The term major histocompatibility complex is arrived at from research oriented for acceptance or rejection of tissues-literally **histocompatibility**-transplanted between different members of the same species.

Originally it was thought to be one gene involved in the process but later studies indicate that it is a "complex"- a set of closely linked genes inherited as a unit. The concept of major histocompatibility was developed by Gorer and Snell during mid 20th Century.

5.2 MHC genes and products

Nomenclature

Human chorosome 6 contain human MHC, known as HLA (human leucocyte antigen). Names of other species for example are BOLA for bovine system, SLA for swine. The name of mouse MHC is H-2 locus located on chromosome 17.

Two major sets of MHC genes, known as **MHC class I** and **MHC class II** and their cell-surface expressed products are involved in T cell responses. The three independent genes that code for human class I MHC molecule are called HLA-A, HLA-B and HLA-C. The MHC class II molecules are obtained from 3 sets of genes --HLA-DP, HLA-DQ and HLA-DR.

Each MHC Class II subregion contains an A & B gene that code for a chain, α or β respectively of a two chain MHC class II molecule. Thus HLA-DPA gene codes for DPα of the DP molecule and HLA -DPB gene codes for the other chain DP-β of the HLA-DP molecule.

Mouse MHC Class I molecules are coded by K, D & L gene H2 has 2 MHC class II regions-rather than 3 in humans known as I-A, I-E that code for I-A α β and I-E α β molecules respectively.

Pattern of MHC molecules expression in different cells

MHC Class I molecules are expressed at varying levels on almost every nucleated cell in the body. MHC II molecules have a more limited distribution than class I molecule. They are present on Antigen presenting cell (APC).

Expression of MHC-I & MHC II molecules are coordinate, in that all molecules of each class can be expressed on the cell surface at the same time. They are however under distinct control.

