BHARATHIDASAN UNIVERSITY

Tiruchirappalli – 620 024,
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Programme: M.Sc., Biotechnology (Marine)

Course Title : Immunology

Course Code : 21 CC7

Unit : II

Major Histocompatability Complex (MHC)

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Introduction :

- Major Histocompatibility Complex (MHC) is set of surface protein located on the cell surface of the nucleated cells.
- It plays more important work to identify the antigen between self and non self body, intracellular recognization and responsible for antigen presentation.
- Histo – tissues ; Compatibility- to living together harmoniously.
- MHC molecules always recognize only T lymphocytes.
- The two types of MHC are worked in immunity.
- T helper (Th) cell recognized by MHC molecules II, and T cytotoxic (TC) cells are recognized by MHC I molecules.
- Definition• "Major Histocompatibility complex is membrane attached protein which work on recognization of antigen between self and non self body and antigen presentation"

History :

- **George Snell(1903-1996)** discovered the first components of the MHC through their role in rejecting transplants in mice, and created the word “histocompatibility”.
- Around a decade later, **Jean Dausset(1916- 2009)** uncovered the first compatibility antigen in humans.
- Experiments by **Baruj Benacerraf (1920- 2011)** in the 1970s provided the first indication that immune reactions are controlled by the MHC genes ('immune response genes’).
- In **1996-Rolf M.Zinkernagel and Peyer C.Doherty** (Nobel laureates for medicine or physiology). Specificity of the cell mediated immune defense.
- Structural studies done by **Don Wiley** and others showed that different MHC proteins different antigens fragments.
- In **1980 K. Ziegler and E.R.Unanue** showed that intra cellular processing of APC is required to activate T Cells.

Types of MHC molecules :

- There are three classes of MHC molecules:
    - ❖ class I
    - ❖class II, and
    - ❖class III.
- Members of the first two classes have a similar shape and both are responsible for displaying antigen to T cells, although they differ in their roles and in the way in which their quaternary or final three - dimensional structures are generated.
- Other molecules classified as MHC class III also play roles in the immune response, although these roles are more varied and generally do not involve direct presentation of antigen fragments to T cells.

MHC Class-I molecule :

✓Class I MHC(45 KD) molecule are a group of major histocompatibility antigen.

✓They are present on the surface of all nucleated cells except nervous tissue and platelets.

✓It present antigen to Tc cells.

✓It bind with CD-8 adhesion molecules of Tc cells.

✓It brings about cell mediated Immune response.

✓α Chain – 45kDa

✓β Chain – 12kDa22

Structure of MHC Class-I molecule :

- It consists two polypeptide chains namely α chain and β2 – microglobulin.
- α chain which is non covalently attached with β2 microglobuline . α chain contain a transmembrane glycoprotein which is encoded by A,B and C gene of grouped HLA.
- α chain is organized by three domains such as α1, α2 and α3 each domain containing 90 amino acids sequences.
- β2 microglobuline is similar in size of α3 and it dose not contain transmembrane proteins.
- When the antigen is internalized and processed inside by proteosome (Ubiquitin, cytosolic degradation), the peptides are produced.
- Peptide is further loaded on the groove of MHC I molecules from endoplasmic reticulum.

