Major Histocompatibility Complex

Dr. Arpita Rakshit, Assistant Professor,
Seth Anandram Jaipuria College, Kolkata

DEFINITION

Major Histocompatibility Complex is a cluster of genes, whose products play a role in discrimination between self and non-self

Role of MHC molecules

- The MHC participates in the development of both humoral and cell mediated immune responses.
- While antibodies may react with antigens alone, most T cells recognize antigen only when it is combined with an MHC molecule.
- MHC molecules act as antigen-presenting structures
- A particular set of MHC molecules expressed by an individual influences the repertoire of antigens to which that individual's TH and TC cells can respond.

Recapitualtion

- Peter Gorer in the mid-1930s, was identifying blood group antigens in inbred strains of mice.
- He identified four groups of genes, designated I through IV, that encoded blood-cell antigens.
- 1940s and 1950s, Gorer and George Snell established that antigens encoded by the genes in the group designated II took part in the rejection of transplanted tumors and other tissue.
- Snell called these genes “histocompatibility genes”
- Histocompatibility-2 (H-2) genes was in reference to Gorer’s group II blood-group antigens in mice.

Organization and Inheritance of the MHC

- The MHC encodes three major Classes of Molecules
  - **Class I MHC genes:** encode glycoproteins expressed on the surface of nearly all nucleated cells
  - **Class II MHC genes:** encode glycoproteins expressed primarily on antigen-presenting cells
  - **Class III MHC genes:** encode various types of proteins that have immune functions

Histocompatibility Genes

Mouse H-2 complex (chromosome-17)

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 (chromosome-6)

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

Class I MHC molecules

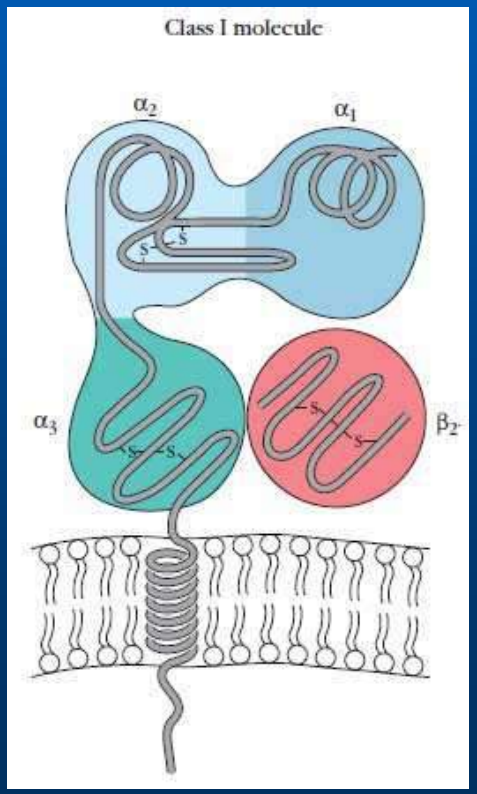
MHC Class-I genes codes for a single polypeptide chain and is expressed on the cell surface along with β2-microglobulin

Complex	H-2						
MHC class	I	II		III		I	
Region	K	IA	IE	S		D	
Gene products	H-2K	IA αβ	IE αβ	C4 proteins	TNF-α TNF-β	H-2D	H-2L

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	C4 proteins	TNF-α TNF-β	HLA-B	HLA-C	HLA-A

Classical class I molecules

- Encoded by the K and D regions in mice
- Encoded by the A, B, and C loci in humans