5.3 Structure of MHC molecules

The simplified structure of MHC I and MHC II are shown in Fig. 5

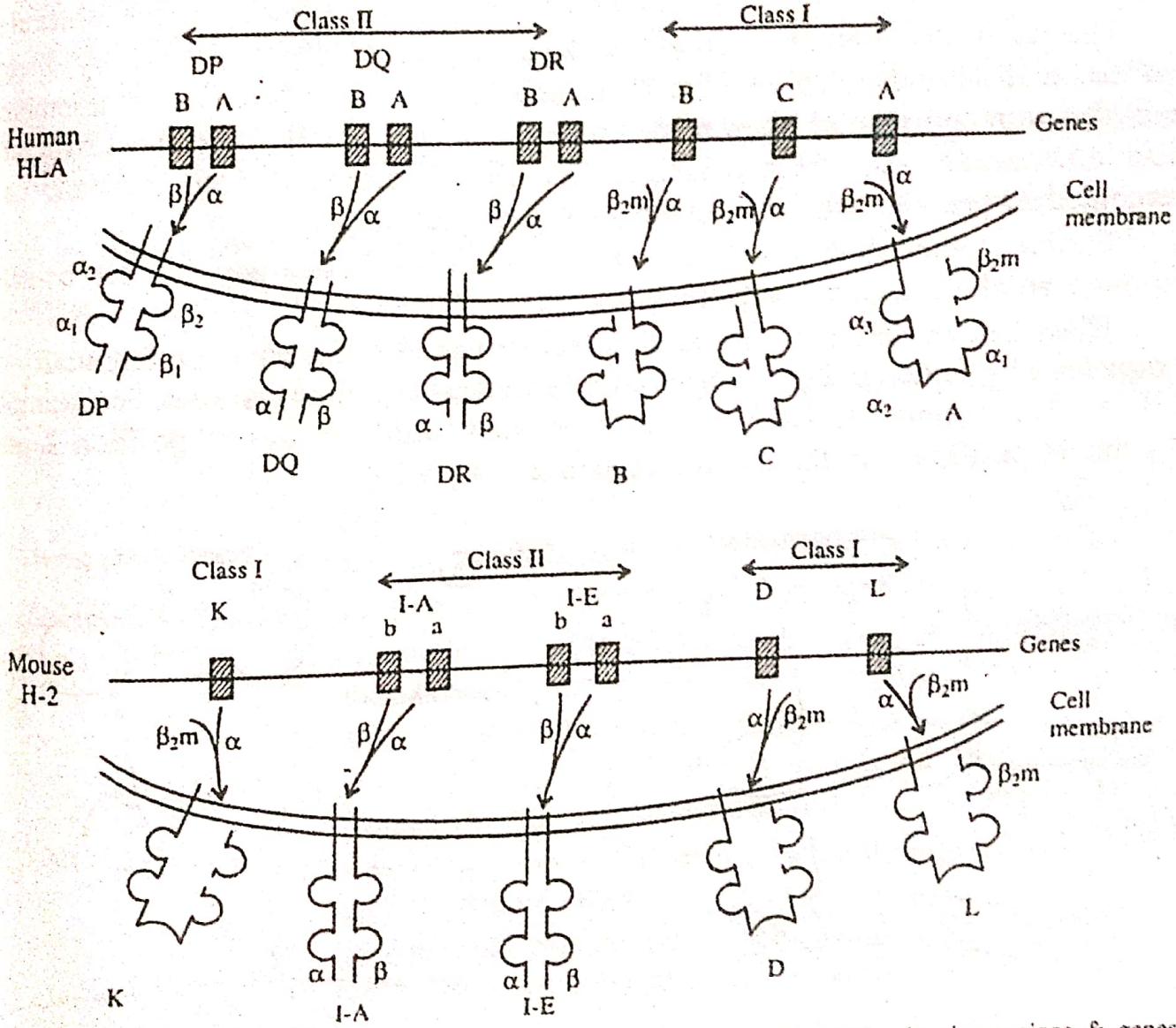

Fig.5.1 a and b Simplified depiction of the human (A) and mouse (B) MHC, showing regions & genes coding for polymorphic MHC Class I and Class II molecules. β_2m = β_2 microglobulin, encoded outside MHC.

5.3.1 Structure of MHC Class I molecules

Each Class I-gene codes for a transmembrane glycoprotein of approximate molecular weight 43 K Da, which is referred to as α, or heavy chain. It has 3 extra cellular domains α_1, α_2, α_3. It is expressed at the surface of a cell in covalent association with a small invariant polypeptide called β_2 microglobulin (β_2 m; molecular weight 12 K Da). β_2 m is coded by another chromosome and has a domain analogous to a single Ig domain.

At the cell surface, MHC I & β_2 m appear as a 4-domain molecule with α_3 & β_2m justaposed closest to the membrane.

The sequence differences between different Class-I molecules is restricted to α_1 & α_2 domains. The α_3 domain is invariant and binds CD8, a T-cell surface molecule.

The α_1 & α_2 domains contain a deep groove or cleft as seen by X-ray crystallographic studies. This groove in the binding site of peptides. the cleft resembles a basket with an irregular floor, made up of amino acid in a β plated sheet structure and surrounding walls form α helices. The cleft is closed at both ends and can accomodate peptides with 8-9 aminoacids in a linear way.

Further studies show that floor of each variant is different and thus can be said to have an allele specific pocket.

Class I molecules can bind to a variety of peptides but binds preferentially to peptides with certain **motifs.** Such motifs are known as **anchor residues.** For example HLA Class-I molecule HLA-A2 binds peptides with peptides at position 2 and valine at position 9 in the peptide sequence. (Fig 5.2b).

