MHC & ANTIGEN PRESENTATION

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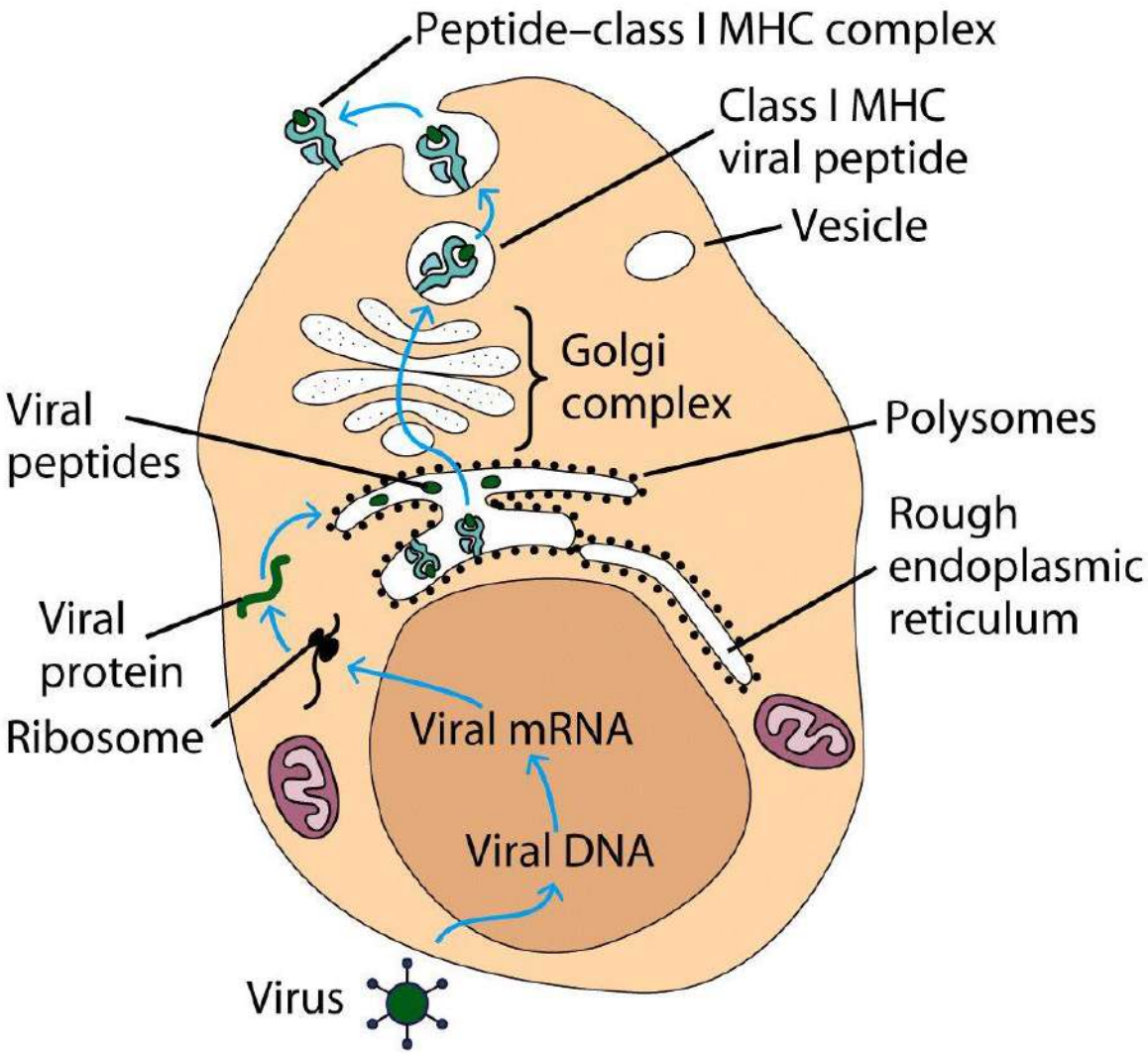
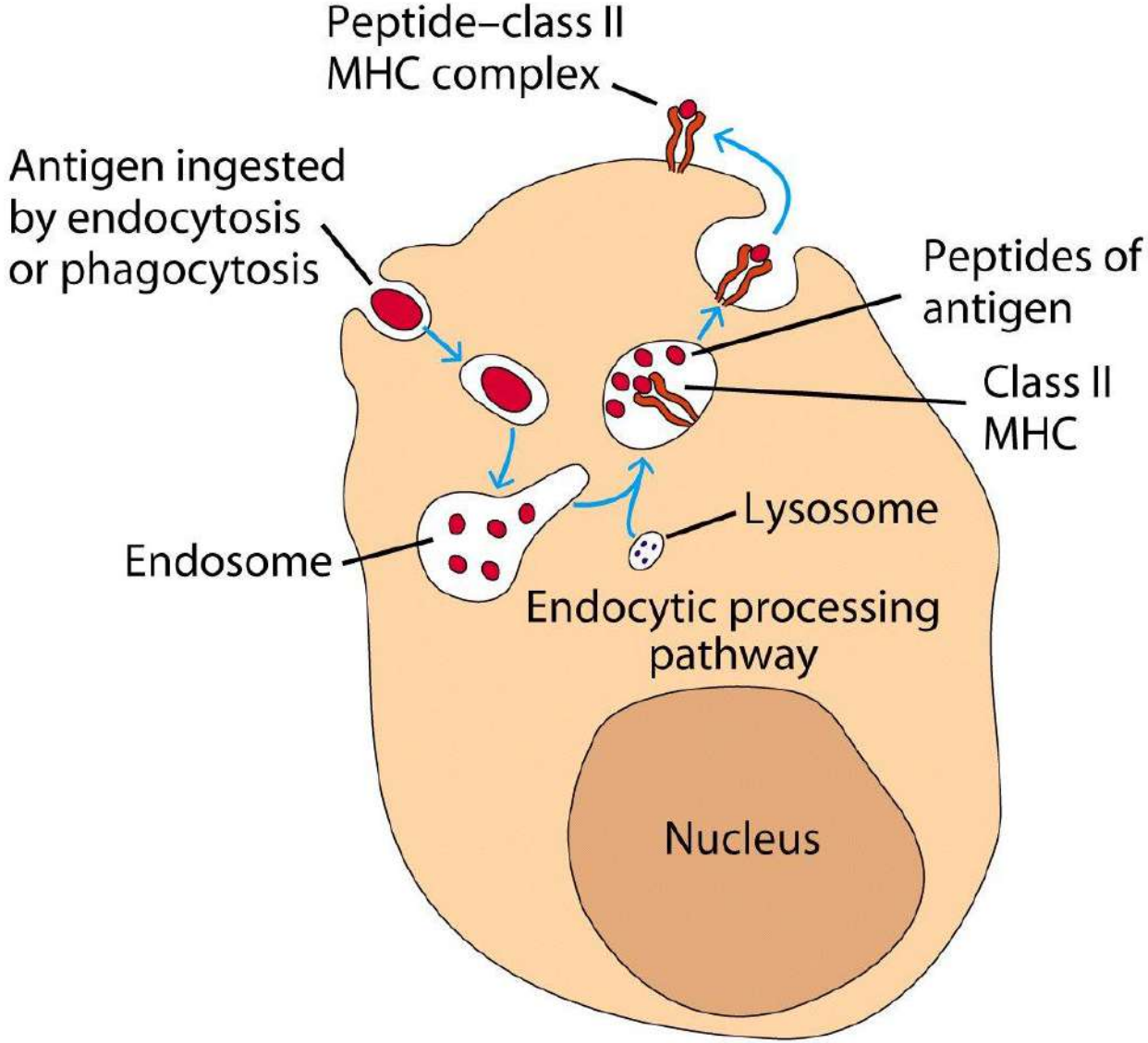
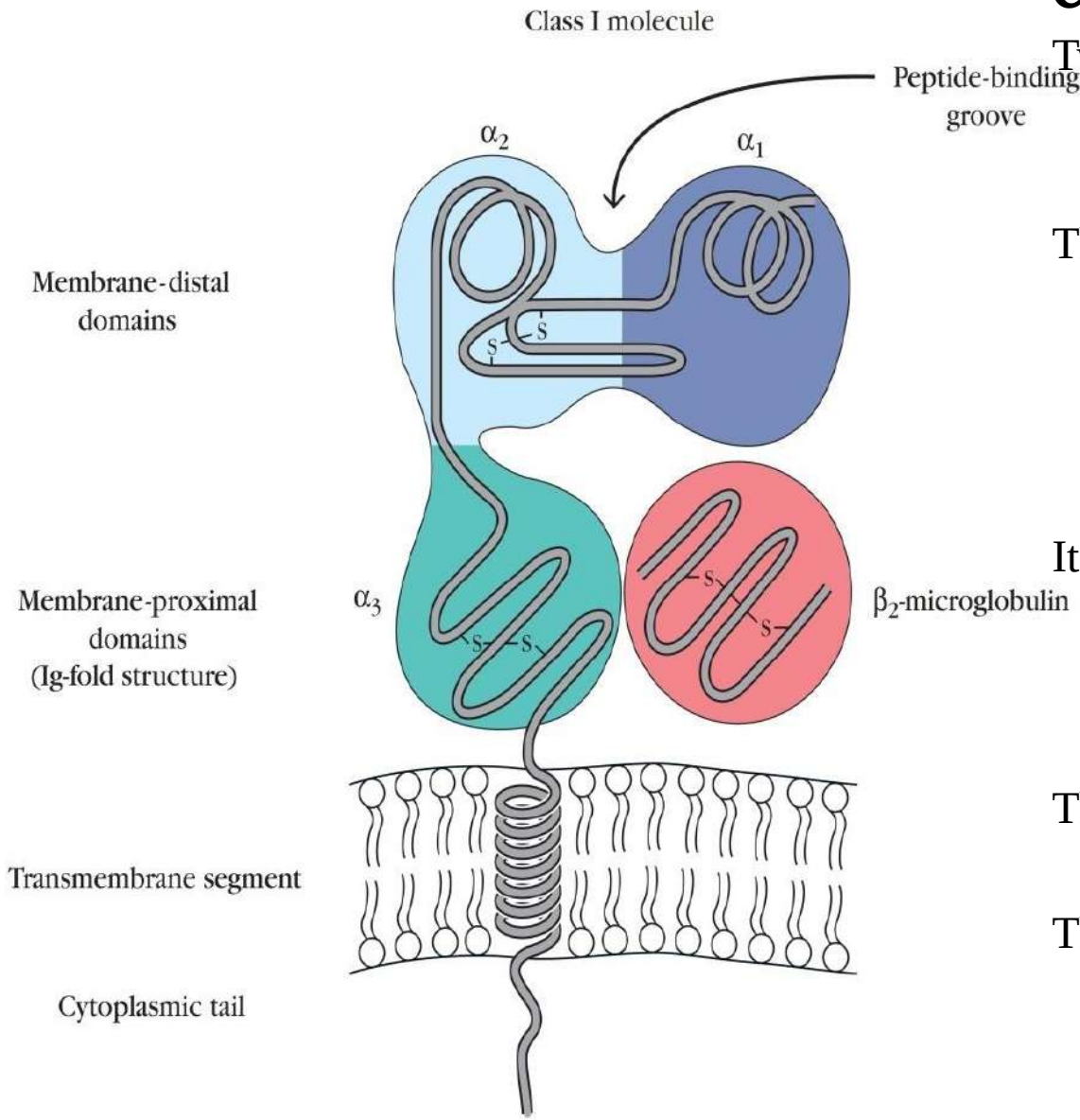
REFERENCE

1. ROITT'S ESSENTIAL IMMUNOLOGY
2. KUBY IMMUNOLOGY
3. CELLULAR AND MOLECULAR IMMUNOLGY ABBAS
4. IMMUNOLGY MALE AND BROSTOFF
5. IMMUNOLOGY KHAN
6. CELL BRUCE ALBERTS


Peptide–class I MHC complex
Class I MHC viral peptide
Vesicle
Golgi complex
Viral peptides
Polysomes
Rough endoplasmic reticulum
Viral protein
Ribosome
Viral mRNA
Viral DNA
Virus


Peptide–class II MHC complex
Antigen ingested by endocytosis or phagocytosis
Peptides of antigen
Class II MHC
Lysosome
Endosome
Endocytic processing pathway
Nucleus



Class I Molecule

Two polypeptides assemble to form a single class I MHC molecule: a 45-kilodalton (kDa) **α chain** and a 12-kD **β_2-microglobulin** molecule .

The **α chain** is organized into **three external domains (α1, α2, and α3)**, each approximately **90 amino acids long**; a **transmembrane domain** of about **25 hydrophobic amino** acids followed by a short stretch of charged (hydrophilic) amino acids; and a **cytoplasmic anchor** segment of **30 amino acids.**

Its companion, **β_2-microglobulin** is similar in size and organization to the α3 domain. **β_2-microglobulin** does not contain a transmembrane region and is noncovalently bound to the MHC class I **α chain**.

The **α1** and **α2 domains** interact to form a platform of **eight antiparallel β strands spanned by two long α-helical regions**.