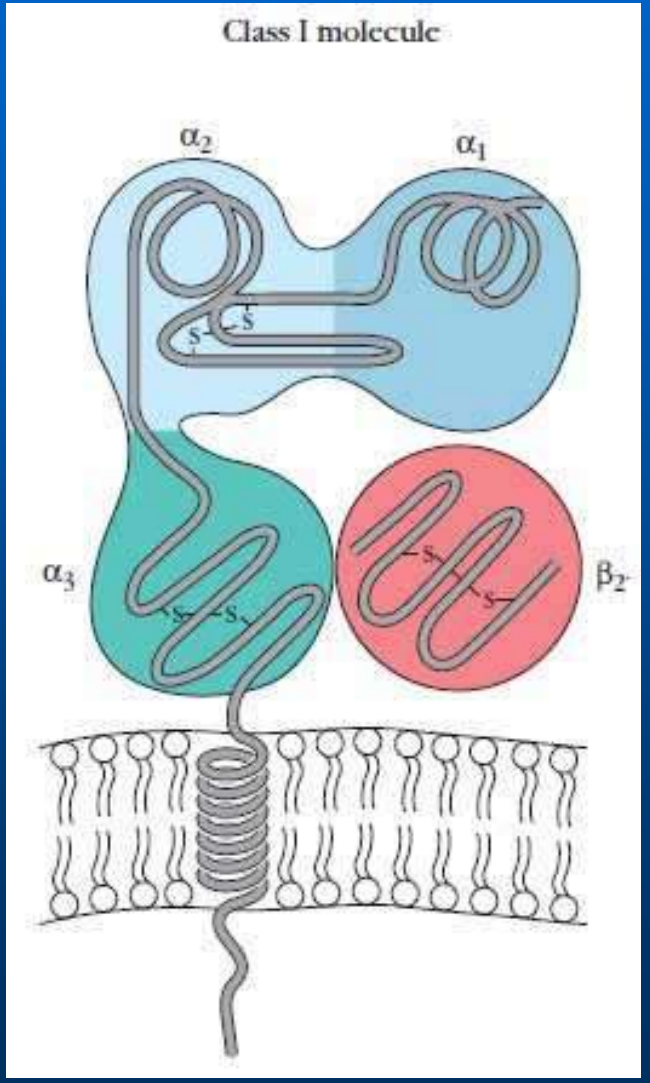


Nonclassical class I genes.

Additional genes or groups of genes within the MHC complex also encode class I molecules e.g. HLA-G (present on trophoblast of placenta and prevent recognition of fetus as foreign)

Class I molecules

- Class I molecules are membrane-bound glycoproteins
- The function as highly specialized antigen-presenting molecules
- Display antigen to Cytotoxic T cells (CD8 cells)
- Each Class I MHC molecules contain
  - a 45-kilodalton (kDa) α chain
  - a 12-kDa β2-microglobulin
- A, B, and C regions of the human HLA complex
- K and D/L regions of the mouse H-2 complex



