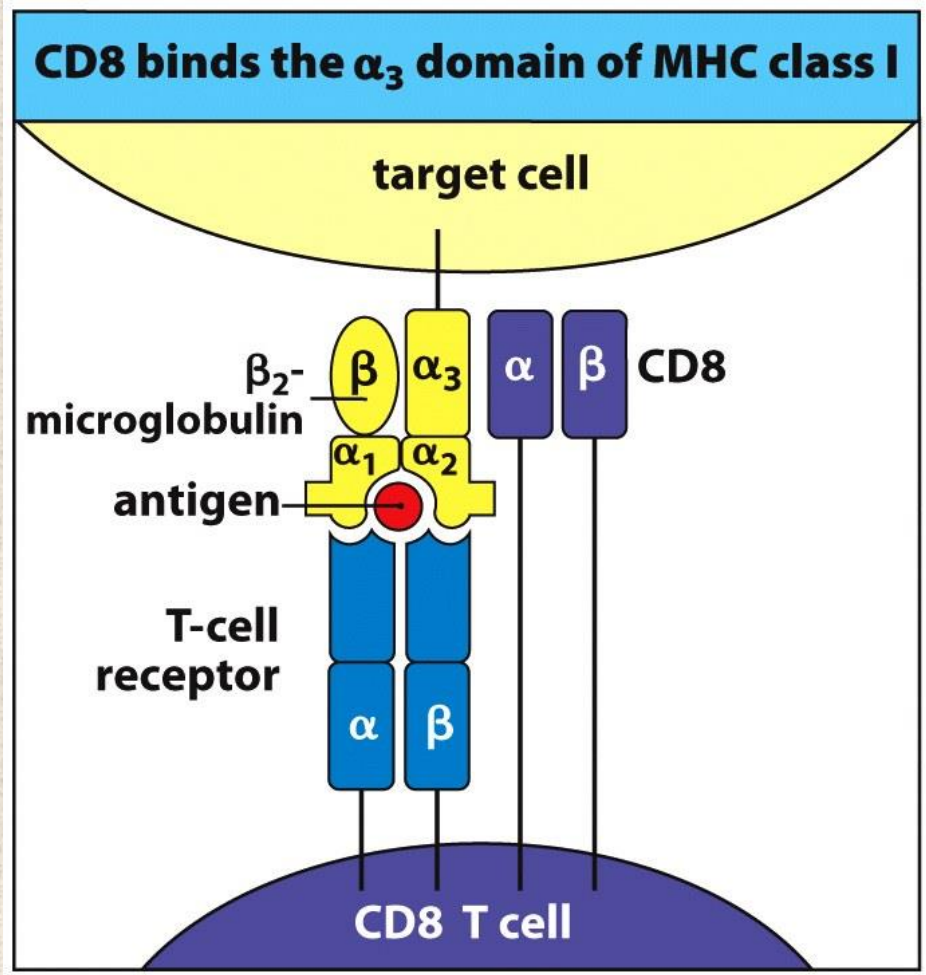
- Endocytosed proteins: bacteria, bacterial product, internalised receptor bound peptide, parts of another cell
- Endosomal degradation
- MHC II alpha and beta chains and an invariant gamma chain produced into the ER by ribosomes
- Specific chaperon (HLA-DM) optimises the structure
- Class II associated invariant chain (CLIP) peptide blocks the antigen binding during the transport
- MHC II & peptide binding in endosomes outside the ER

Presentation of intracellular antigens by MHC I: continous in all cells and platelets