The structure forms a **deep groove, or cleft** , with the long α helices as sides and the **β** strands of the sheet as the bottom. This ***peptide-binding groove*** **is located on the top surface of the class I MHC molecule, and it is large enough to bind a peptide of 8 to 10 amino acids.**

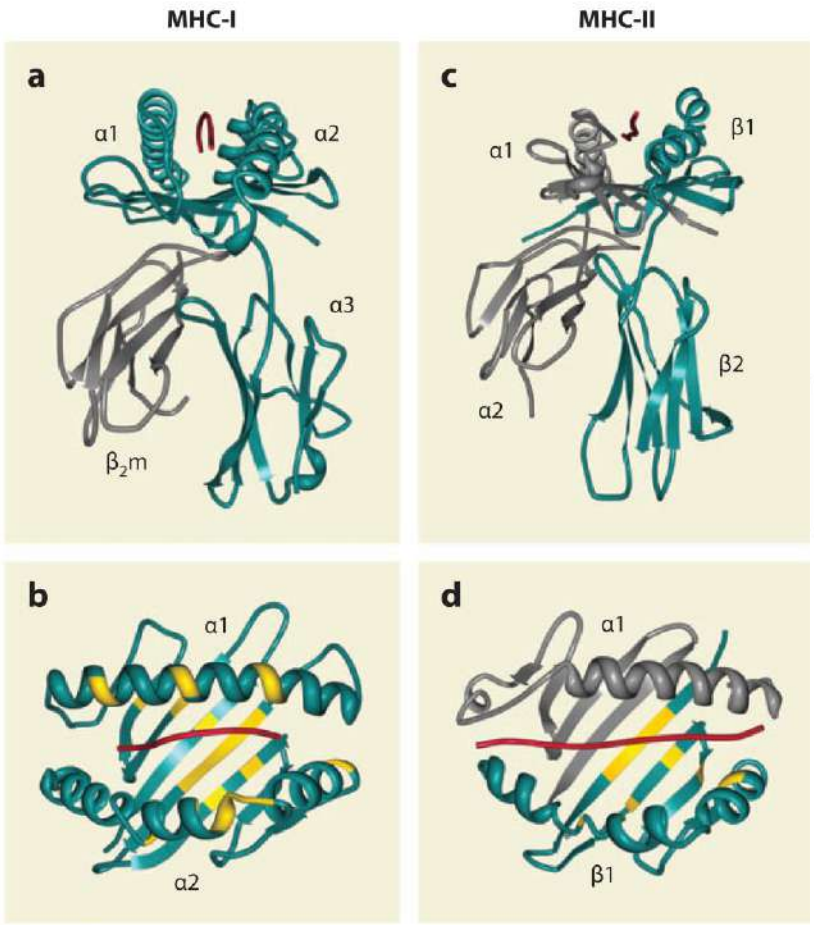


Figure 1

Three-dimensional structures of MHC-I and MHC-II molecules with peptide ligands. (*a*,*b*) Structure of the MHC-I molecule: HLA-A2 complexed with residues 58–66 of the influenza matrix protein (232) (*teal*, MHC-I heavy chain; *gray*, β_2-microglobulin; *red*, peptide). (*c*,*d*) Structure of the MHC-II molecule: HLA-DR1 complexed with residues 306–318 of influenza hemagglutinin (233) (*gray*, MHC-II α chain; *teal*, MHC-II β chain; *red*, peptide). Ribbon diagrams

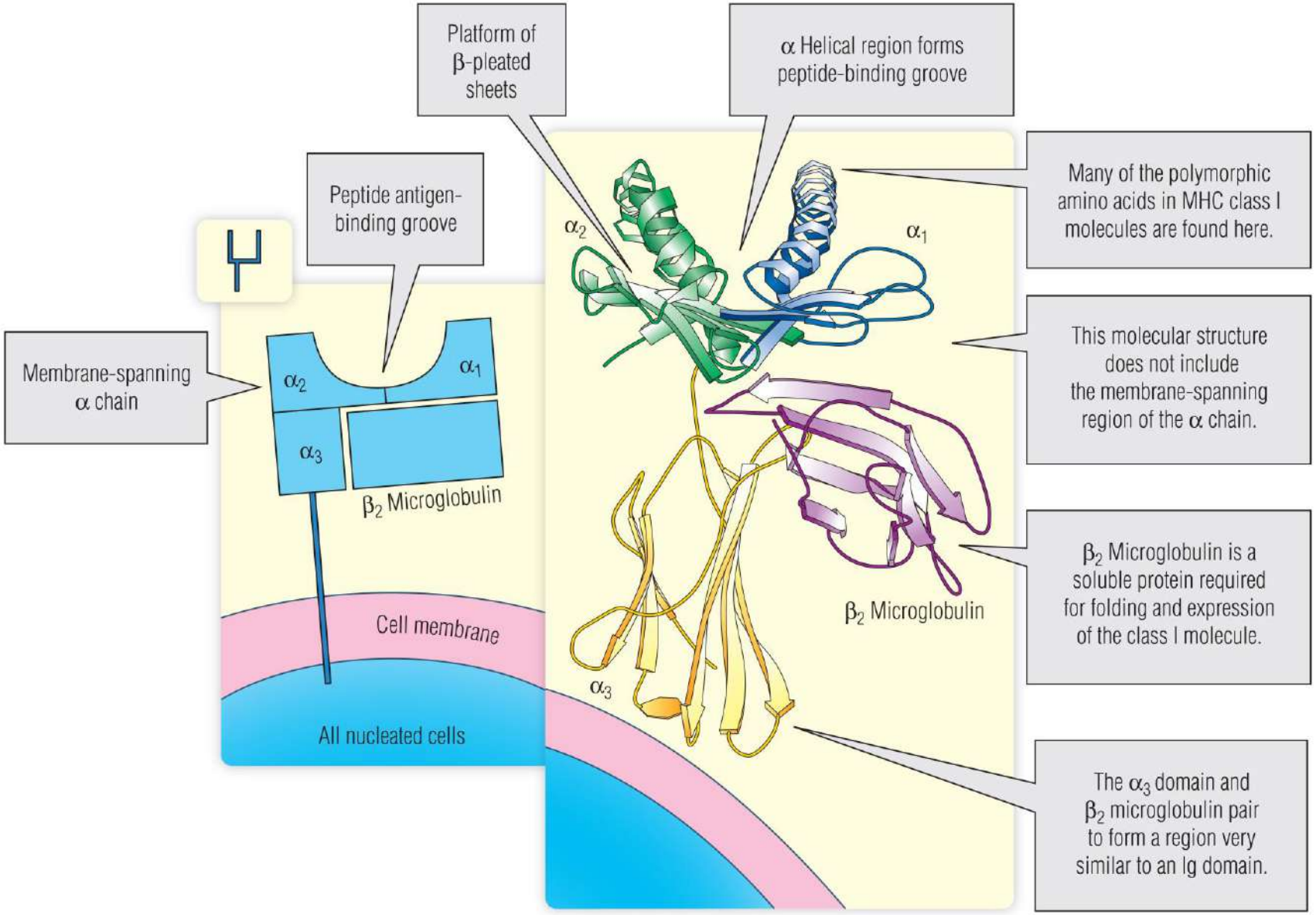
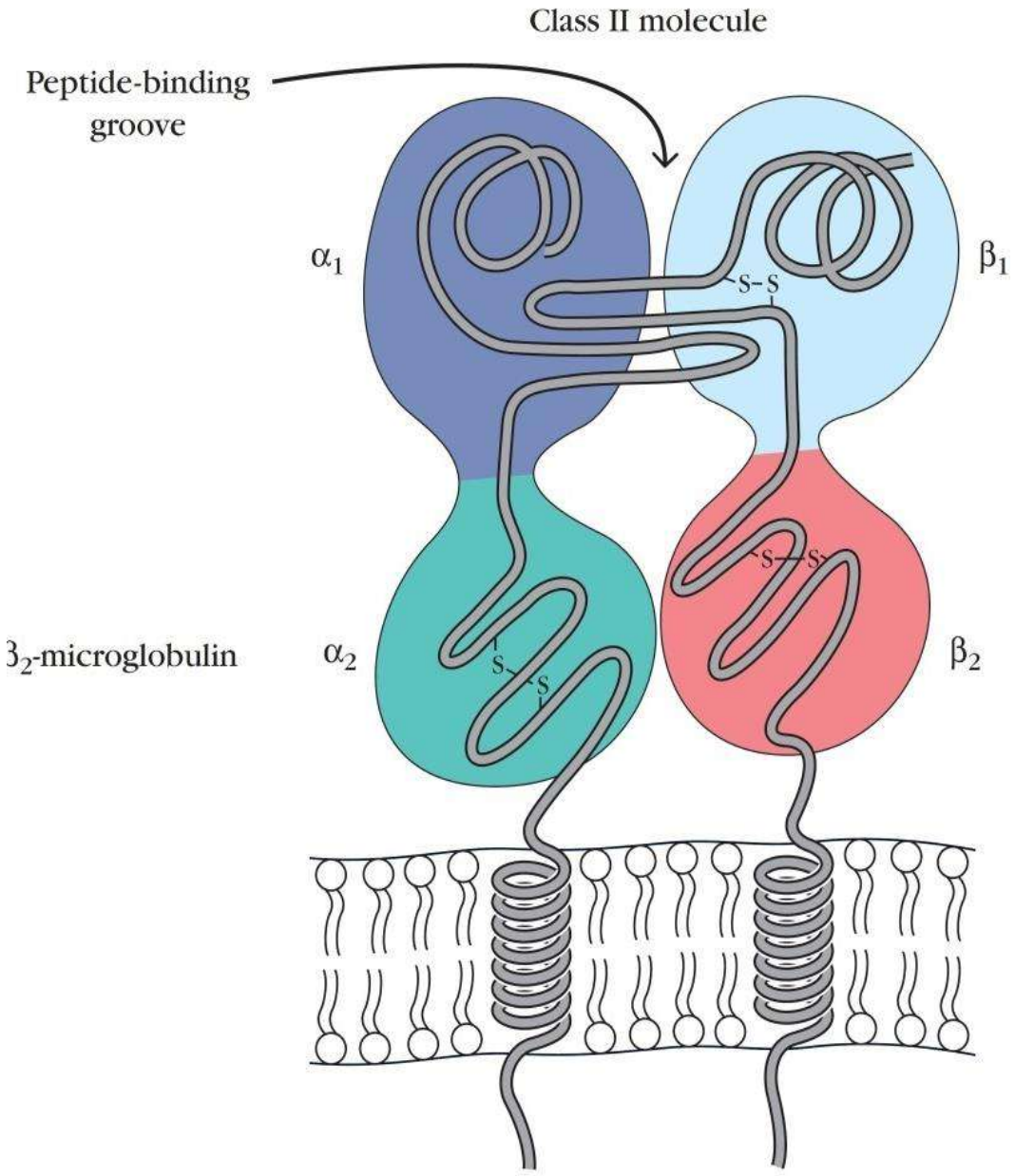


Fig 8.4 Structure of major histocompatibility complex (MHC) class I molecules. *Ig*, immunoglobulin.



Class II Molecule

Class II MHC molecules contain two different polypeptide chains, a **33-kDa α chain** and **a 28-kDa β chain,** which associate by noncovalent interactions.

Class II MHC molecules are membrane bound glycoproteins that contain external domains, a transmembrane segment, and a cytoplasmic anchor segment.

Each chain in a class II molecule contains two external domains: **α**1 and **α**2 domains in one chain and **β**1 and **β**2 domains in the other.

The **α**1 and **β**1 domains form the peptide-binding groove for processed antigen. The peptide-binding groove of class II molecules is composed of a **floor of eight antiparallel β strands and sides of antiparallel α helices, where peptides typically ranging from 13 to 18 amino acids can bind.**

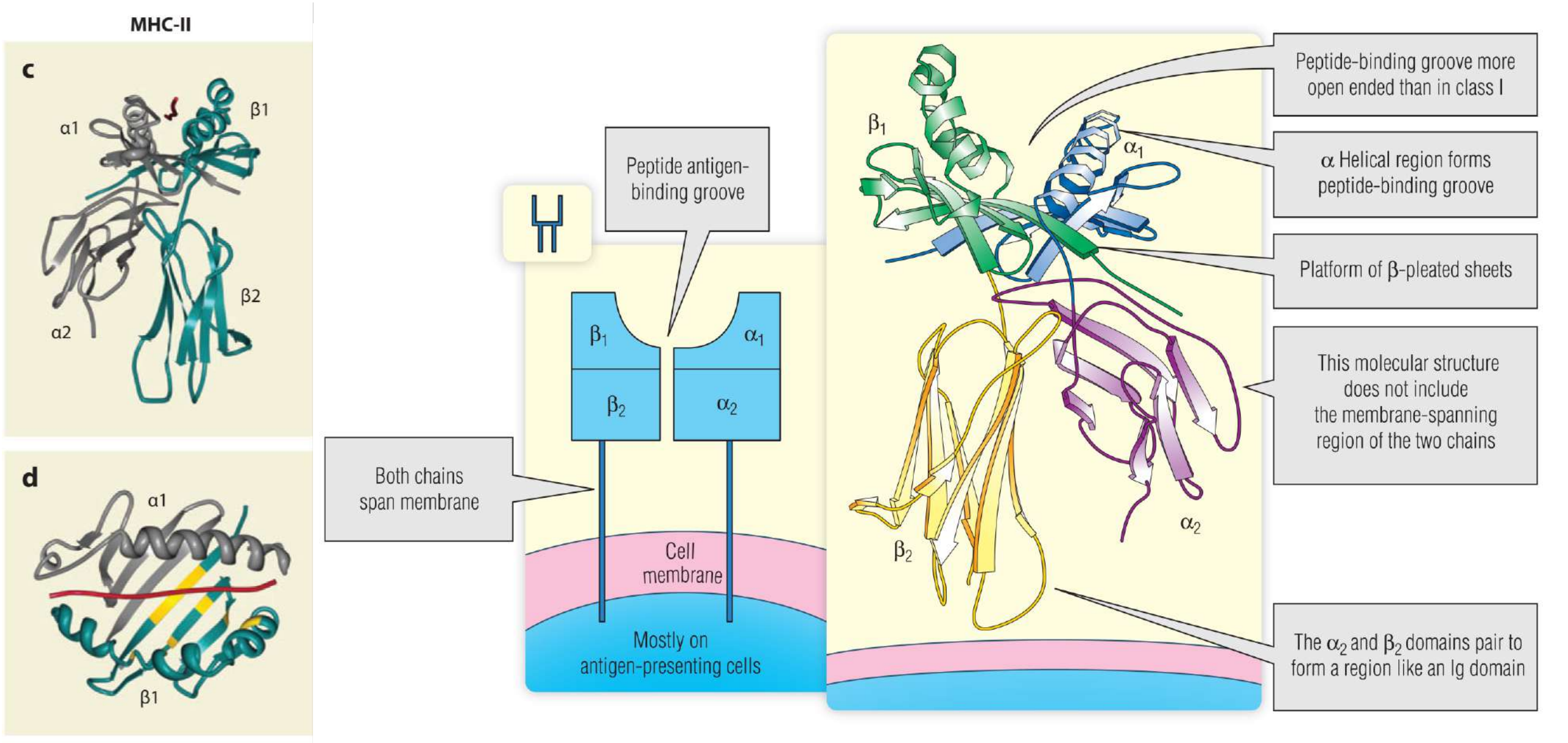


Fig 8.5 Structure of major histocompatibility complex (MHC) class II molecules. *Ig,* immunoglobulin. (Modified from Roitt I, Brostoff J, Male D. *Immunology*, ed 6. London: Mosby; 2001.)

