# Major Histocompatibility Complex

## PART-3

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# MHC molecule and Peptide interaction

- **In human, various allelic form of class I & II MHC mol. have been identify.**
- **Single Individual have only**
  - ✓ **Up to 6 different class I MHC mol.**
  - ✓ **12 or more different class II MHC mol.**

?

**Limited number of MHC molecule able to present huge variants of antigenic peptide for T-Cell?**

**Yes**

**“MHC molecules can bind numerous variants of antigenic peptide”**

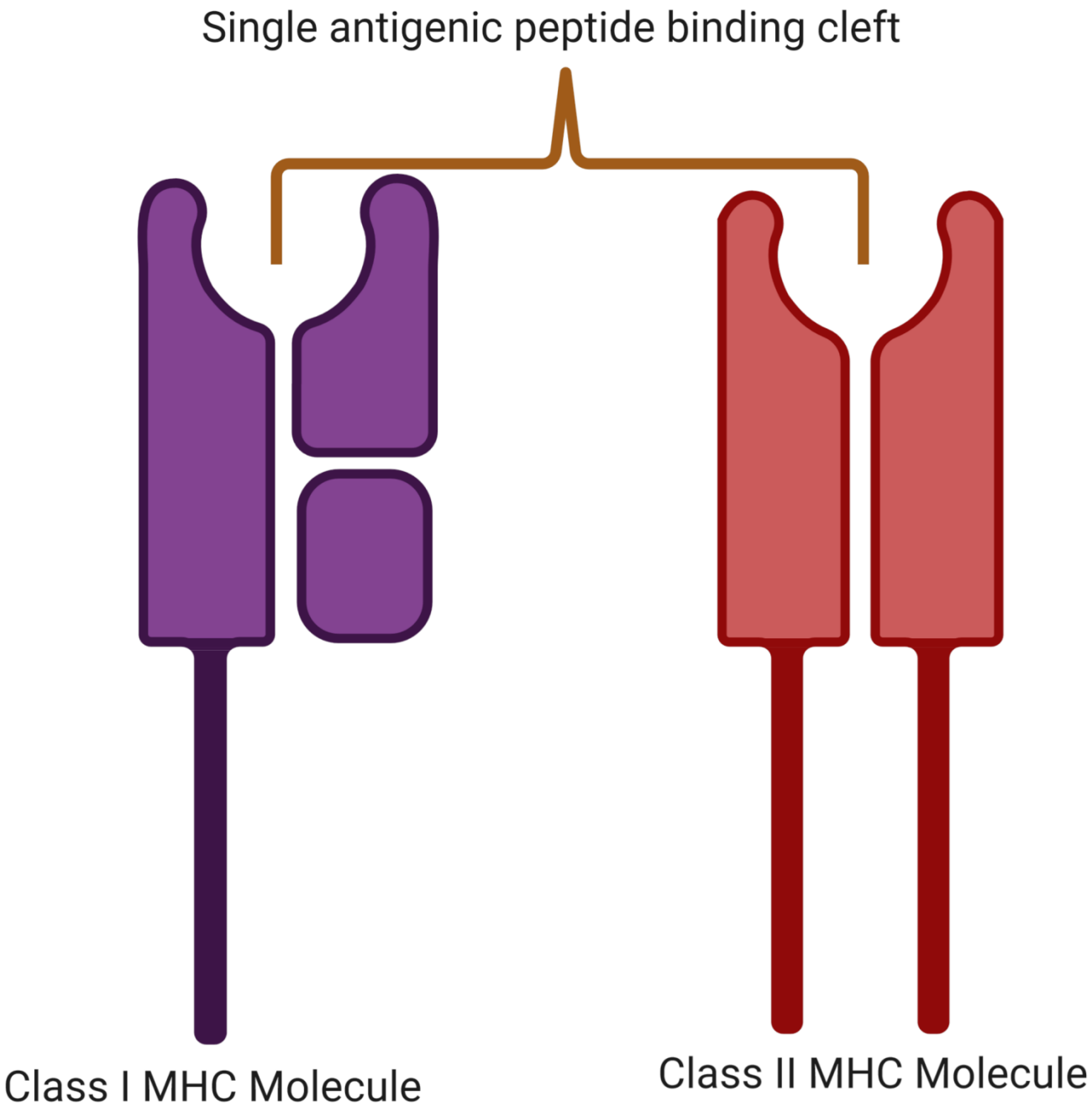
Let us discuss how?