Presentation of extracellular antigens by MHC II: in APCs, after phagocytosis

MHC Restriction



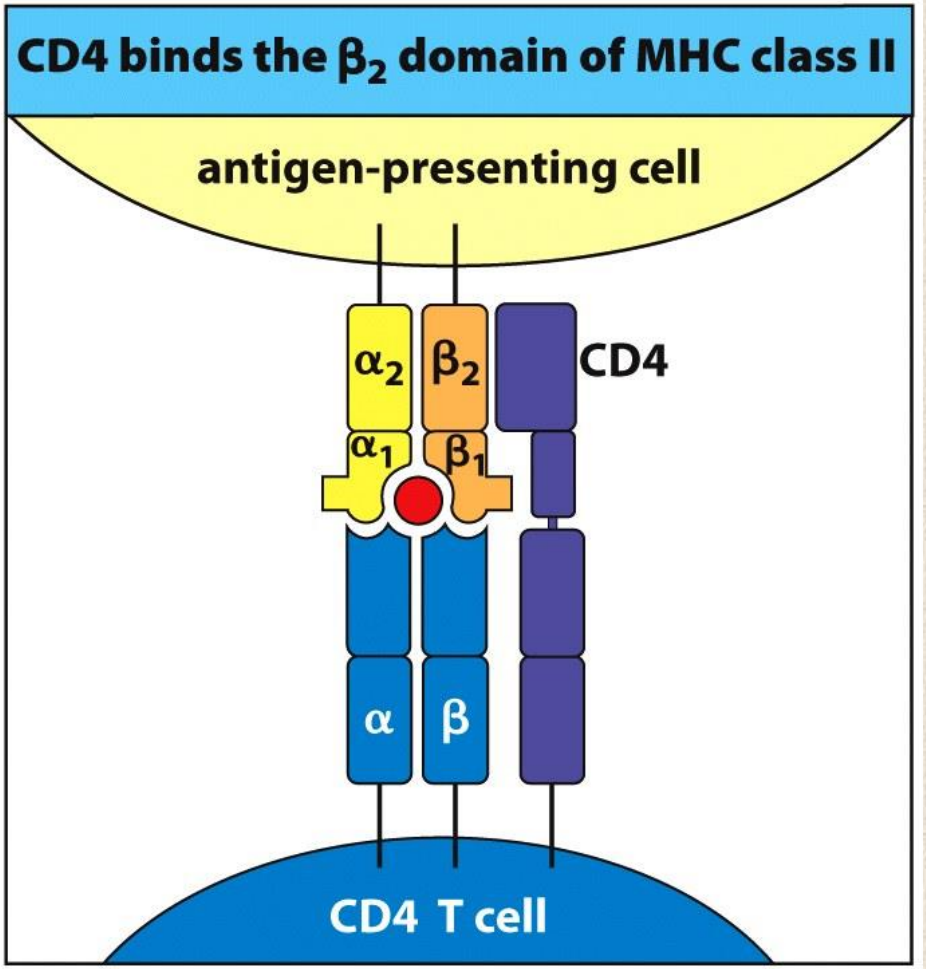


Figure 5.14 The Immune System, 3ed. (© Garland Science 2009)

MHC I – CD8

MHC II – CD4

How do pathogens avoid detection?

MHC-I

Herpes simplex – produces a protein which inhibits TAP

Adenovirus – produces a protein, which binds to and retains MHC-I in the ER

Cytomegalovirus – accelerates MHC-I translocation to the cytosol for degradation

HIV – accumulate mutations faster than the adaptive immune system can cope with

MHC-II

Helicobacter pylori – encodes a 95kD protein toxin, which increases the pH of the lysosomes, inhibiting protease activity