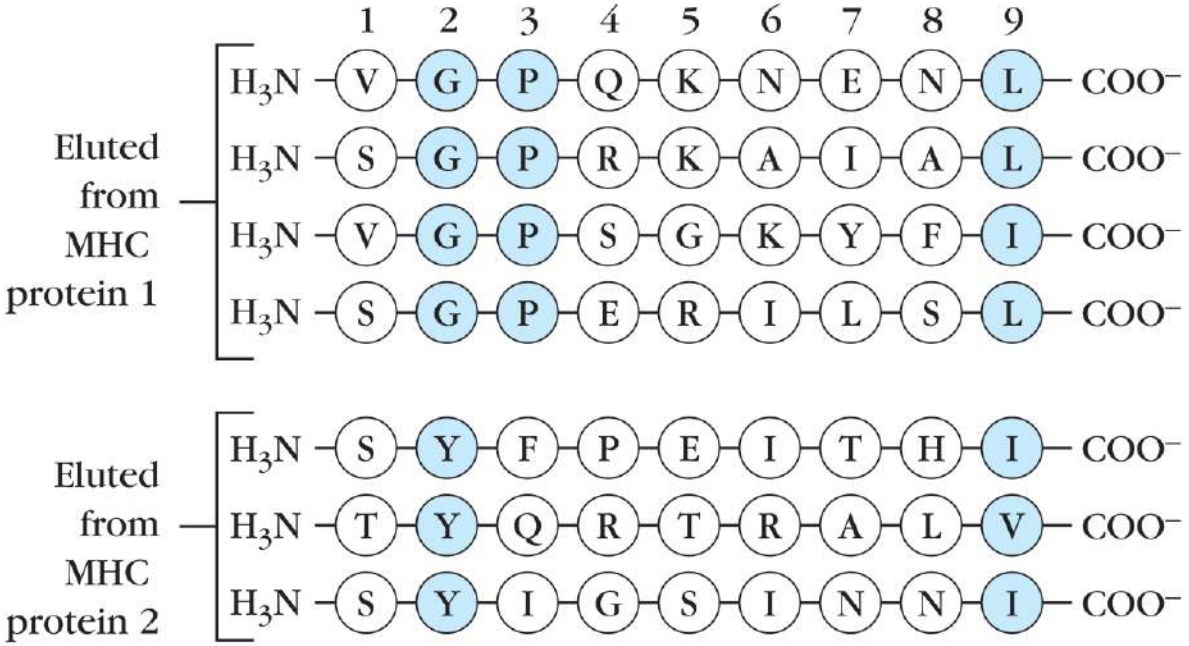


FIGURE 8-5 Examples of anchor residues (blue) in nonameric peptides eluted from two different class I MHC molecules. Anchor residues, at positions 2/3 and 9, that interact with the class I MHC molecule tend to be hydrophobic amino acids. The two MHC proteins bind peptides with different anchor residues. *[Data*

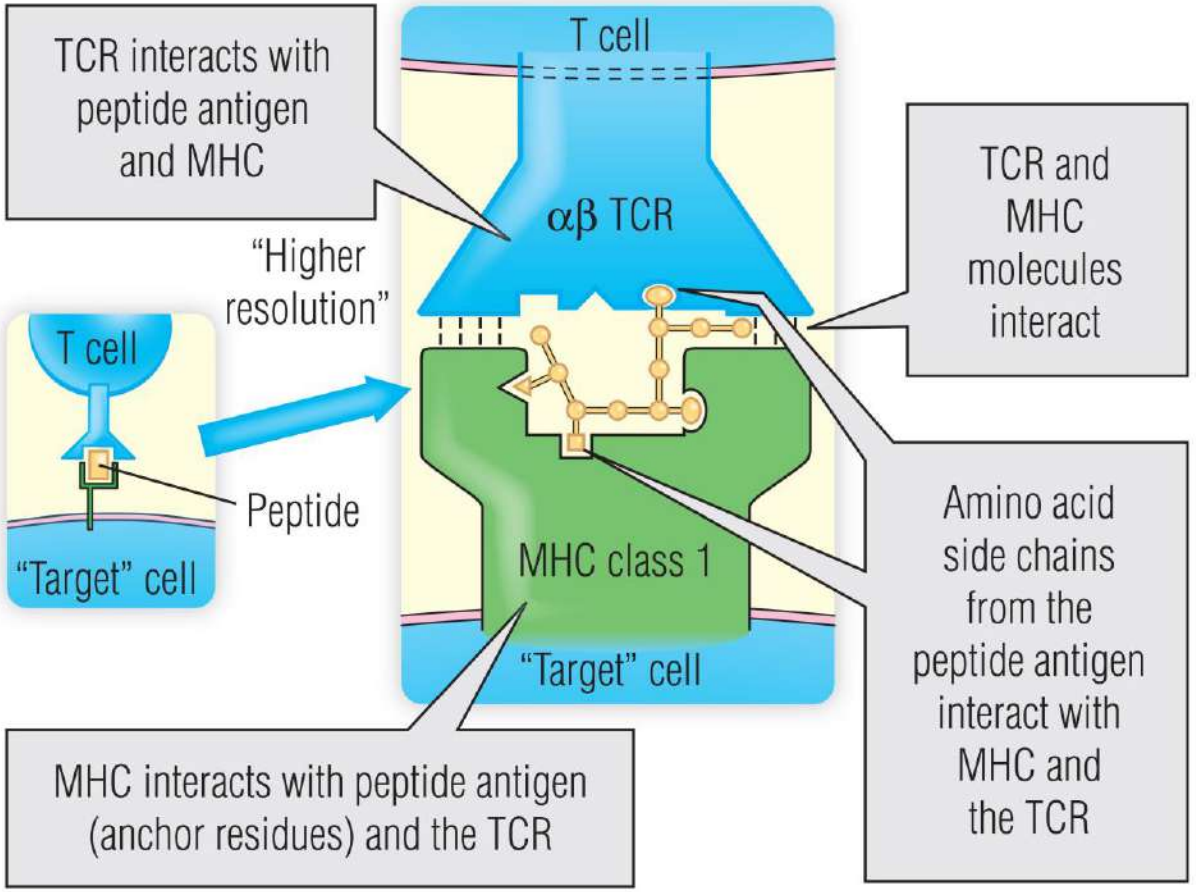
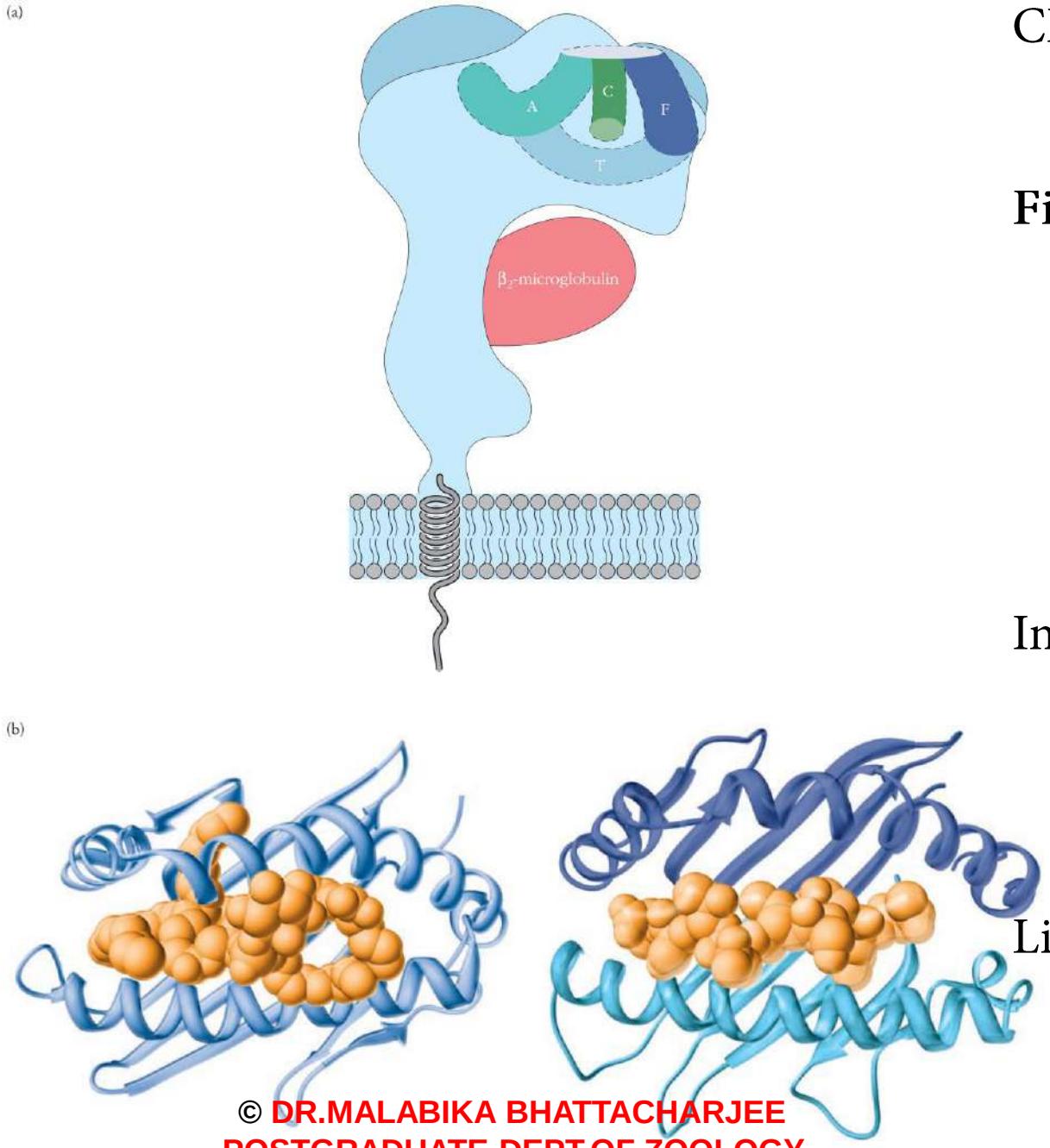


Fig 8.7 Structure of major histocompatibility complex (MHC)–antigen–T-cell receptor (TCR) complex.



CD1 molecules share structural similarity to classical MHC class I but overlap functionally with MHC class II.

Five human CD1 genes are known; all are encoded on a chromosome separate from the classical class I molecules and display very limited polymorphism. Much like classical MHC class I, CD1 proteins are formed by a **transmembrane heavy chain, composed of three extracellular α domains**, which associates noncovalently with **β_2-microglobulin**.

In terms of **trafficking and expression profile**, however, most **CD1 molecules resemble MHC class II proteins**, moving intracellularly to endosomal compartments, where they associate with exogenous antigen.

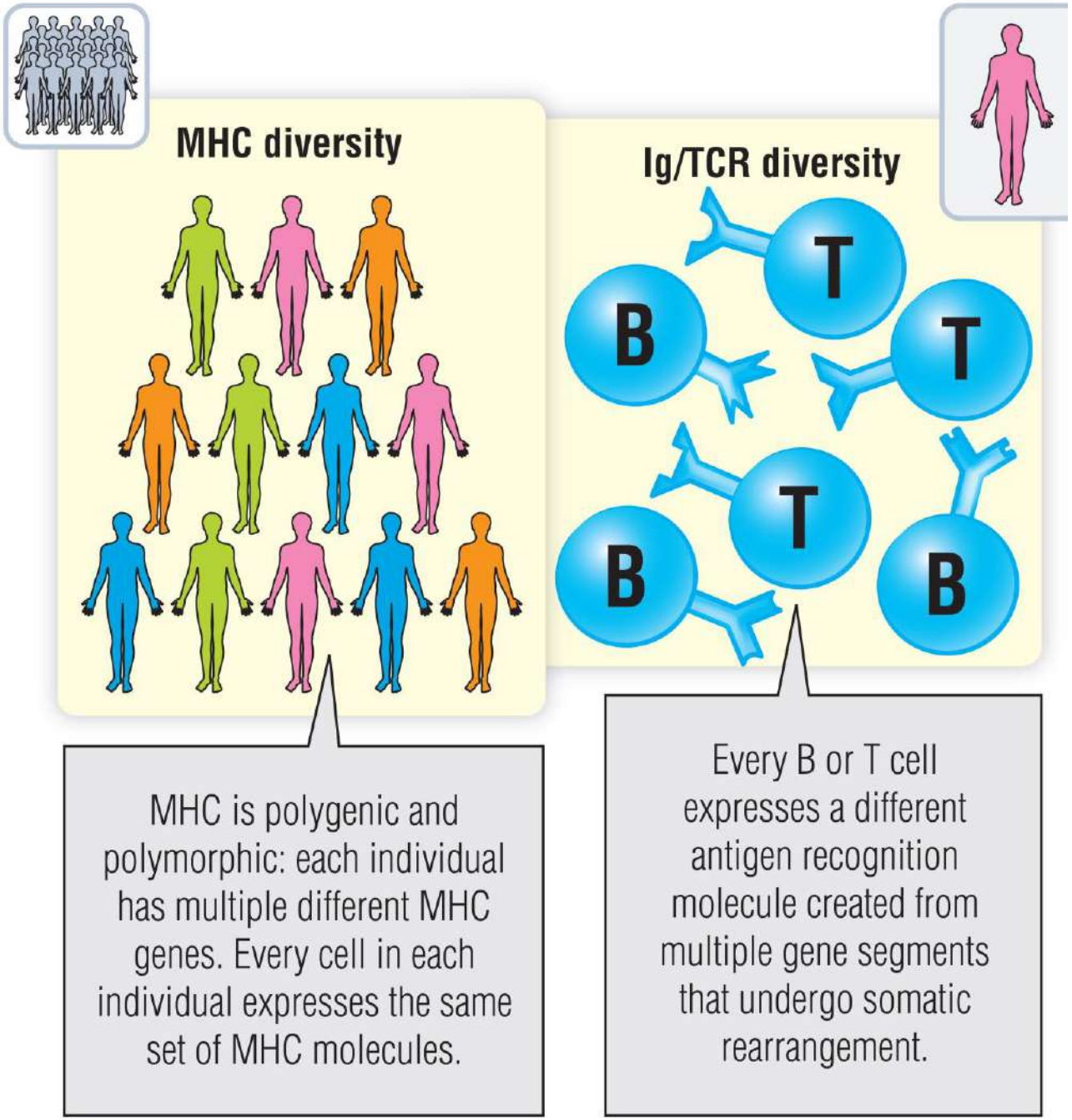
Like MHC class II molecules, CD1 proteins are expressed by many immune cell types, including thymocytes, B cells, and DCs, although some members of the family have also been found on hepatocytes and epithelial cells.