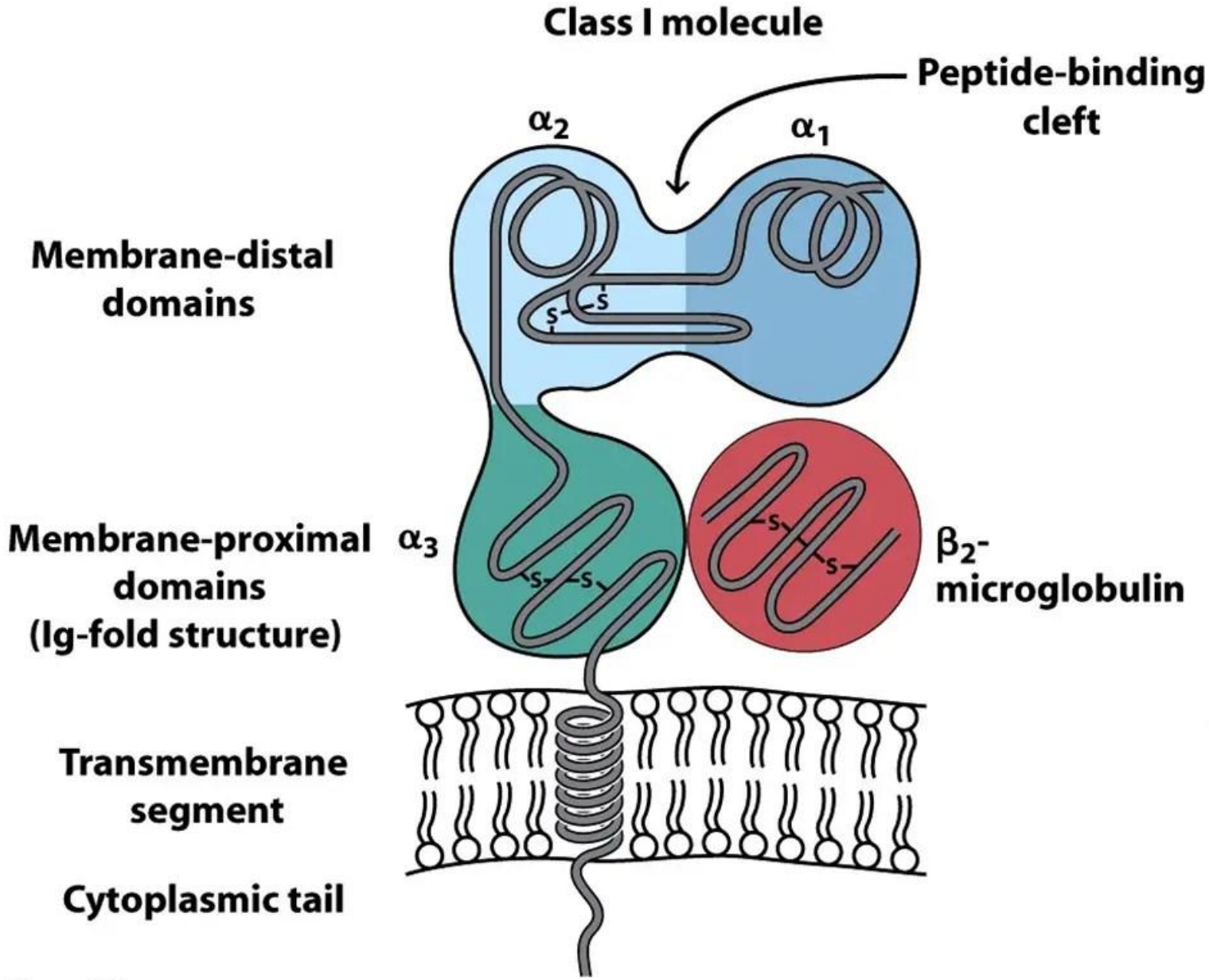


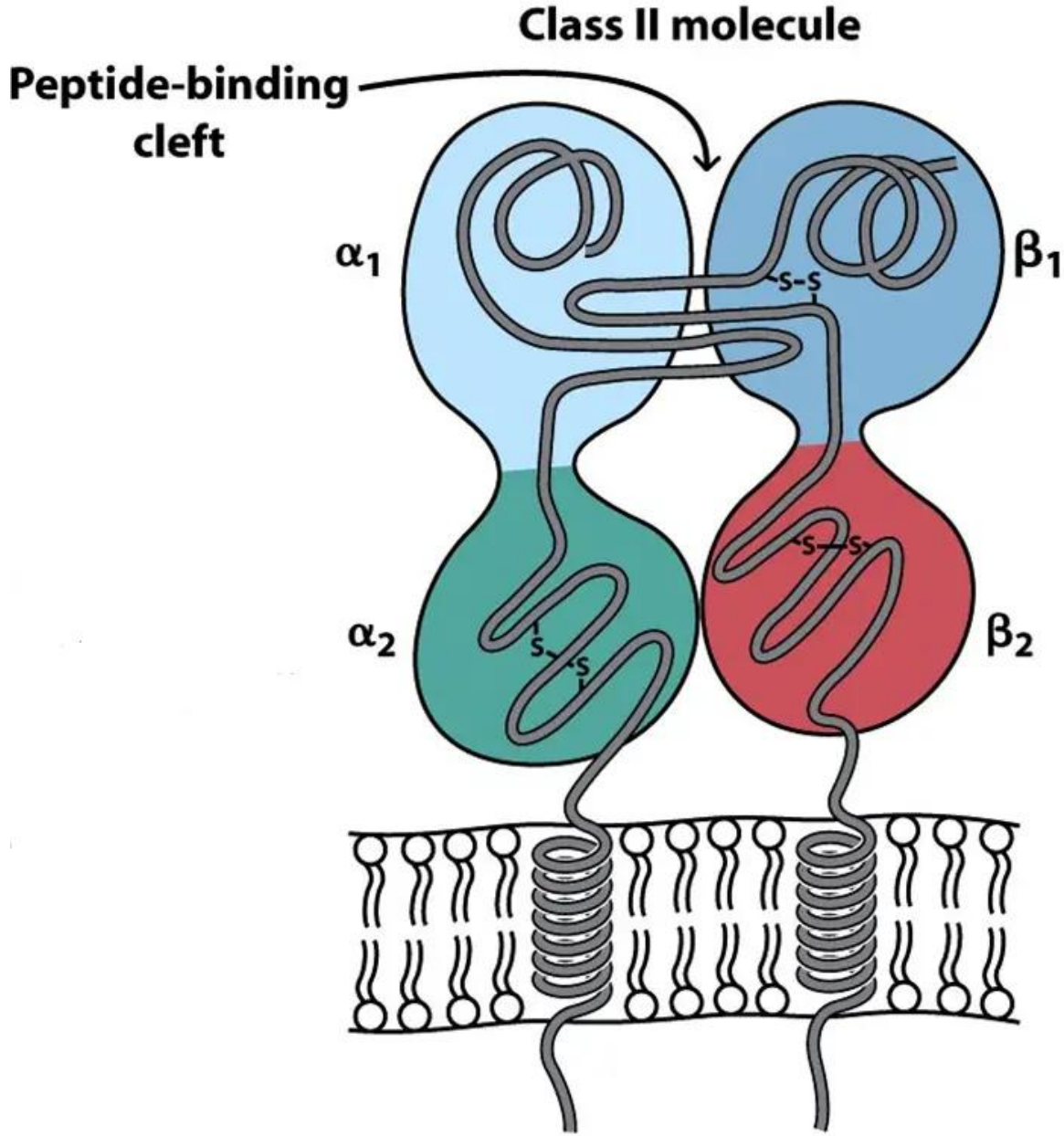
Figure 8-3
Kuby IMMUNOLOGY, Sixth Edition