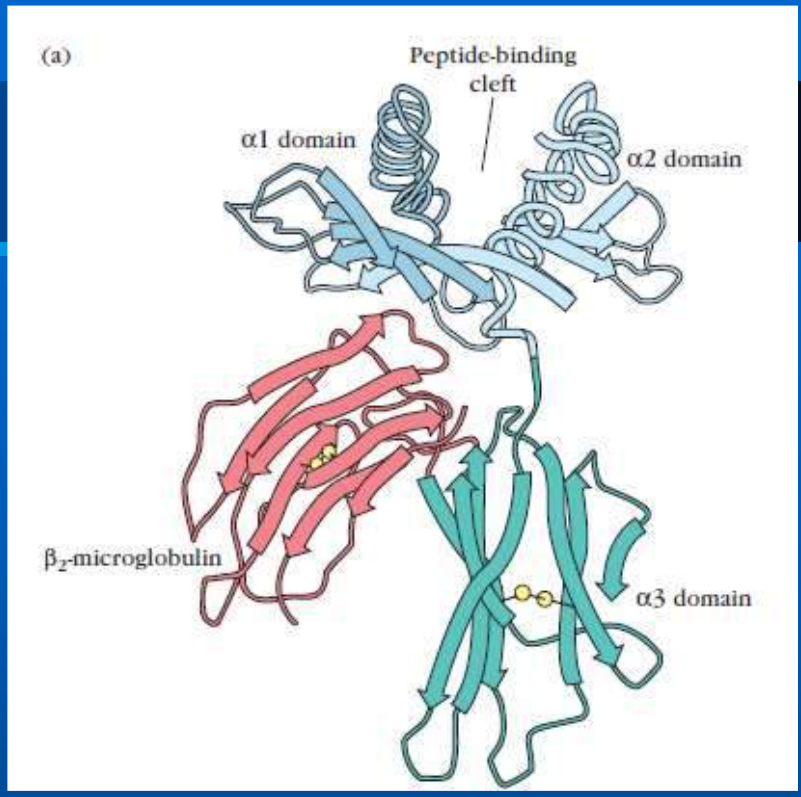
Class I α chain

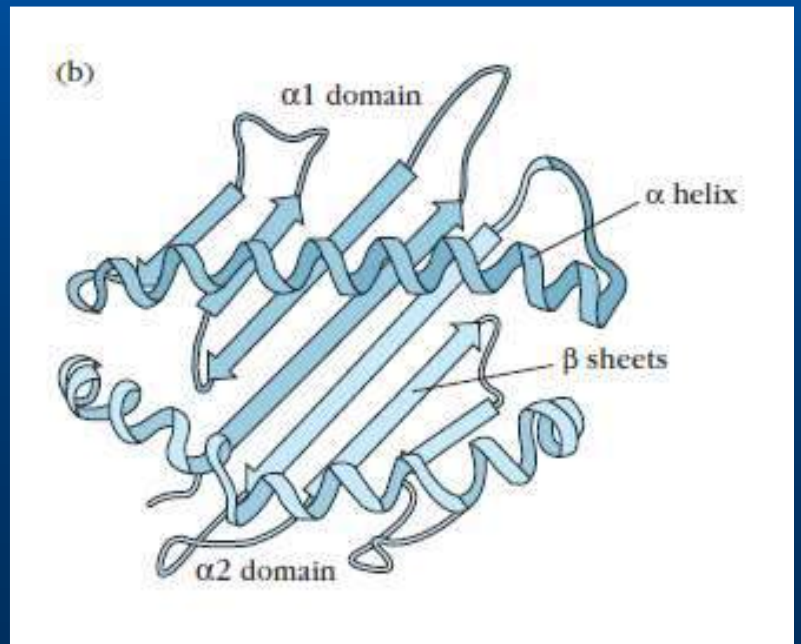
- The α chain is anchored in the plasma membrane and is organized into 3 external domain each containing approximately 90 amino acids;
  - a transmembrane domain of about 25 hydrophobic amino acids
  - a cytoplasmic anchor segment of 30 amino acids.

The 1 and 2 domains interact to form a platform of eight antiparallel strands spanned by two long -helical regions.

The structure forms a deep groove, or cleft, approximately 25 Å 10 Å 11 Å

The cleft bind a peptide of 8–10 amino acids.





β_2-Microglobulin

- β_2-Microglobulin encoded by a highly conserved gene located on a different chromosome.
- Association of the chain with β_2-microglobulin is required for expression of class I molecules on cell membranes.
- β_2-Microglobulin interacts extensively with the α3 domain and also interacts with amino acids of the α1 and α2 domains
- The β_2-microglobulin is similar in size and organization to the 3 domain;
- It does not contain a transmembrane region
- It is noncovalently bound to the class I glycoprotein.
- Sequence data reveal homology between the β_2-microglobulin, and the constant-region domains in immunoglobulins.
- Hence it belongs to immunoglobulin superfamily

Class II MHC molecules

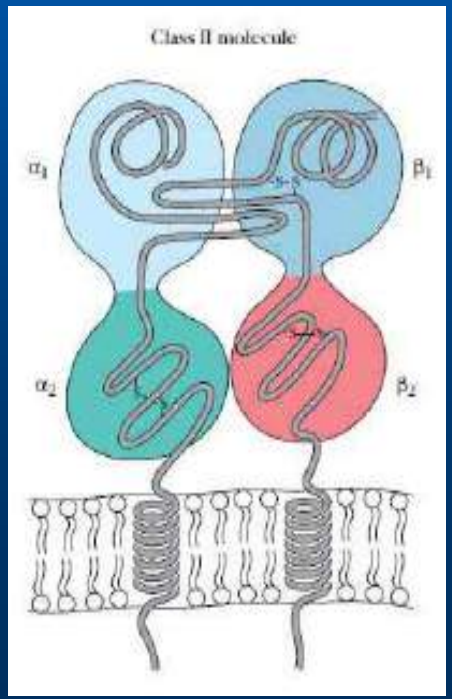
MHC Class-II proteins comprise of two polypeptide chain and is expressed on the cell surface

Complex	H-2						
MHC class	I	II		III			I
Region	K	IA	IE	S			D
Gene products	H-2K	IA αβ	IE αβ	C4 proteins	TNF-α TNF-β	H-2D	H-2L

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	C4 proteins	TNF-α TNF-β		HLA-B	HLA-C	HLA-A