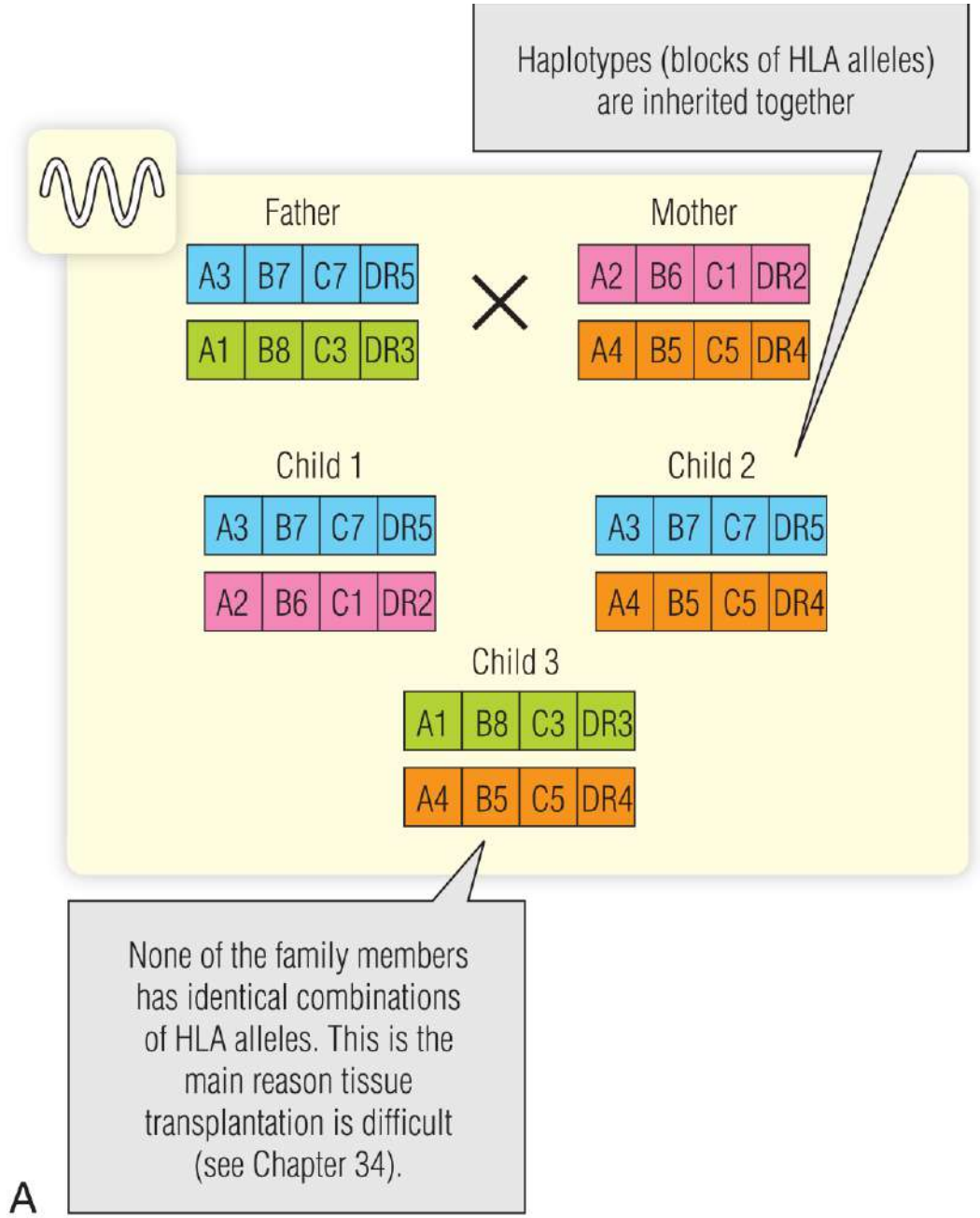
It is now hypothesized that **short-chain self-lipids** with relatively low affinity are loaded onto **CD1 molecules** in the ER, shortly after translation, and allow proper CD1 protein folding.

These **self-antigen loaded CD1 molecules** then travel to the cell surface, where in some cases exogenous lipids may be exchanged with these low-affinity self-antigens.

Like with **MHC class II molecules, after endocytosis and movement to lower pH environments, CD1 proteins are believed to exchange their self peptide**, low-affinity binding partners for **exogenously derived long-chain, high-affinity lipid antigens resident in phagolysosomes or late endosomes**.

These newly loaded CD1 molecules then return to the cell surface for recognition by CD1-restricted T cells.





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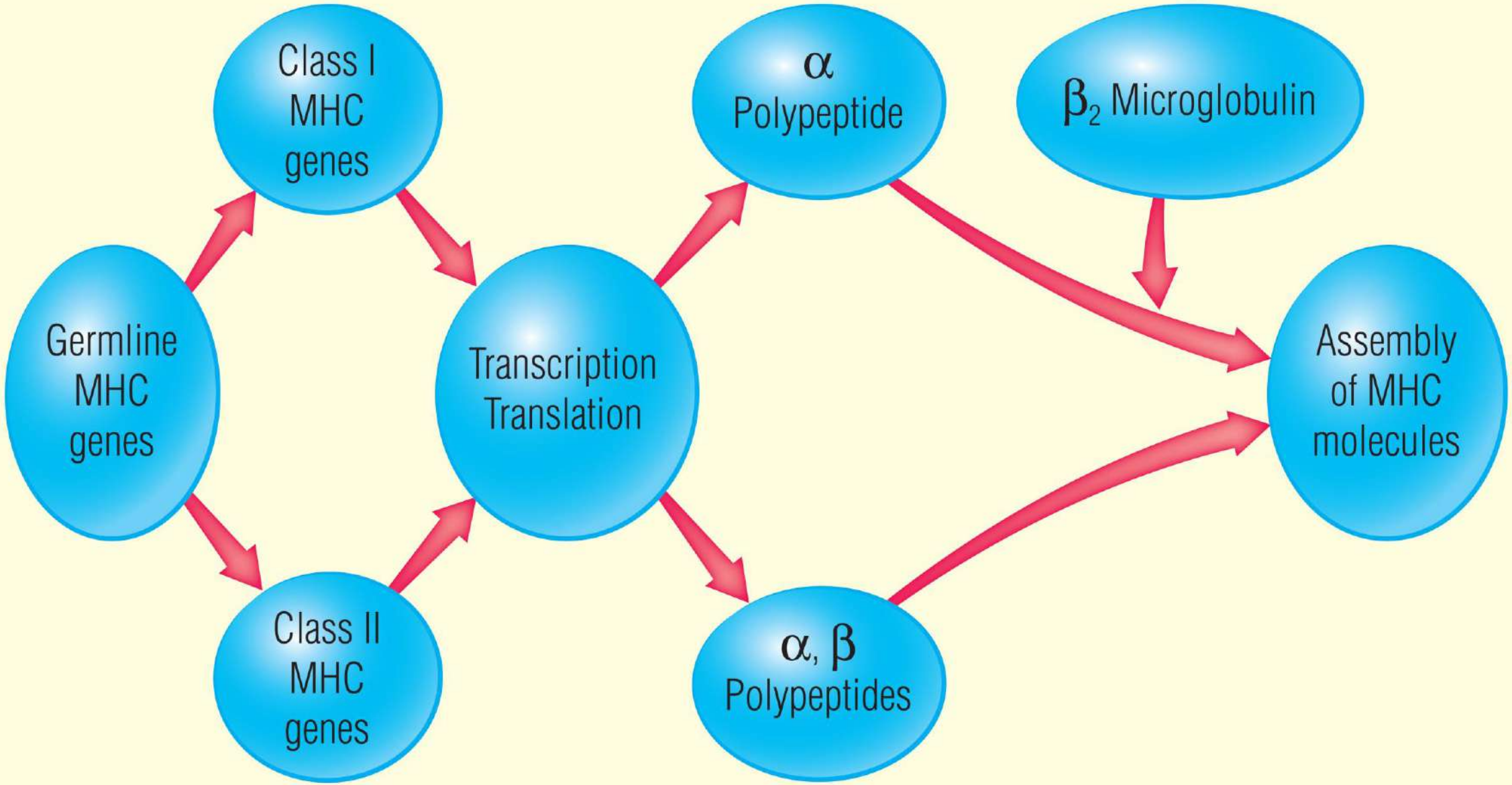
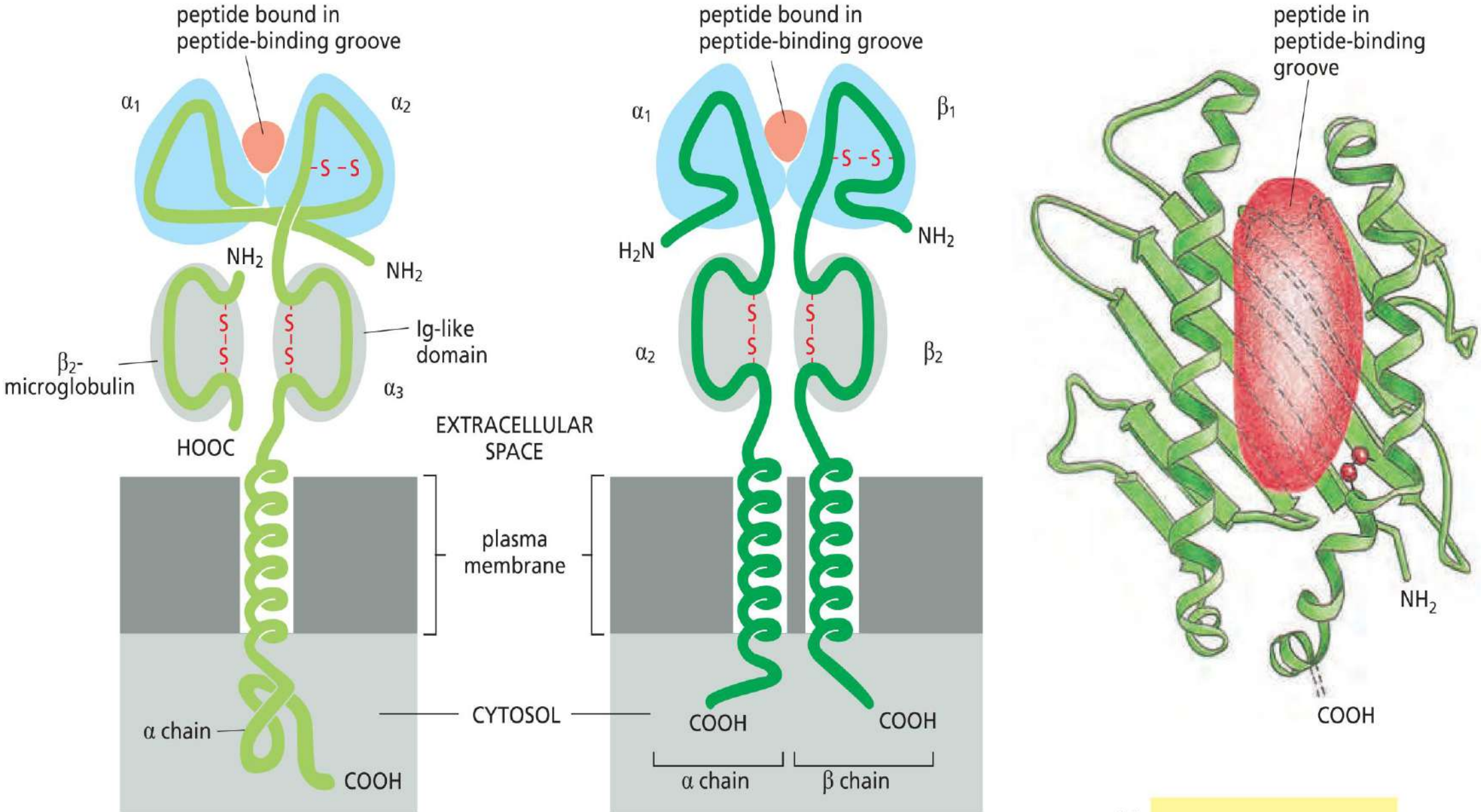