Class-II MHC molecules :

- ✓Class II MHC molecule are present on the surface of antigen presenting cell and cell which engulfed the foreign antigen.
- ✓It binds with the exogenous(endocytic degradation) antigens.
- ✓It binds with CD4 adhesion molecules TH cells.
- ✓It also consist of two polypeptide chains namely α chain and β chain.
- ✓Antigen is processed inside the endosome and peptide is further loaded on groove of MHC II molecules.

Structure of MHC Class-II molecule :

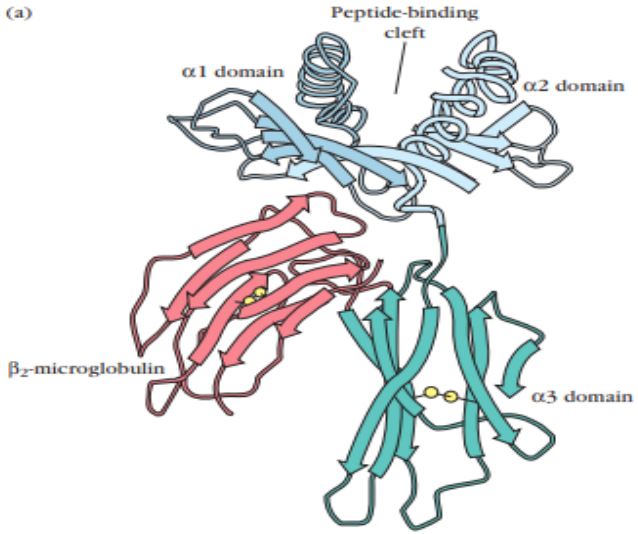
- The class II MHC Molecule consists of two polypeptide chain namely α chain (33 kDa) and β (28kDa) chain.
- The both chain are attached noncovalently.
- Each chain contains two units. The two units of α chain are called α1 and α2. The two domains of β chains are called β1 and β2.
- β2 and α2 are transmembrane domains anchoring the MHC to plasma membrane.
- The α1 and β1 domains jointly bear a peptide binding groove.

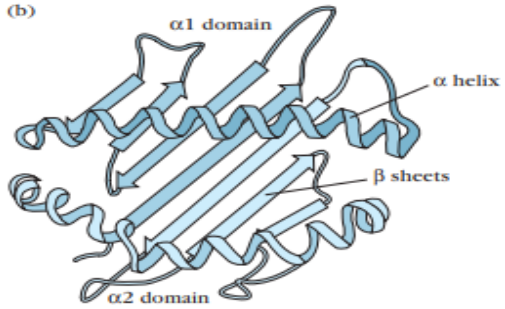

Class II molecule
Peptide-binding cleft
α1
β1
α2
β2
S-S
S-S
S-S

Peptide Binding groove :

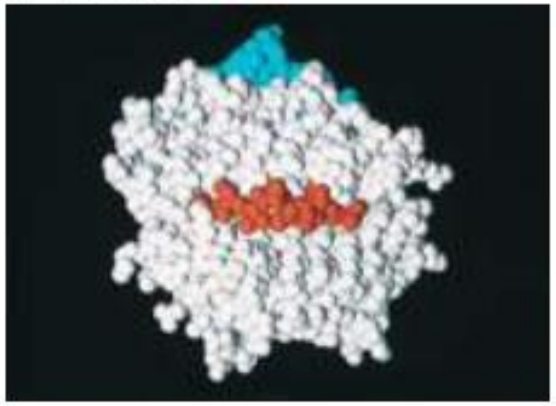
	Class I molecules	Class II molecules
Peptide-binding domain	α1/α2	α1/β1
Nature of peptide-binding cleft	Closed at both ends	Open at both ends
General size of bound peptides	8–10 amino acids	13–18 amino acids
Peptide motifs involved in binding to MHC molecule	Anchor residues at both ends of peptide; generally hydrophobic carboxyl-terminal anchor	Anchor residues distributed along the length of the peptide
Nature of bound peptide	Extended structure in which both ends interact with MHC cleft but middle arches up away from MHC molecule	Extended structure that is held at a constant elevation above the floor of MHC cleft