- **The broad specificity between antigenic peptides and MHC molecules is often referred to as “Promiscuous.”**
- **Association between antigenic peptide and MHC molecules are very stable under specific physiological conditions such as-**
  - **$K_d$ value range from approx. $10^{-6}$ to $10^{-10}$**

# Characteristic features of antigenic peptide-MHC molecule interaction

- Class I and Class II MHC molecules have a single antigenic peptide binding cleft.
- Generally accommodates one antigenic peptides at a time.
- Processed antigenic peptides must be compatible with MHC binding cleft.
- Compatible pair promote the interaction and activation of concerned immune cell.

- **Peptide binding cleft is protected with a specific peptide (ERp57 in case of Class I MHC molecule) before encounter the antigenic peptide.**
- **Only few antigenic peptide-MHC molecules complex are capable to induce the immune response.**
- **MHC molecules express both self and non-self (antigenic) peptide on the surface of antigen presenting cells.**
- **T-cells capable to discriminate self and non-self (antigenic) peptide.**
- **After recognition, T-cell respond accordingly.**


Single antigenic peptide binding cleft
Class I MHC Molecule
Class II MHC Molecule

# Class I MHC Molecule-Peptide Interaction

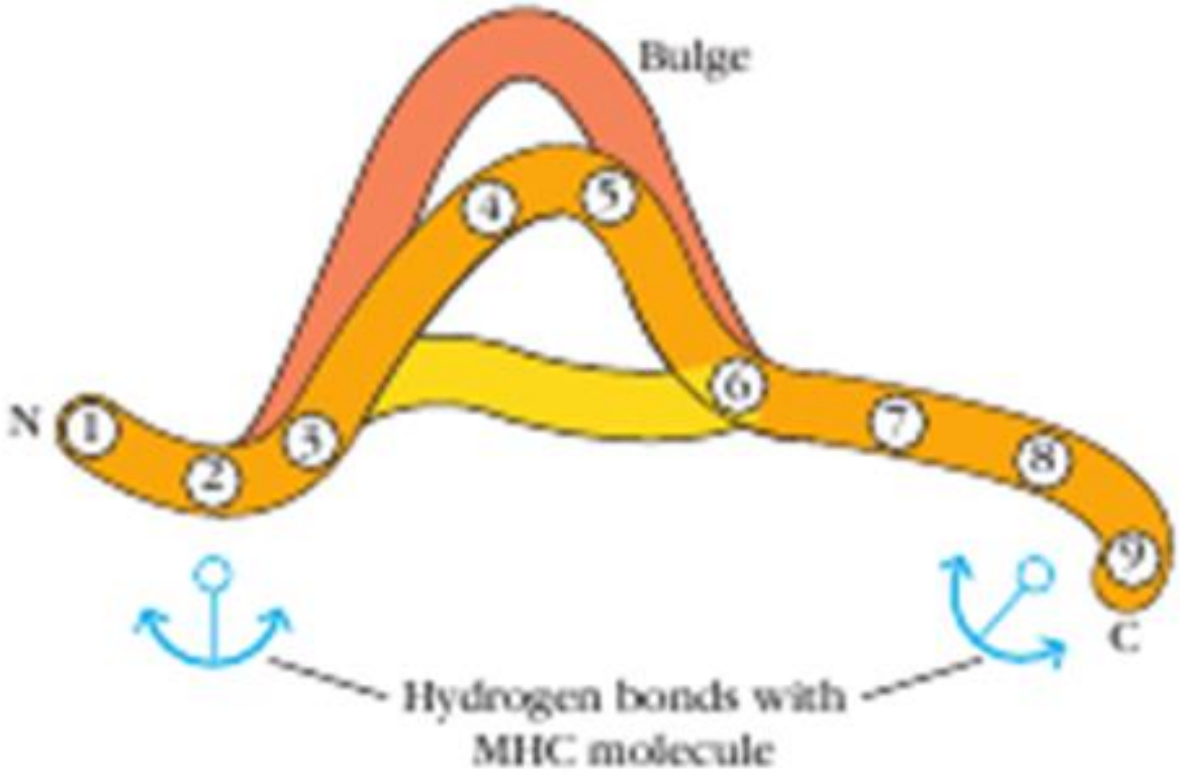
- **Antigenic peptides are bind with class I molecule and expressed on the surface of APCs for $CD8^+$ T lymphocyte cell.**
- **Antigenic peptides are derived from endogenous altered antigenic proteins.**
- **Interaction between antigenic peptides and class I MHC molecules occur inside the Rough Endoplasmic Reticulum.**
- **This process referred as endogenous processing pathway.**