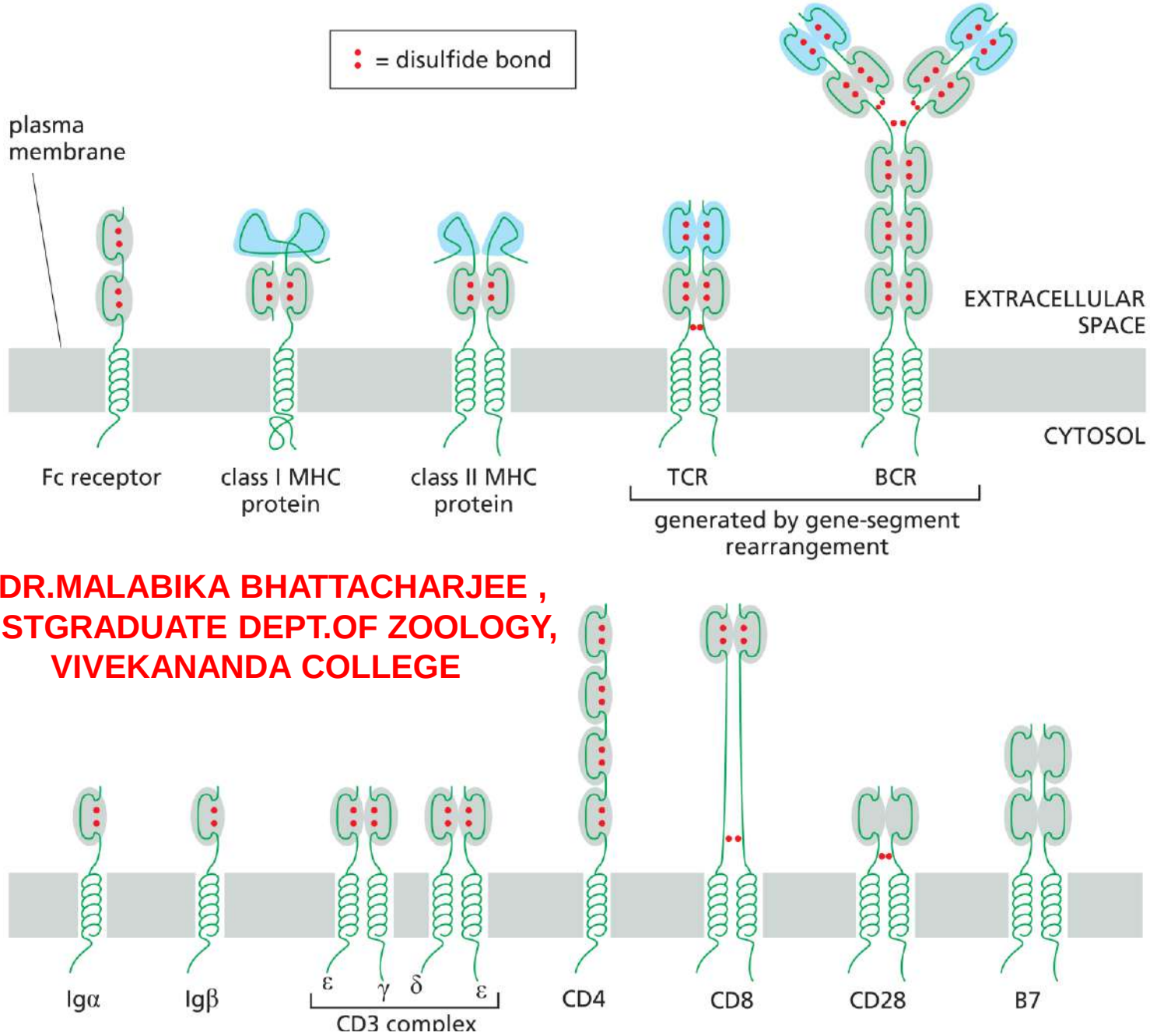


(A) CLASS I MHC PROTEIN

(B) CLASS II MHC PROTEIN

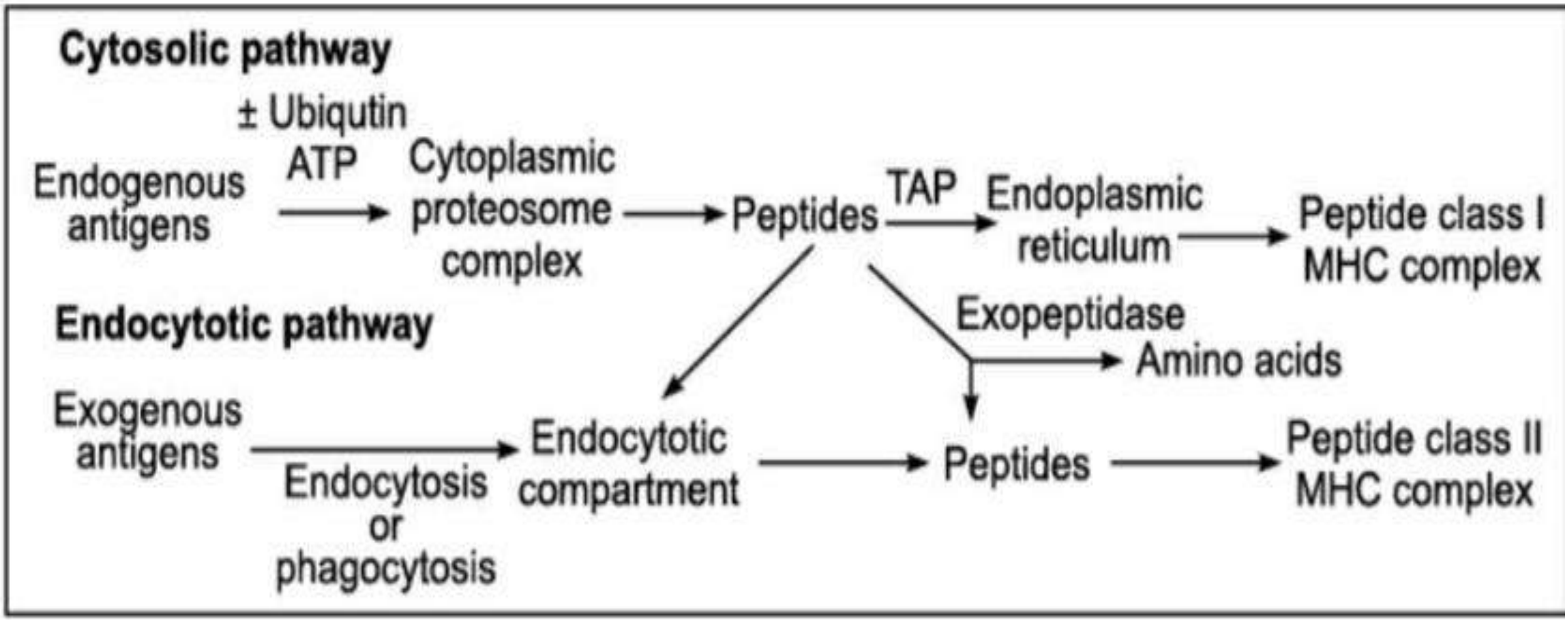
(C) TOP VIEW OF BINDING GROOVE OF CLASS I MHC PROTEIN

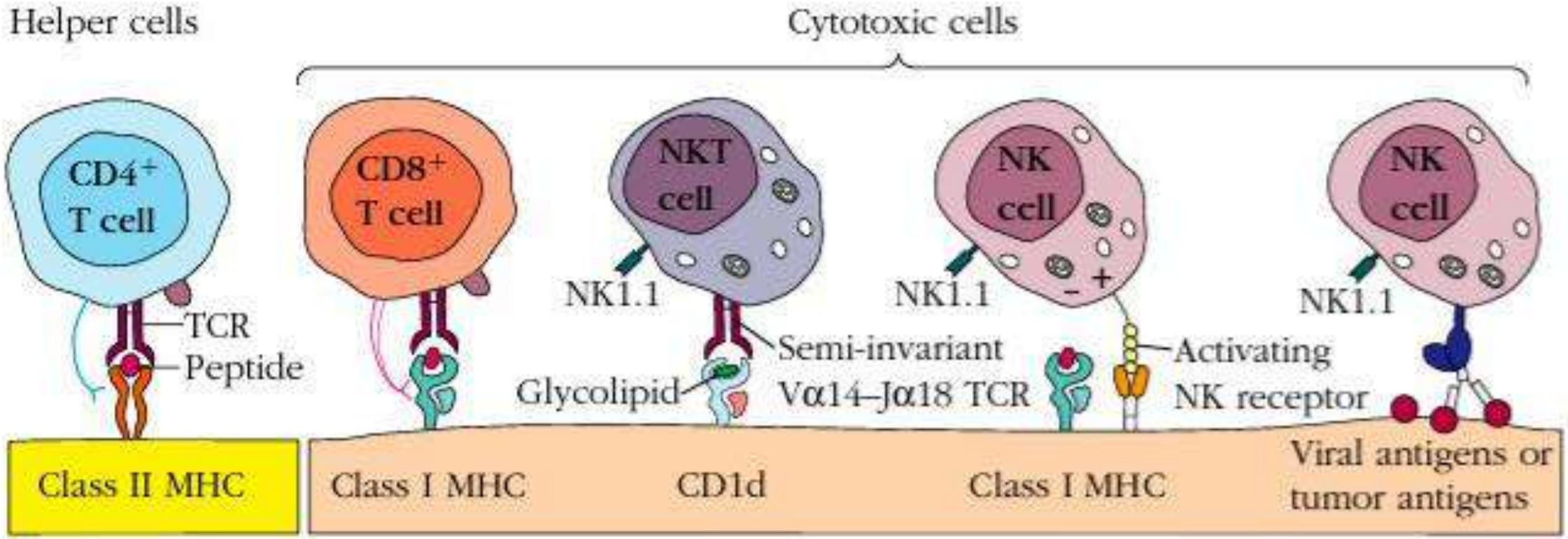
	Class I	Class II
Genetic loci	*HLA-A, HLA-B, HLA-C*	*HLA-DP, HLA-DQ, HLA-DR*
Chain structure	α chain + β_2-microglobulin	α chain + β chain
Cell distribution	Most nucleated cells	Dendritic cells, B cells, macrophages, thymus epithelial cells, some others
Presents antigen to	Cytotoxic T cells	Helper T cells, regulatory T cells
Source of peptide fragments	Mainly proteins made in cytoplasm	Mainly endocytosed plasma membrane and extracellular proteins
Polymorphic domains	$\alpha_1 + \alpha_2$	$\alpha_1 + \beta_1$
Recognition by co-receptor	CD8	CD4

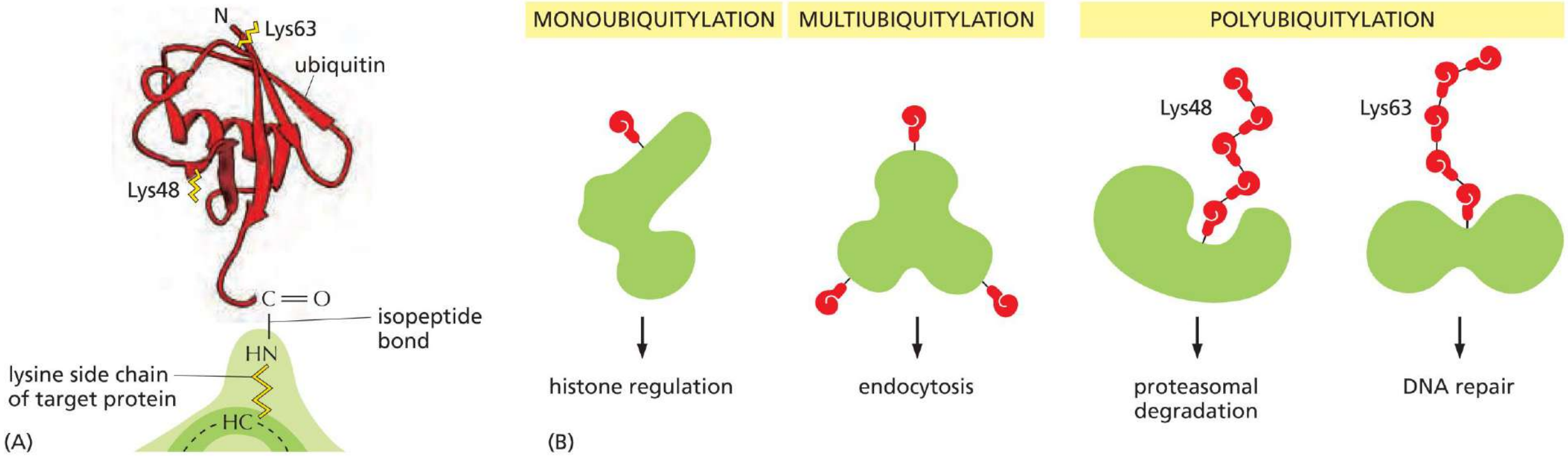


Many Cell-Surface Proteins Belong to the Ig Superfamily

1. Most of the proteins that mediate antigen recognition and cell–cell recognition in the immune system contain one or more Ig or Ig-like domains, suggesting that the proteins have a common evolutionary history.
2. Included in this very large **Ig superfamily are antibodies, TCRs, MHC proteins, the CD4, CD8, and CD28 co-receptors,** the ***B7 co-stimulatory proteins***, and most of the ***invariant polypeptide chains associated with TCRs and BCRs, as well as the various Fc receptors on lymphocytes and other leukocytes***.
3. Many of these proteins are dimers or higher oligomers, in which Ig or Ig-like domains of one chain interact with those in another





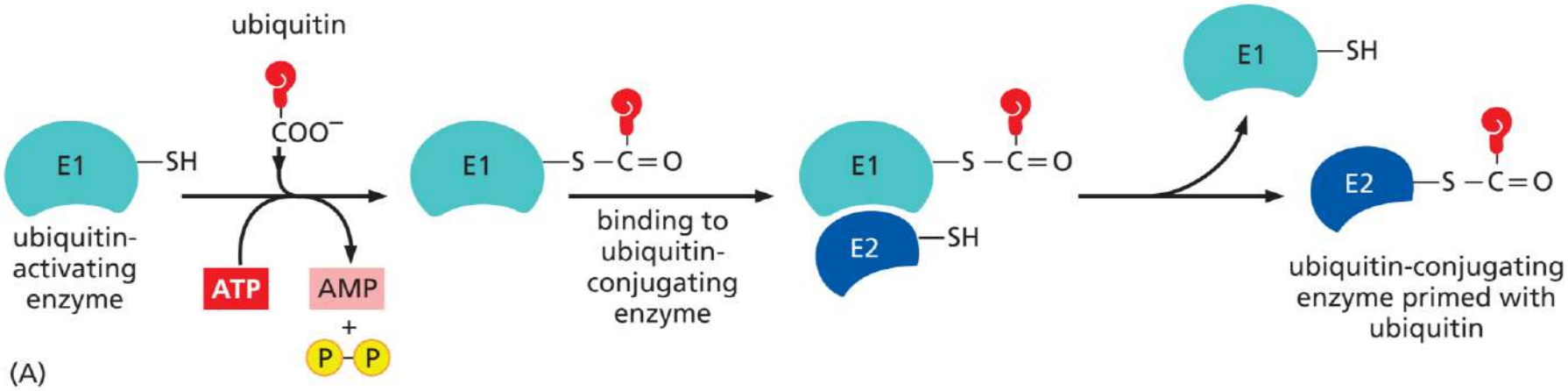


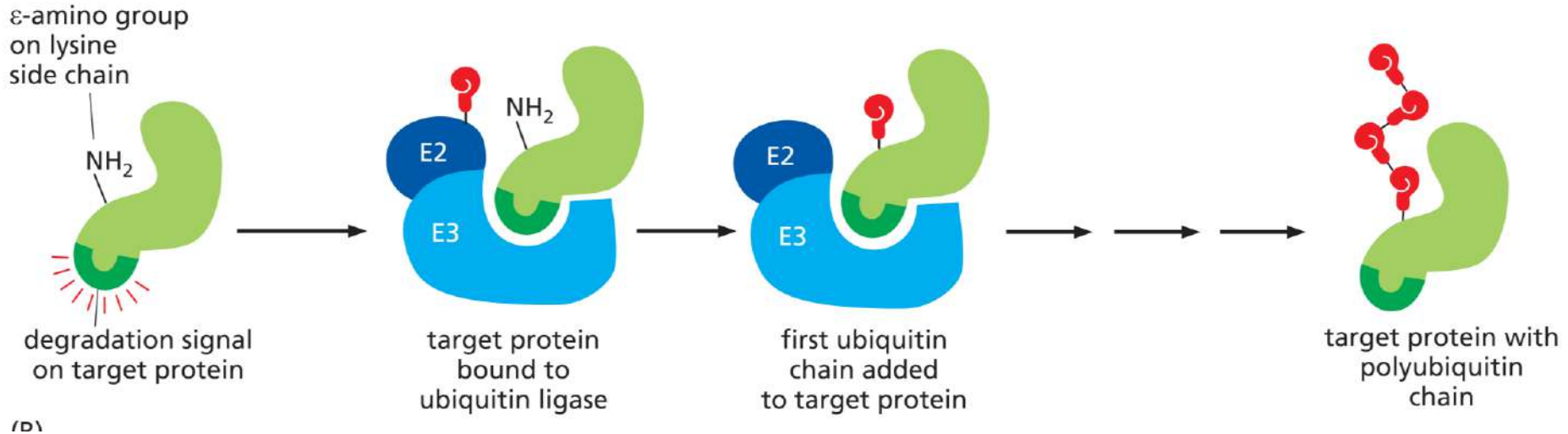
The marking of proteins by ubiquitin.