MHC Class I

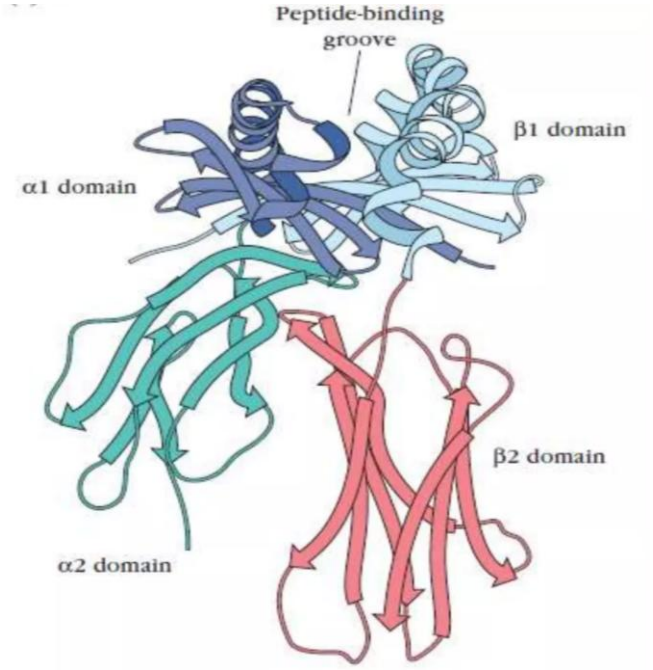


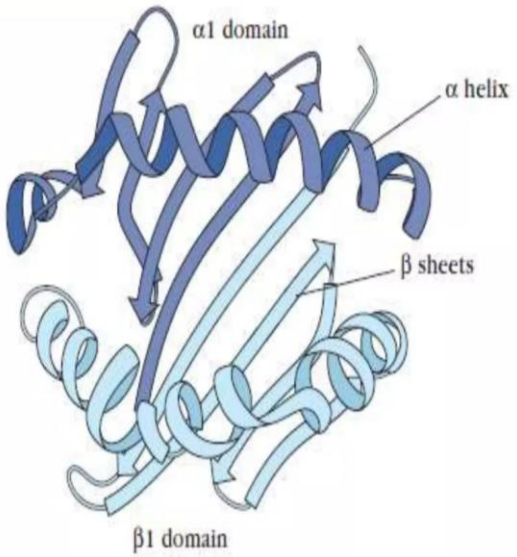


(a) Class I MHC

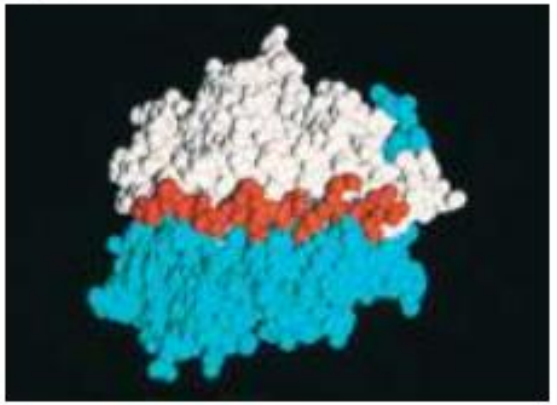


MHC Class II





(b) Class II MHC



MHC Class III molecule :

- ✓There are several serum proteases which involve in the complement system that come under the group of class III MHC molecules.
- ✓Class III MHC molecules do not have any involvement in antigen presentation.
- ✓The complement components such as asC2, C4A, and C4B, and factor B are the most important compounds involved as class III MHC molecules. Apart from these tumor necrosis factors α and β and some heat shock proteins also come under this category.

General Organization of MHC :