Septicemia (toxic shock syndrome) caused by superantigens

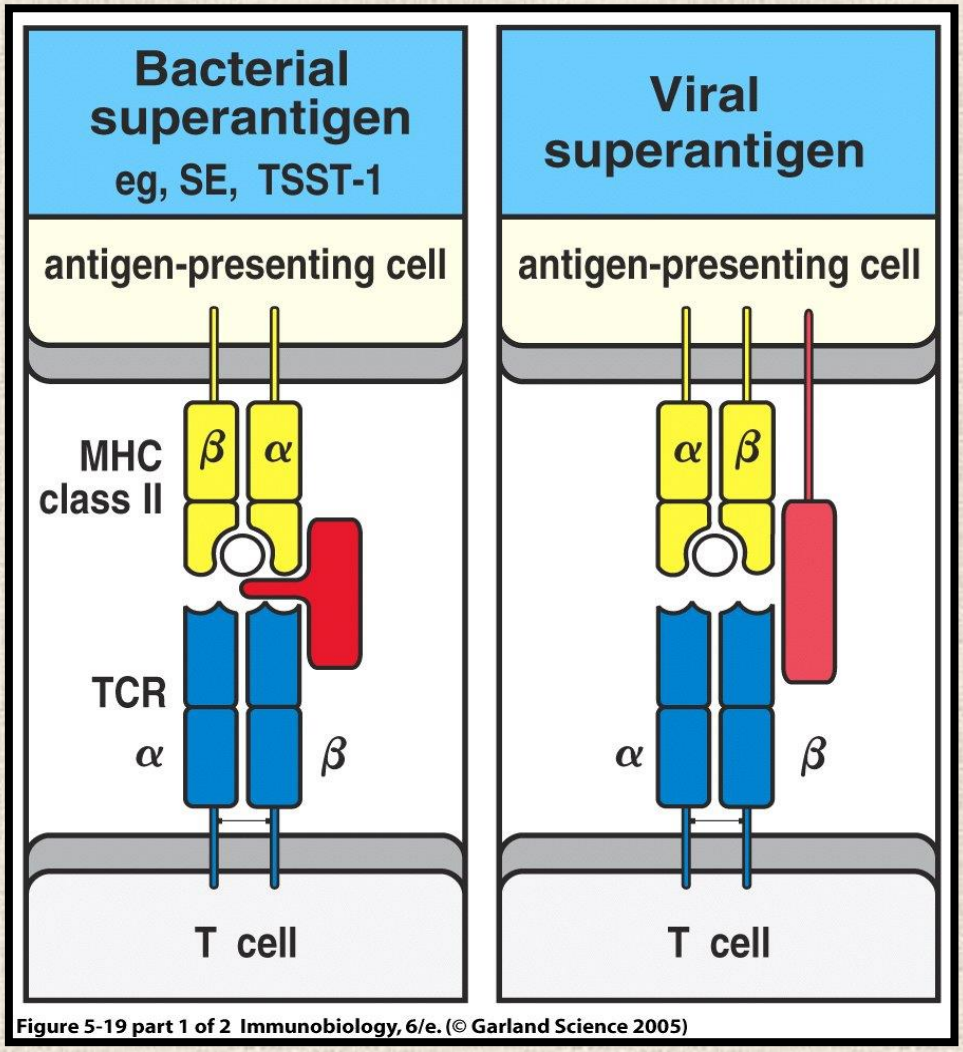


Figure 5-19 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Compared to a normal antigen-induced T-cell response the endotoxins (Sags) are capable of activating much higher number of the T-cells in *nonspecific* manner. This causes a massive immune response with irregular cytokine production (toxic shock syndrome) that is not specific to any epitope on the SAg.

T cells activated nonspecifically overproduce cytokines resulting systemic toxicity with general catastrophe of bioregulation, („Cytokine tsunami")

Definition of Toxis Shock Syndrome (septicemia, blood-poisoning)

Toxic shock syndrome (septicemia/blood-poisoning) is a life-threatening complication of certain types of bacterial or viral infections. Often toxic shock syndrome results from toxins produced by ***Staphylococcus aureus*** and ***group A Streptococcus*** bacteria, or some viral toxins.

Toxic shock syndrome has been associated primarily with the use of superabsorbent tampons, but risk factors now include skin wounds and surgery.

Physiological T cell activation is antigen-specific and well controlled, however, the T cell activation in toxic shock syndrome is none-specific and irregular. Clinical symptoms caused by irregular and mass production of cytokines („cytokine-tsunami”).