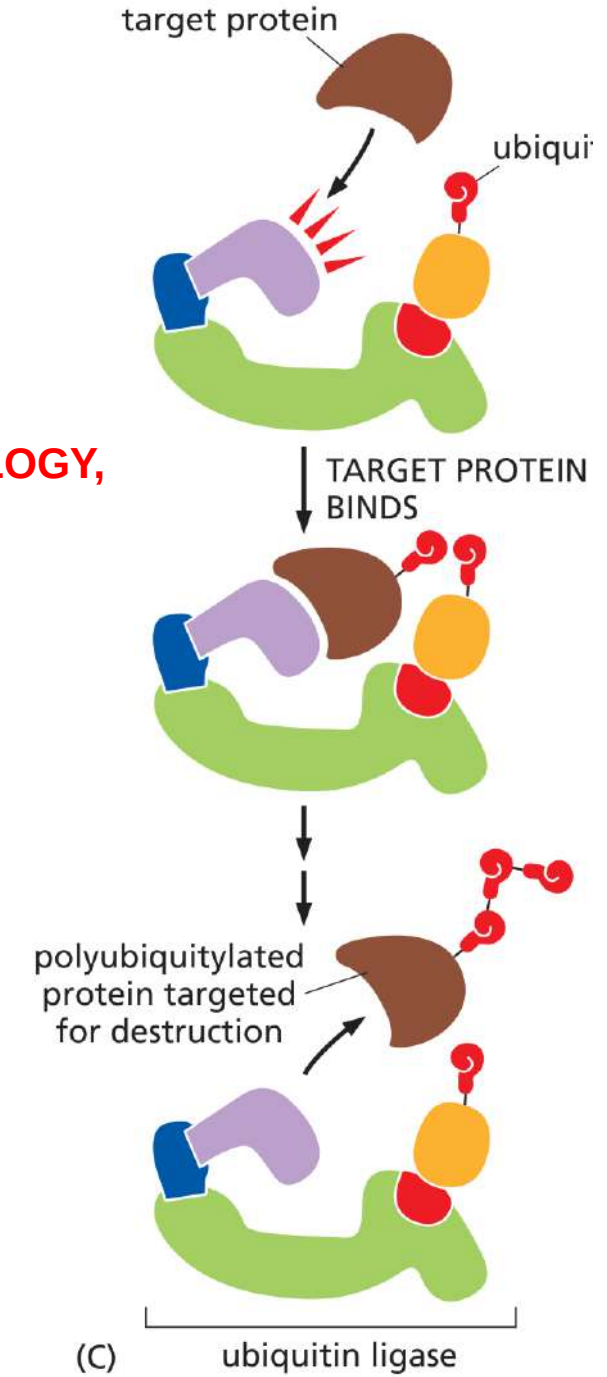
(A)The three-dimensional structure of ubiquitin, a small protein of 76 amino acids. A family of special enzymes couples its ***carboxyl end to the amino group of a lysine side chain*** in a target protein molecule, forming an isopeptide bond.

(B)Some modification patterns that have specific meanings to the cell. Note that the two types of polyubiquitylation differ in the way the ubiquitin molecules are linked together. Linkage through **Lys48 *signifies degradation by the proteasome***, whereas that through Lys63 has other meanings.

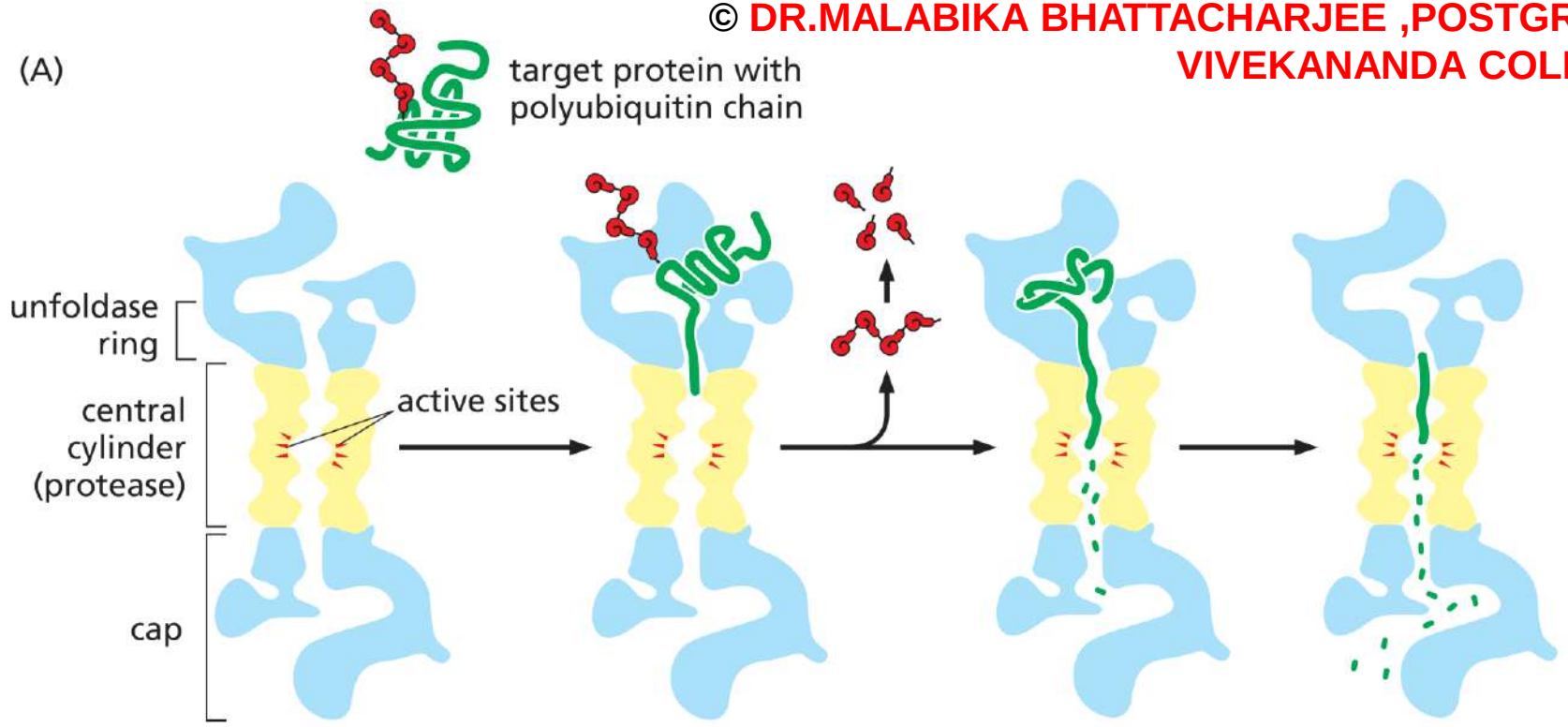
(C)Ubiquitin markings are "read" by proteins that specifically recognize each type of modification.

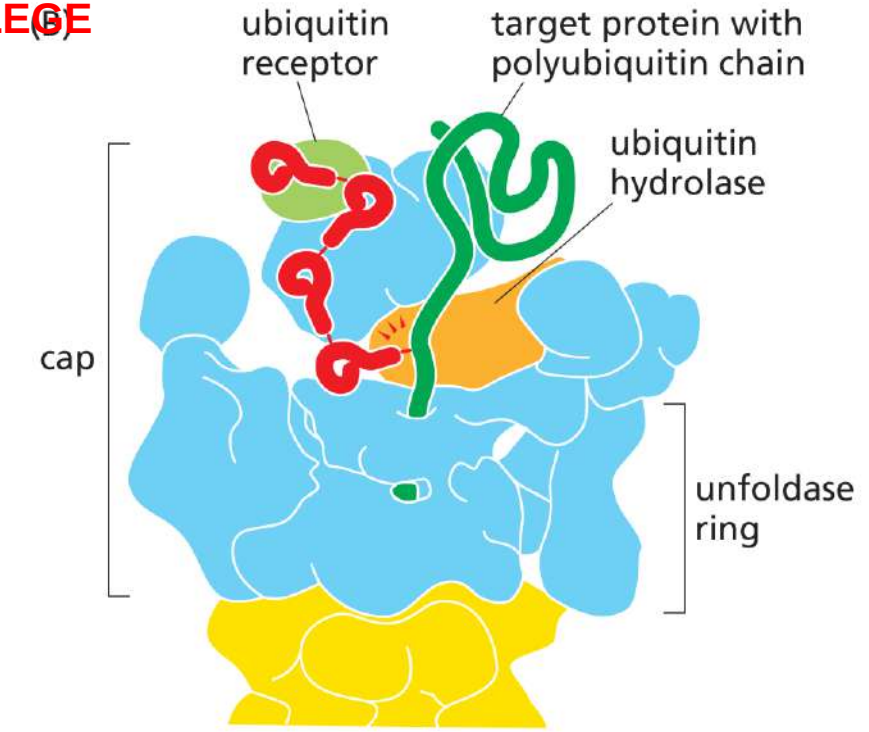






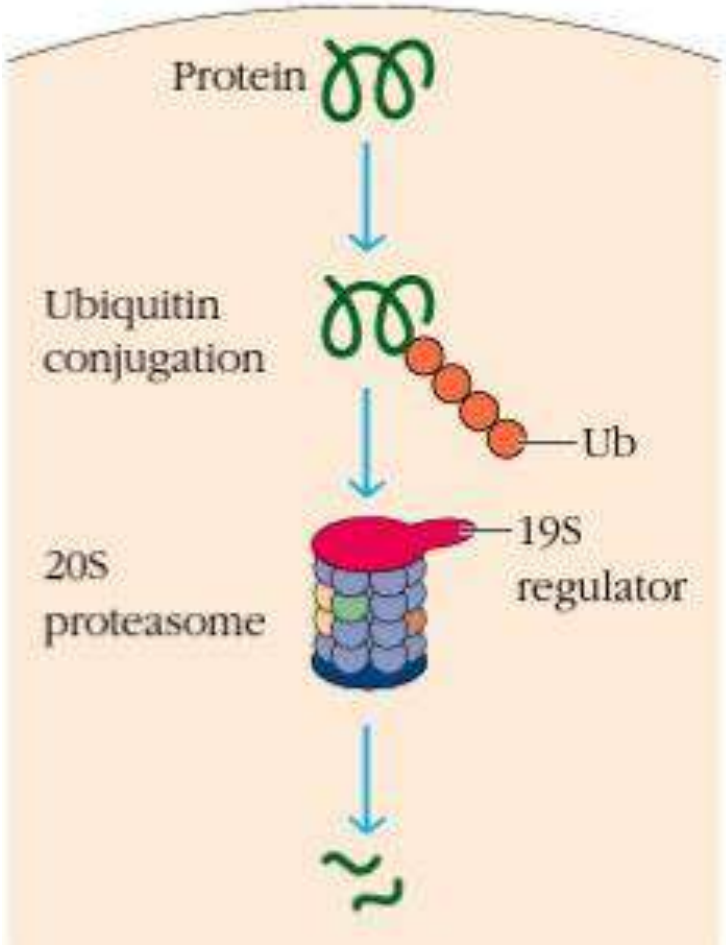
1. The C-terminus of ubiquitin is initially activated through its **high-energy thioester linkage to a cysteine side chain on the E1 protein**.
2. This reaction requires ATP, and it proceeds via a covalent AMP-ubiquitin intermediate.
3. The activated ubiquitin on E1, also known as the ubiquitin-activating enzyme, is then transferred to the cysteines on a set of E2 molecules.
4. These E2s exist as complexes with an even larger family of E3 molecules.

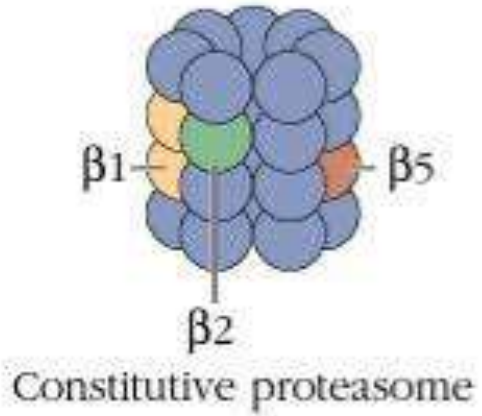


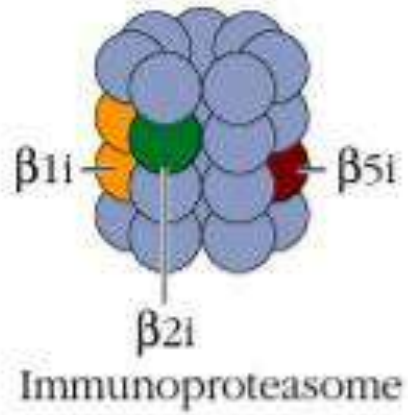


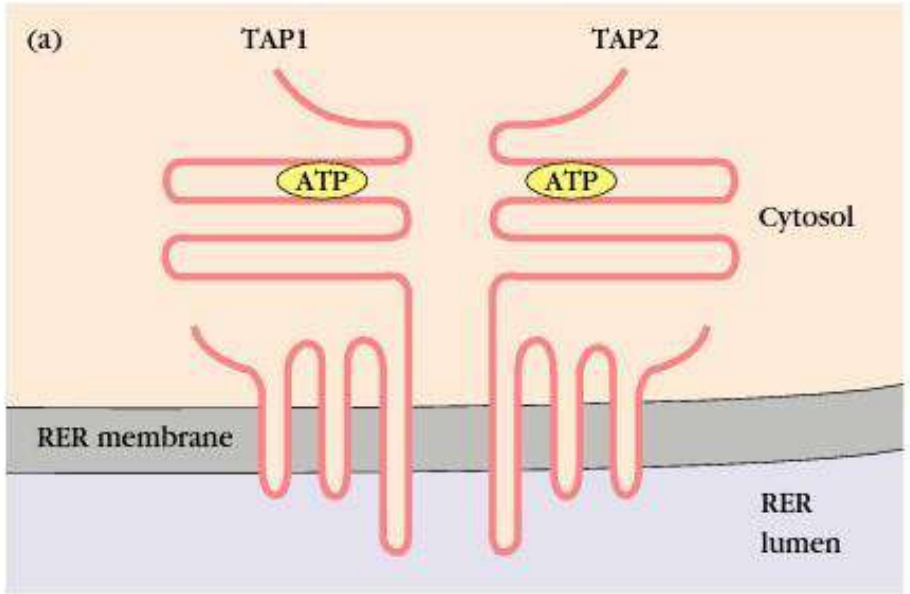
Processive protein digestion by the proteasome.