Major Histocompatibility Complex

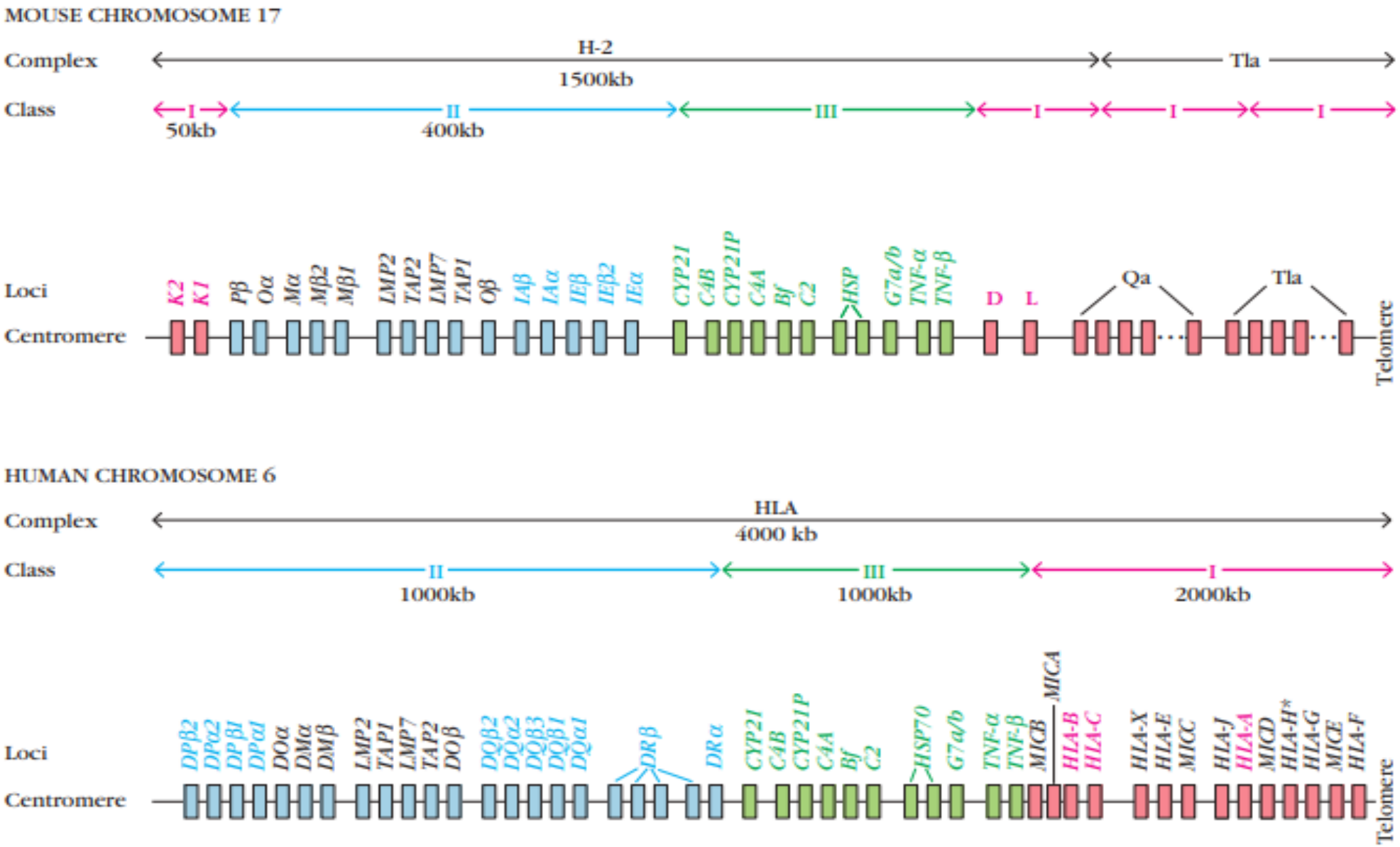
- MHC is a collection of genes arrayed within a long continuous stretch of DNA on
  - chromosome 6 – humans
  - chromosome 17 – mice
- MHC is referred to as
  - HLA complex – humans
  - H-2 complex – mice

Mouse H-2 complex

Complex	H–2						
MHC class	I	II		III		I	
Region	K	IA	IE	S		D	
Gene products	H–2K	IA αβ	IE αβ	C′ proteins	TNF-α TNF-β	H–2D	H–2L

Human HLA complex

Complex	HLA							
MHC class	II			III		I		
Region	DP	DQ	DR	C4, C2, BF		B	C	A
Gene products	DP αβ	DQ αβ	DR αβ	C′ proteins	TNF-α TNF-β	HLA-B	HLA-C	HLA-A