- **Every Class I MHC molecule have slightly different rule for peptide bindings**

- **All nucleated cells are able to express approx. $10^{-5}$ copies of class I MHC molecule and each with its own promiscuity rules.**

- **Inherited Class I MHC allele will determine specificity of antigenic peptide with class I MHC molecule.**

- **Antigenic peptides are 8-10 AAs (9 AAs are common) long.**




## Conformation of antigenic peptide of Class I MHC molecule

**Reference:** Kuby –Immunology; 7th Edition by Judith A. Owen, Jenni Punt, Sharon A. Stranford and Patricia P. Jones; Chapter-8: The Major Histocompatibility Complex and Antigen Presentation; Page: 267

- **Specific amino acid residues are found at particular site of the antigenic peptide.**

- **Class I MHC molecule able to bind with thousands of different antigenic peptide due to presence of the similar amino acid residues at specific site.**

- **Specific sites amino acids (antigenic peptide) anchor the cleft of MHC molecule, they are called anchor residues.**

- **Allelic variants of class I MHC molecules have different amino acid residues in the antigenic peptide binding cleft.**

- **Class I MHC molecule contains-**
  - ✓ **Carboxyl-terminal anchor (at position 9) - contain hydrophobic residues such as leucine and isoleucine.**
  - ✓ **Amino-terminal anchor (at position $2^{nd}$ or $2^{nd}$ and $3^{rd}$).**

- **Carboxyl-terminal anchor and Amino-terminal anchor firmly bind with peptide binding cleft.**
- **Amino acid residues between Carboxyl-terminal anchor and Amino-terminal anchor form a arch.**
- **Centre of arch (antigenic peptide) is bulge out from the cleft of MHC molecule .**
- **Centre of arch is interact with TCR.**

# Class II MHC Molecule-Peptide Interaction

- Antigenic peptides are bind with class II molecule and expressed on the surface of APCs for $CD4^+$ T lymphocyte cell.
- Class II MHC molecules also bind diverse antigenic peptide.
- Antigenic peptides are derived from exogenous protein (either self or nonself).
- Exogenous antigenic peptides are processed through exogenous processing pathway.

- **Antigenic peptides of class II MHC molecule derived from**
  - ✓**Self membrane bound protein or**
  - ✓**Foreign protein**
- **These protein uptake by cell through phagocytosis**
- **Uptake protein further processed through exogenous pathway.**
- **Antigenic peptides of class II MHC molecule contain 13 -18 amino acid residues.**

- **Antigenic peptides binding cleft of class II MHC molecule open at both end.**
- **Due to open at both end, accommodate longer antigenic peptide than class I MHC molecule.**
- **Central core of 13 amino acid residues determine the ability of antigenic peptide to bind class II MHC molecules.**
- **Unlike class I antigenic peptide, Class II antigenic peptides have internal conserved sequence motifs.**

- **Antigenic peptide of class II molecule bind inside the cleft with hydrogen bond.**

- **Hydrogen bond distributed throughout the binding site.**

- **Internal conserved sequence motifs contain 7-10 amino acids provide major contact point.**

- **Major contact point contains**
  - ✓**Amino terminus -aromatic or hydrophobic amino acid residues**
  - ✓**Middle portion –Hydrophobic residues**
  - ✓**Carboxyl terminus- Hydrophobic residues**
- **Many antigenic peptide have proline amino acid at second position and carboxyl terminal end.**
- **Proline amino acid contributes to peptide binding promiscuity.**

# Thanks