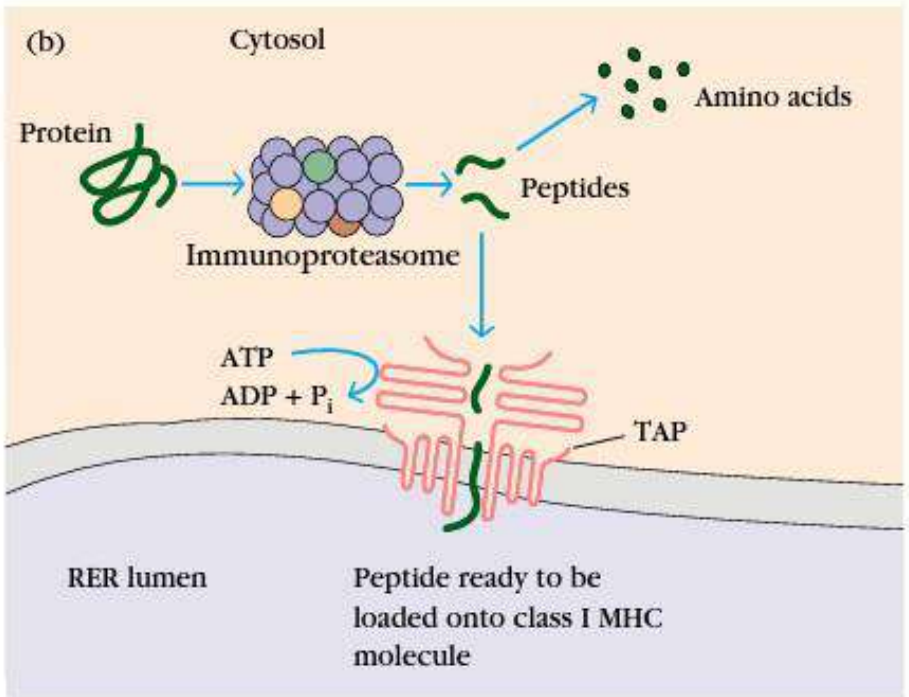
1. The proteasome cap recognizes proteins marked by a polyubiquitin chain, and subsequently translocates them into the proteasome core, where they are digested. At an early stage, the ubiquitin is cleaved from the substrate protein and is recycled.
2. Translocation into the core of the proteasome is ***mediated by a ring of ATPases*** that unfold the substrate protein as it is threaded through the ring and into the proteasome core.
3. Detailed structure of the proteasome cap. The cap includes a ubiquitin receptor, which holds a ubiquitylated protein in place while it begins to be pulled into the proteasome core, and a ubiquitin hydrolase, which cleaves ubiquitin from the doomed protein.