Source: https://www.slideshare.net/akshaygmore27/mhc-haplotypes

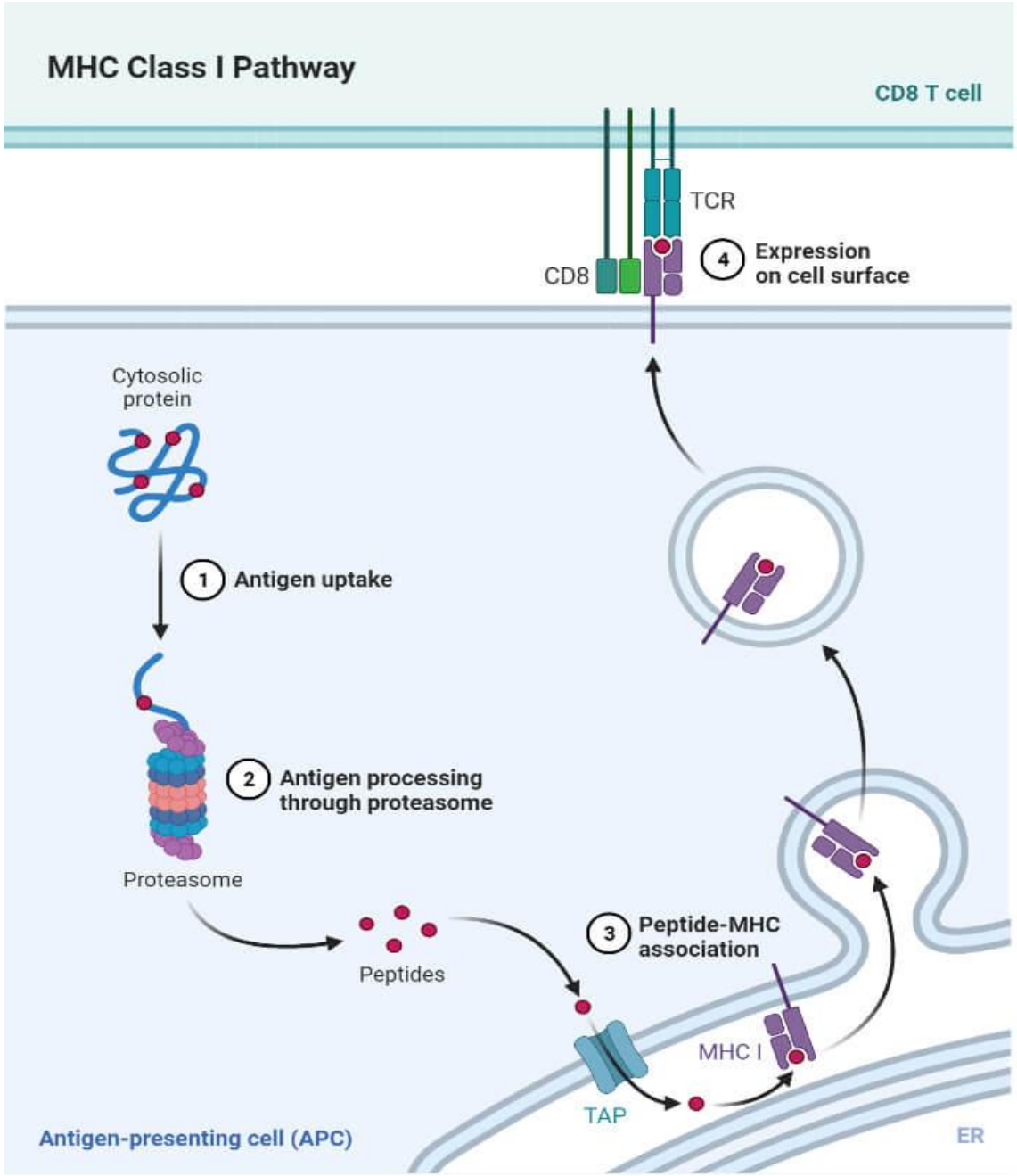
Distribution of MHC molecules :

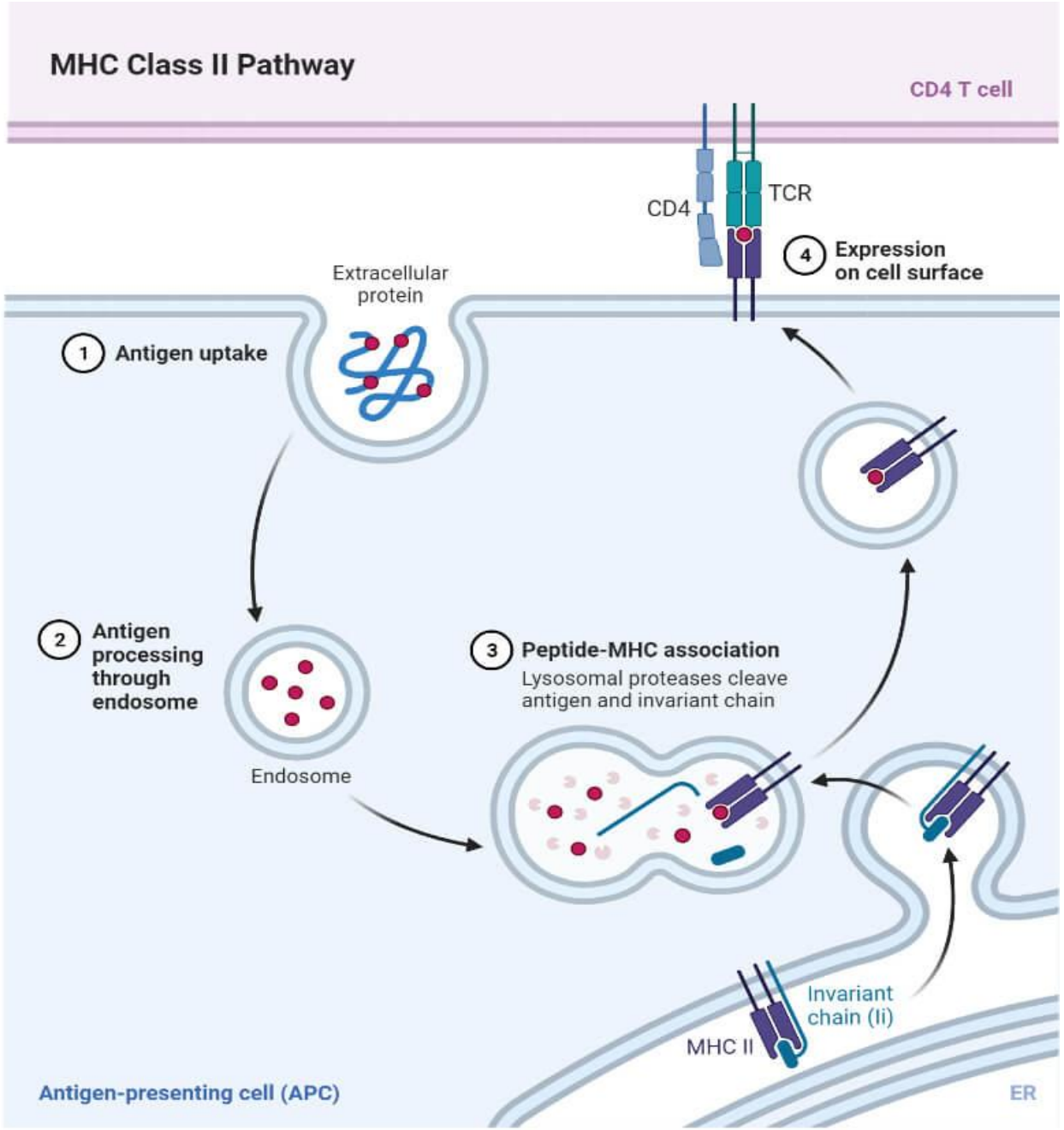
- Essentially, all nucleated cells carry classical class I molecules.
- These are abundantly expressed on lymphoid cells, less so on the liver, lung, and kidney, and only sparsely on the brain and skeletal muscle.
- In humans, the surface of the villous trophoblast lacks HLA-A and -B and bears HLA G, which does not appear on any other body cell.
- Class II molecules are also restricted in their expression, being present only on antigen-presenting cells (APCs) such as B-cells, dendritic cells, and macrophages and on the thymic epithelium.
- When activated by agents such as interferon g, capillary endothelia, and many epithelial cells in tissues other than the thymus, they can develop surface class II and increase expression of class I.
- They function as cell surface markers enabling infected cells to signal cytotoxic and helper T-cells.