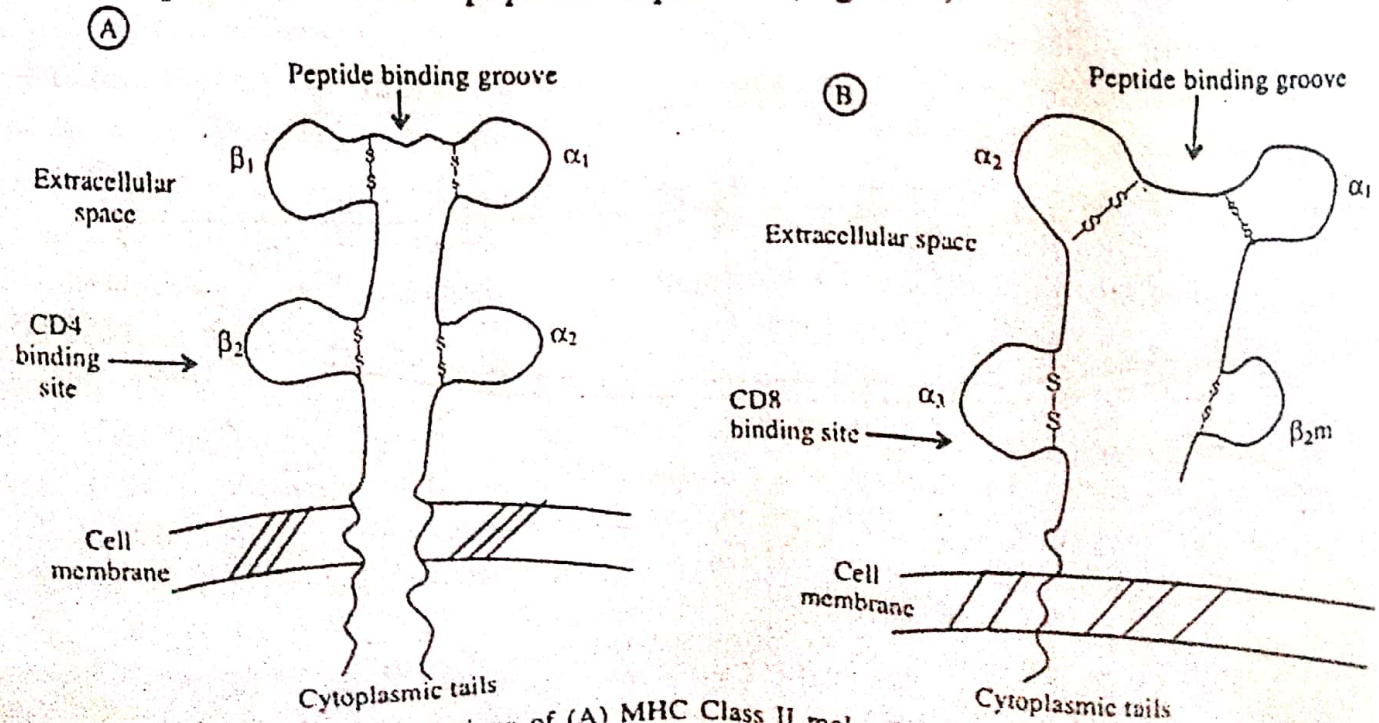

Fig. 5.2A & B. Depictions of (A) MHC Class II molecule (B) MHC Class-I molecule.

5.3.2 Structure of MHC class II molecule

MHC Clas-II α & β genes code for chains of approximate molecular weight 35,000 Da respectively. Each chain is a transmembrane glycoprotein molecule with cytoplasmic tails and extracellular Ig-like domains, the domains referred to as α_1, α_2 and $\beta_1$and β_2. It is made up of variable or polymorphic regions α_1 and β_2 and invariant or nonpolymorphic regions α_2 and β_2. The T-cell molecule CD4 binds to the invariant region.

The peptide binding groove of MHC II molecule in formed by interaction between domains of different chains, the α_1 and β_1 domain. The floor consists of 8 β-pleated sheets with each α_1 and β_1 contributing 4 each. The groove is open at both ends, allowing larger peptides to bind. The MHC Class-I binds peptide varying in length from 12 to approximately 17 aminoacids in a linear array.

Peptide binding to MHC Class II also exhibit motifs. Because the length of peptides are variable the motif is generally seen in the central region of the peptide, the region that fits inside the MHC class-II binding groove. (Fig. 5.2A).

5.4 Function of MHC molecules

MHC Class I :
(1) Associated with antigenic peptides of infecting pathogens produced within the host cell.
(2) Vesicular transport of MHC-I peptide complex to the infected cells membrane.
(3) Interaction with TCR of Tc cells; co-induction by CD8 molecule.
(4) Activation of Tc cell and destruction of infected cell.

MHC-Class II :
(1) Vescicular transport towards endolysome.
(2) Fragmentation of foreign peptides by lysomal enzymes present in endolysome; peptides derives from phagocytosed pathogen.
(3) Association of MHC-Class II with foreign peptide.
(4) vescicular transport to cell membrane and expression/ presentation of foreign peptide MHC II complex.
(5) Association with TCR of T_H cells; co-induction of T_H cells with CD4 molucules.
(6) Secretion of cytokines by TH cells, recruitment of macrophages, NK cells & Tc cells to infection site and formation of their effector population.