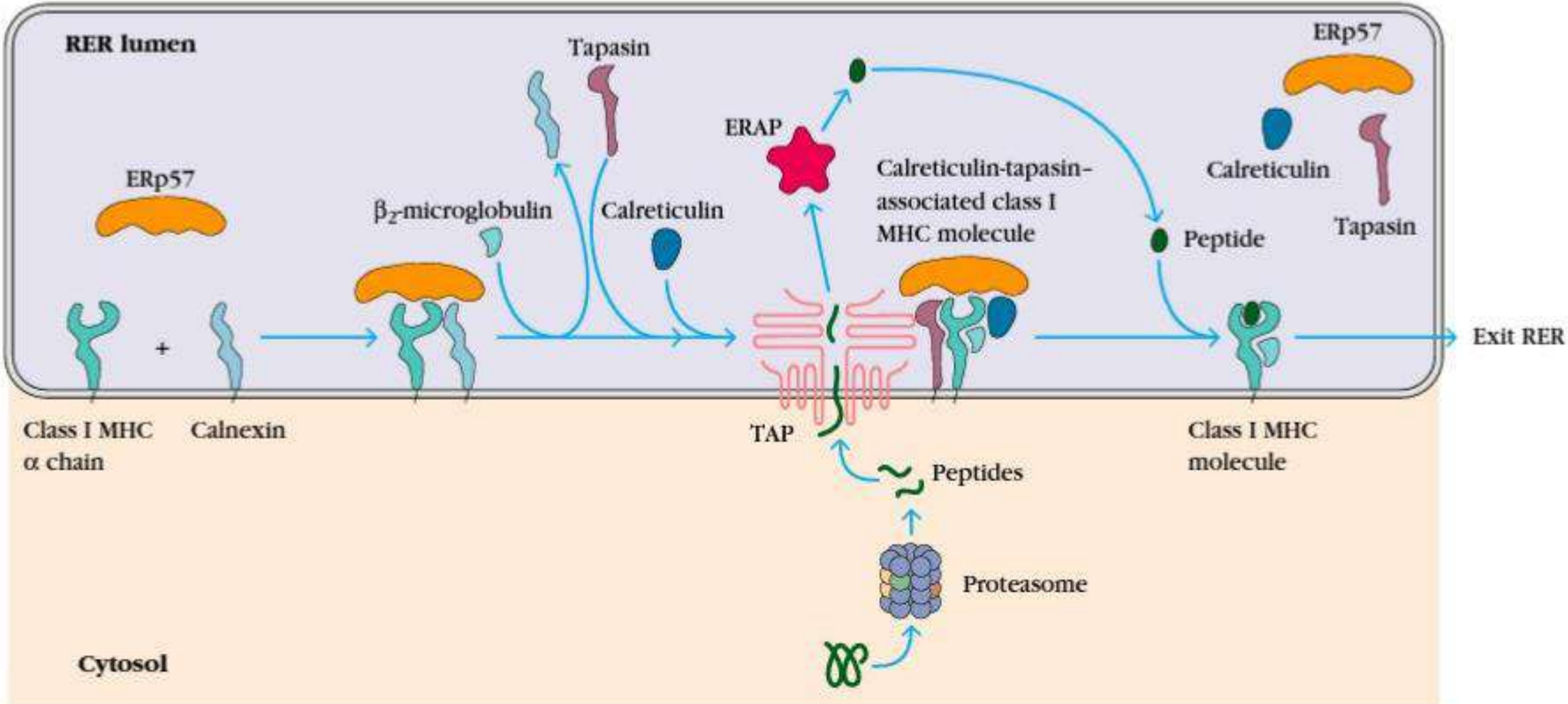


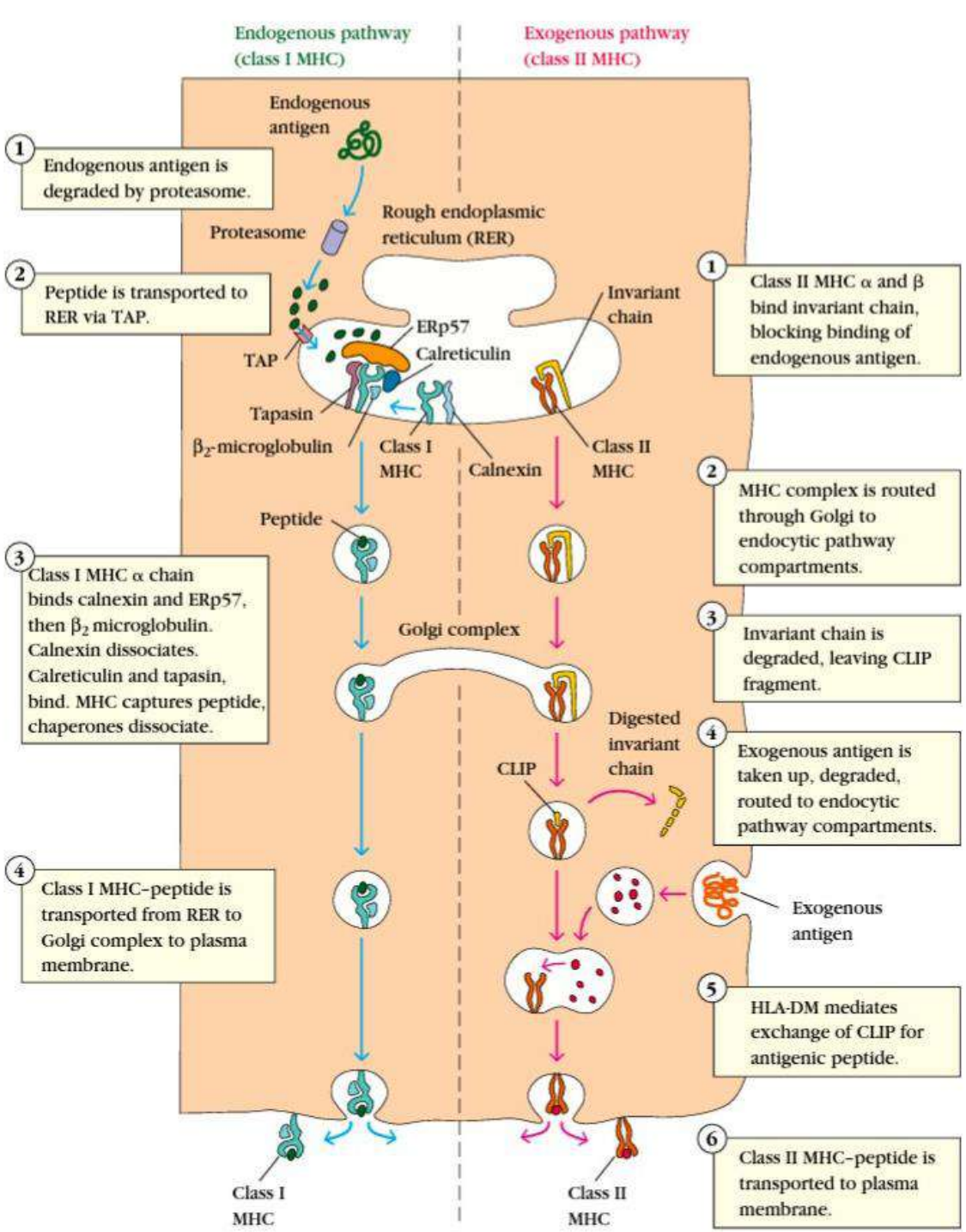












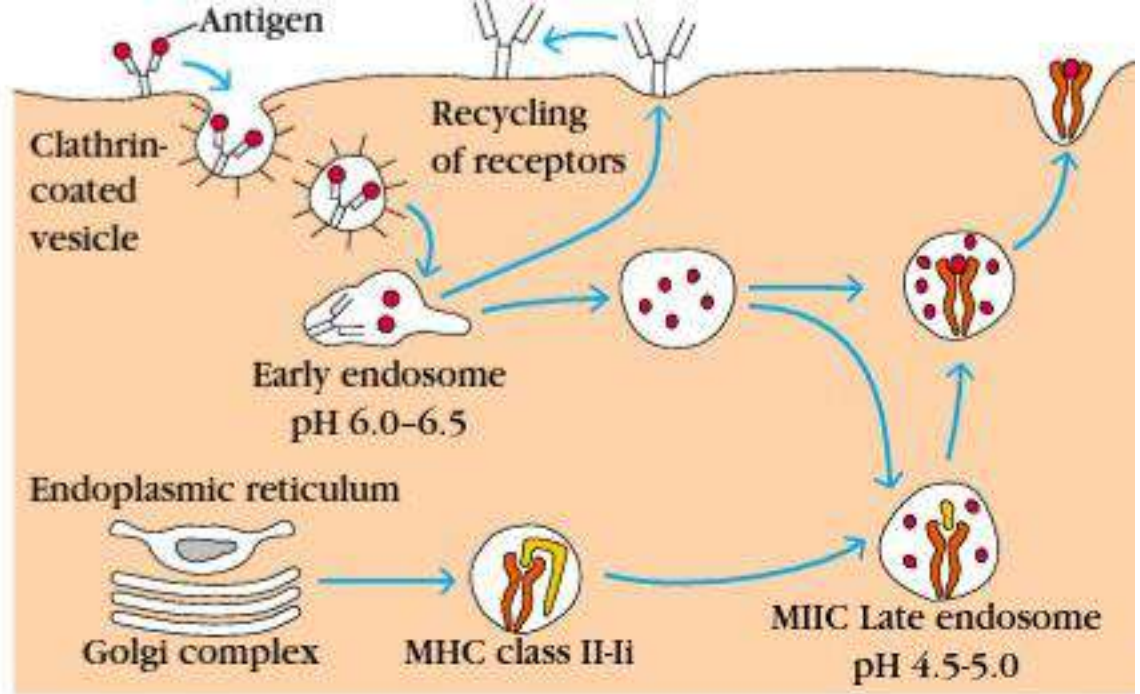
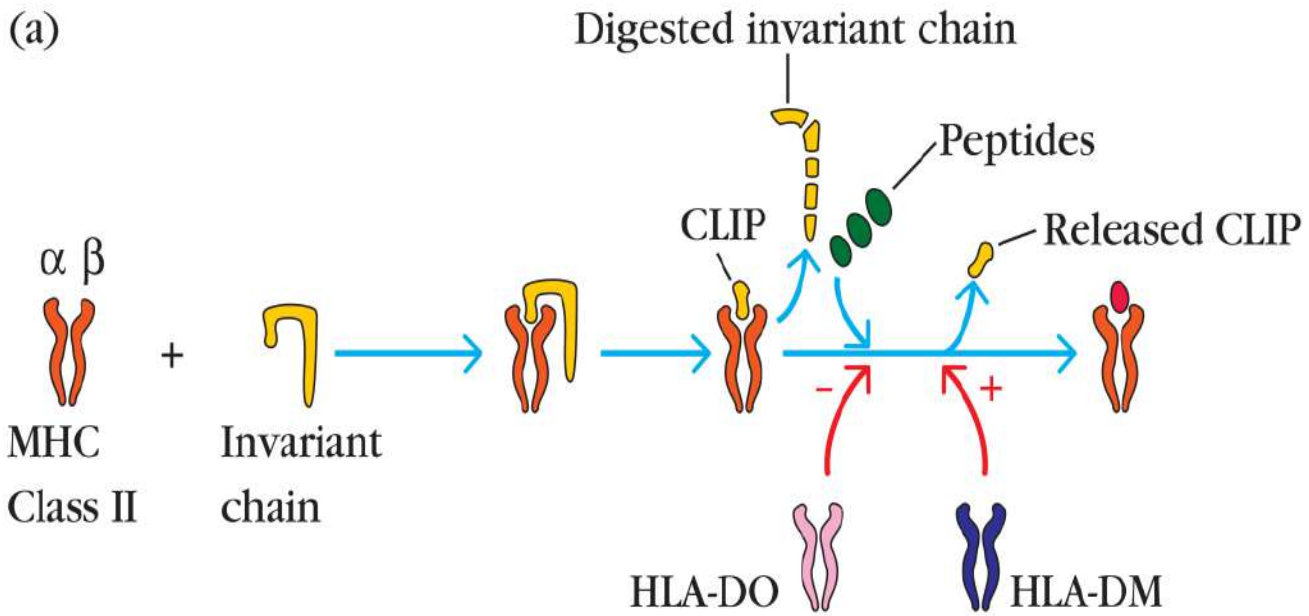
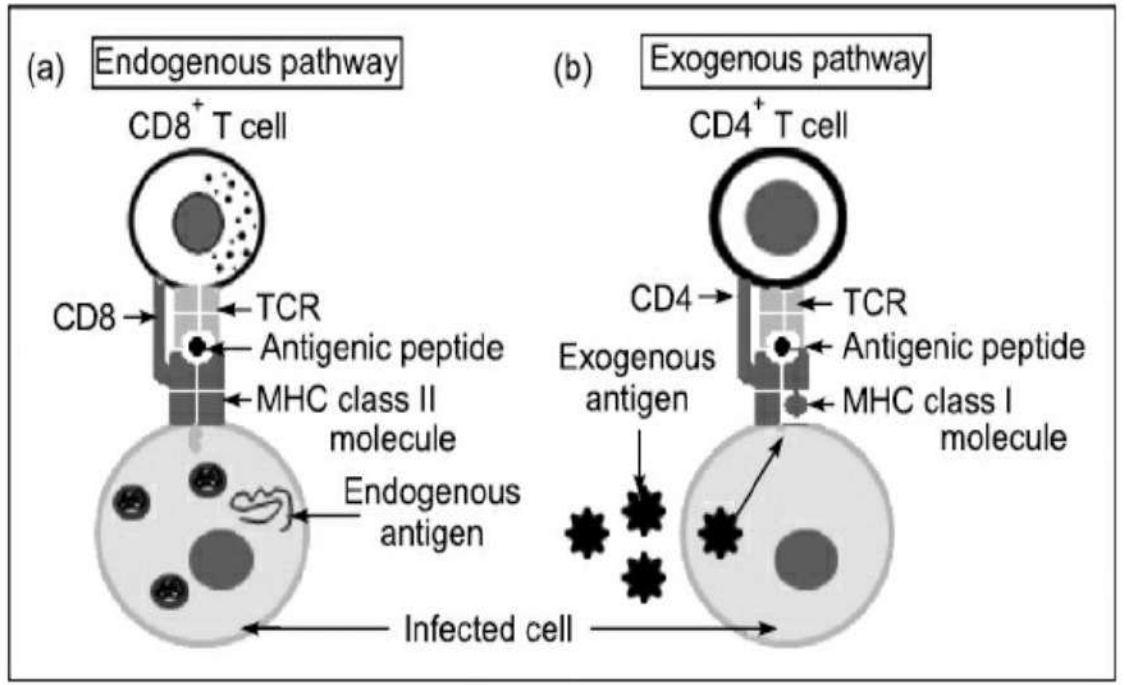
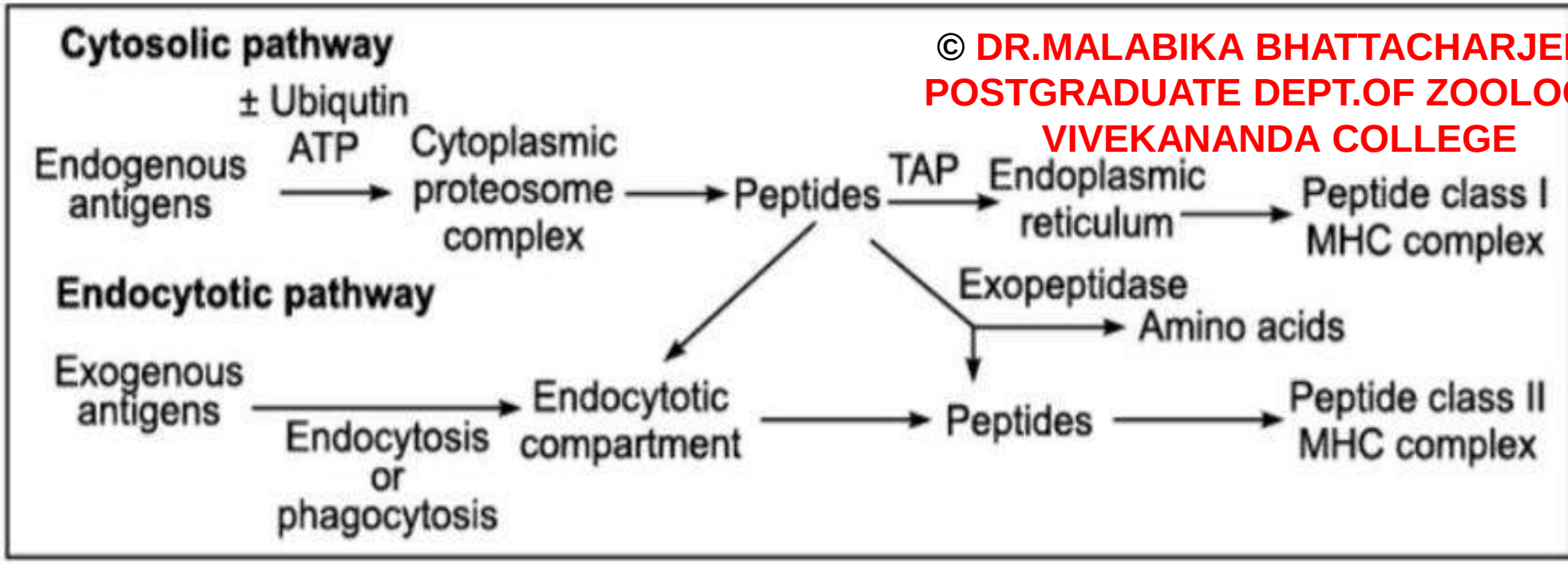
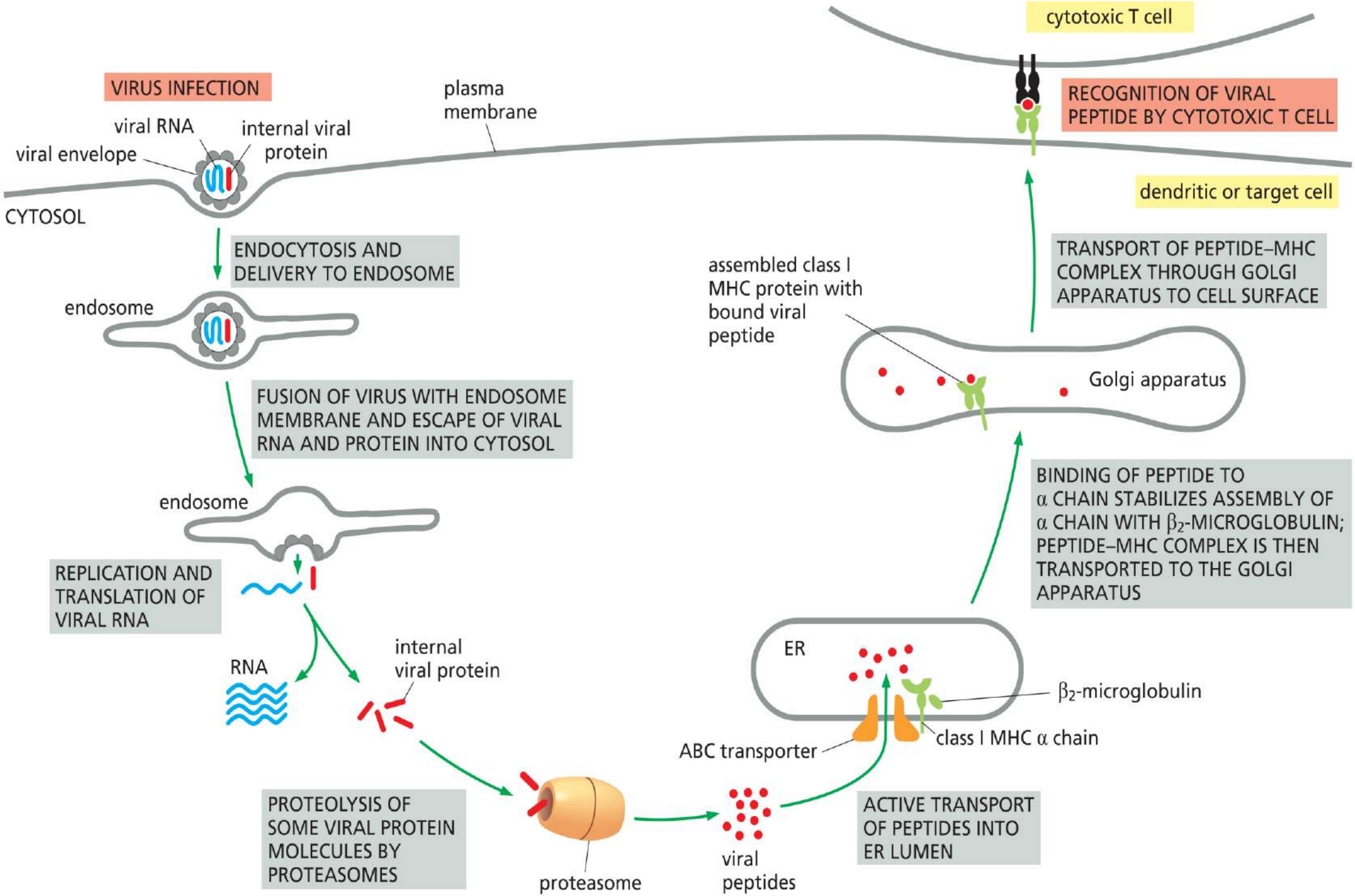


FIGURE 8-19 Generation of antigenic peptides in the exogenous processing pathway. Internalized exogenous antigen moves through several acidic compartments ending in specialized MIIC late endosomes, where it is degraded into peptide fragments which associate with class II MHC molecules transported in vesicles from the Golgi complex. The cell shown here is a B cell which internalizes antigen by receptor-mediated endocytosis, with the membrane-bound antibody functioning as an antigen-specific receptor.









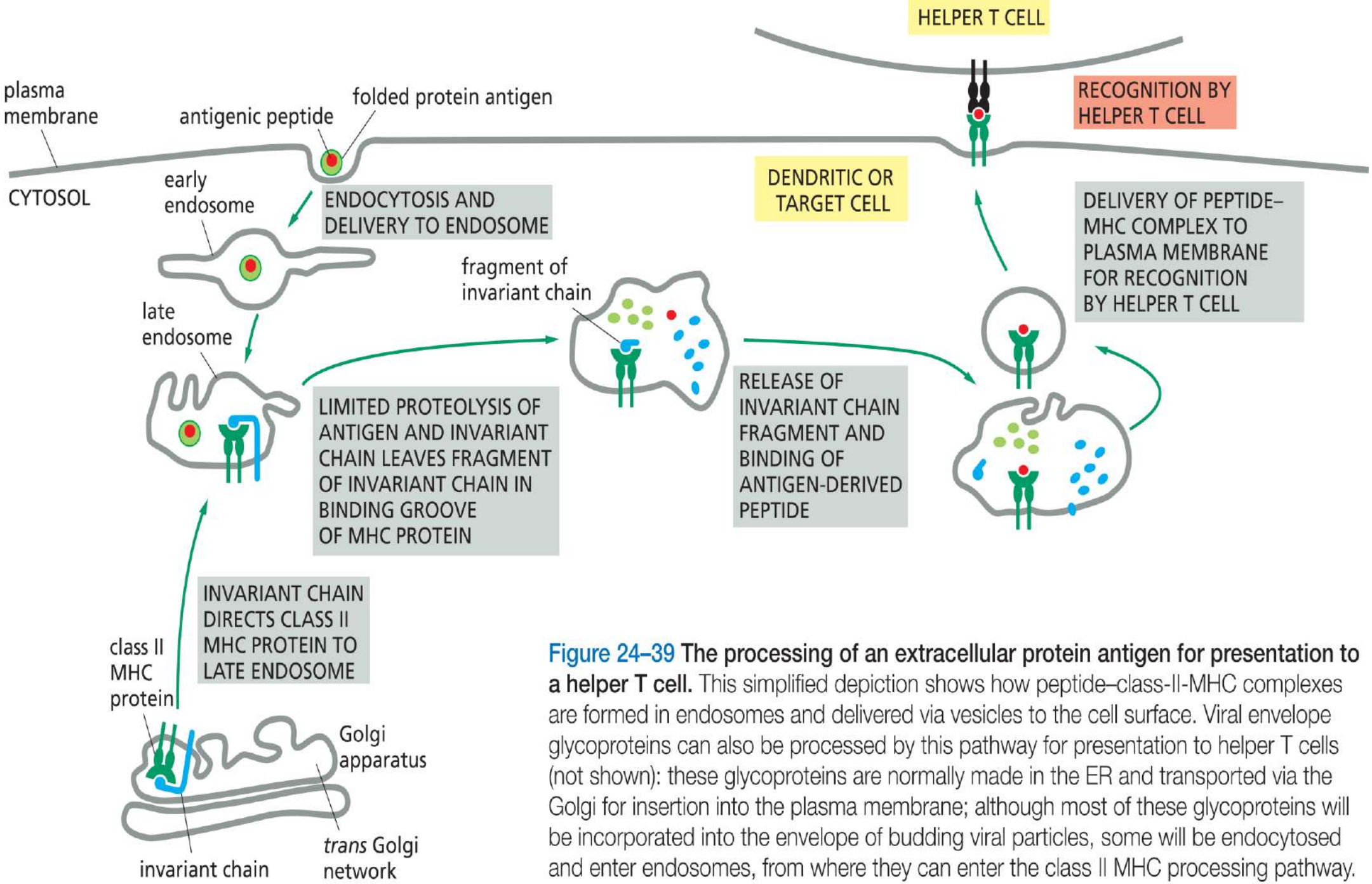


Figure 24–39 The processing of an extracellular protein antigen for presentation to a helper T cell. This simplified depiction shows how peptide–class-II-MHC complexes are formed in endosomes and delivered via vesicles to the cell surface. Viral envelope glycoproteins can also be processed by this pathway for presentation to helper T cells (not shown): these glycoproteins are normally made in the ER and transported via the Golgi for insertion into the plasma membrane; although most of these glycoproteins will be incorporated into the envelope of budding viral particles, some will be endocytosed and enter endosomes, from where they can enter the class II MHC processing pathway.