Antigen Presentation of MHC Class I : (Cytosolic Pathway)

- Class I MHC molecules involve in presenting **intracellular or endogenous pathogens or antigens**. Intracellular pathogens refer to those organisms which live and replicates inside the host cell. An example of this type of pathogen is a virus.
- Under normal condition the MHC class I molecules forms a complex with the self-peptides or self-antigens. While, in case of any viral infection, the MHC class I molecules present the peptide derived from the virus which is then further recognized by T cells.
- Cell components such as a nucleus, endoplasmic reticulum and Golgi apparatus play an important role in antigen processing and presentation.
- When a virus infected a normal cell, the viral DNA moves inside the cell and produce viral proteins with the help of the host cell mechanisms. The viral proteins are synthesized in the cytosol.
- The cytoplasm also contains a cylindrical protein complex called the proteasome. The main function of the proteosome is to degrade the unwanted or damaged protein into smaller peptides. At the time of viral infection, the viral proteins interacted with the proteosomes present in the cytoplasm.

- The processing took place in the cytosol and as a result, the proteins are degraded into smaller peptides (8-15 amino acid long).
- In the next step, these fragmented peptides are transported into the endoplasmic reticulum. The transport took place due to a peptide delivery system called the transporter associated with antigen processing (TAP). TAP is made up of two domains or subunits called TAP 1 and TAP 2.
- Inside the endoplasmic reticulum the α and β chains of MHC class I molecules are synthesized and by the help of a group of chaperone proteins, the MHC class I molecule is formed and moves towards the TAP. As a result, the peptides bind at the peptide-binding site of the class I MHC molecule inside the endoplasmic reticulum and forms the MHC class I-peptide complex.
- In the next step, the MHC class I- peptide complex moves to the surface of the Golgi apparatus and by the help of secretory vesicle, it moves towards the surface of the plasma membrane.
- Once the MHC class I-peptide complex reaches the cell surface, the T cell receptors recognize the antigen peptide complex. Moreover, the co-receptor CD8 of the T cell attaches with the α_3 domain of the MHC class I molecule. Hence, the antigen is presented to the T cells.

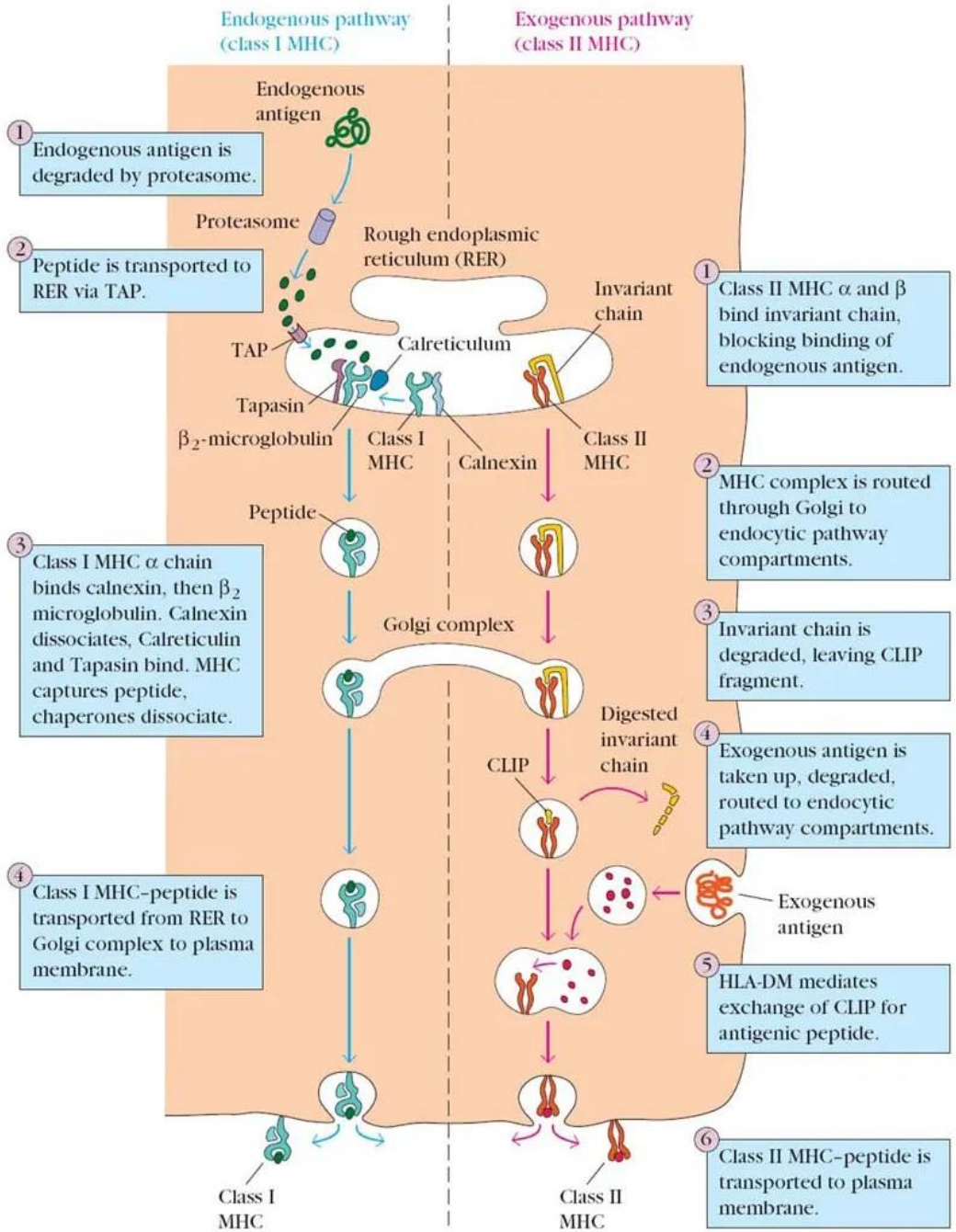

MHC Class I Pathway
CD8 T cell
TCR
CD8
4 Expression on cell surface
Cytosolic protein
1 Antigen uptake
2 Antigen processing through proteasome
Proteasome
Peptides
3 Peptide-MHC association
MHC I
TAP
Antigen-presenting cell (APC)
ER


MHC Class II Pathway
CD4 T cell
CD4
TCR
4 Expression on cell surface
Extracellular protein
1 Antigen uptake
2 Antigen processing through endosome
Endosome
3 Peptide-MHC association
Lysosomal proteases cleave antigen and invariant chain
Invariant chain (Ii)
MHC II
Antigen-presenting cell (APC)
ER

MHC Class II : (Endocytic Pathway)

- MHC class II molecules are responsible for presenting exogenous or extracellular pathogen or antigen.
- The extracellular pathogen refers to the organisms which can grow and reproduce outside of the host cell. Bacteria, exotoxins, parasites are examples of extracellular antigens. These antigens are taken up by the cell by endocytosis or phagocytosis.
- Only the antigen-presenting cells involved in antigen processing and presentation by MHC class II molecules. These cells include B cells, macrophages, and dendritic cells.
- The pathway took place only after the engulfment of the antigen by the antigen-presenting cells.
- Inside the cell, the antigen carries a covering called an endosome. The endosome is fused with the lysosome present in the cytoplasm and forms endolysosomes. As a result, the foreign protein is degraded by the proteolytic enzyme present inside the lysosome and small peptides are formed.

- The class II MHC molecules are synthesized and formed in the endoplasmic reticulum.
- The α and β chain of the molecule is also associated with the invariant chain. This association helps to restrict the binding of self-antigen with the class II MHC molecule.
- The invariant chain- MHC complex is then transported from the endoplasmic reticulum to the Golgi apparatus and from the Golgi apparatus to another vesicle. Inside the vesicle, the invariant chain is digested and only a small fragment (Class II-associated invariant chain polypeptide: CLIP) is attached with the molecule.
- In the next step, the vesicle containing the MHC class II molecule is then fused with the vesicle containing fragmented peptides. The fragmented peptide is then bound with the MHC class II molecule by displacing the CLIP. This newly formed MHC class II-peptide complex is then transported to the surface of the cell.
- Once at the cell surface, the antigen is presented to the T cells. The T cell recognizes the peptide bound with the MHC class II molecule by the help of the T cell receptor and the CD4 co-receptor binds with the β_2 domain of the class II MHC molecule.



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