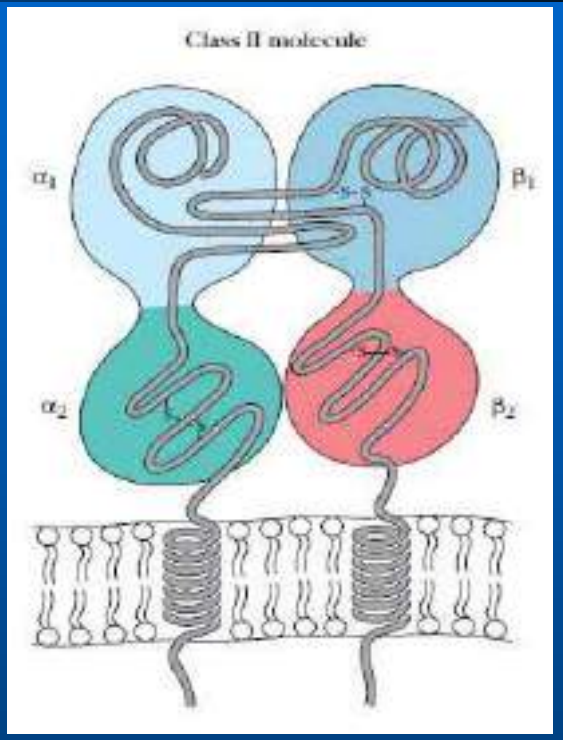
Class II MHC molecules

- Encoded by the IA and IE regions in mice
- Encoded by the DP, DQ, and DR loci in humans
- Each Class II molecules contain two different polypeptide chains, α 33-kDa chain and a 28-kDa β chain,

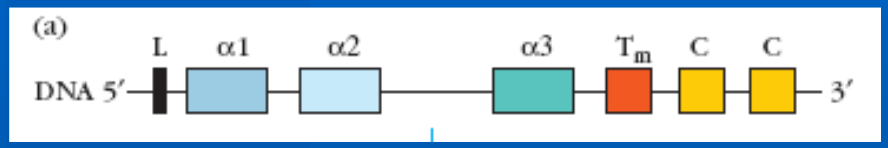


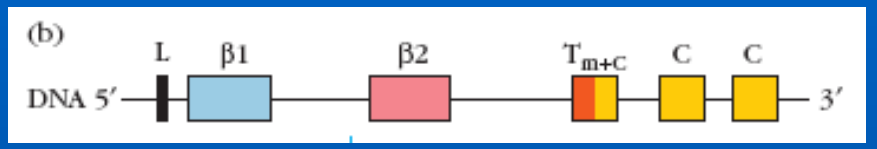
Class II MHC molecule

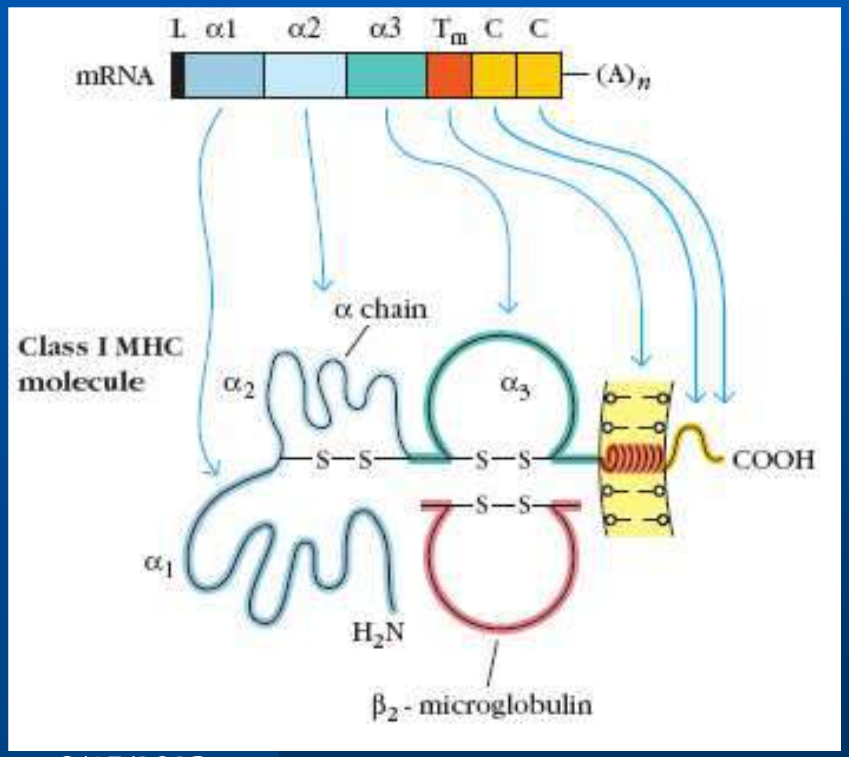
- Class II molecules are membrane-bound glycoproteins having external domains, a transmembrane segment, and a cytoplasmic anchor segment
- Each polypeptide has two external domains: α1, α2 and β1, β2 domains
- The membrane-proximal α2 and β2 domains are classified under the immunoglobulin superfamily.
- The membrane-distal domains forms the antigen binding cleft for processed antigen
- However, the class II molecule lacks the conserved residues that bind to the terminal residues of short peptides
- The cleft formed by Class II molecules are open-ended groove

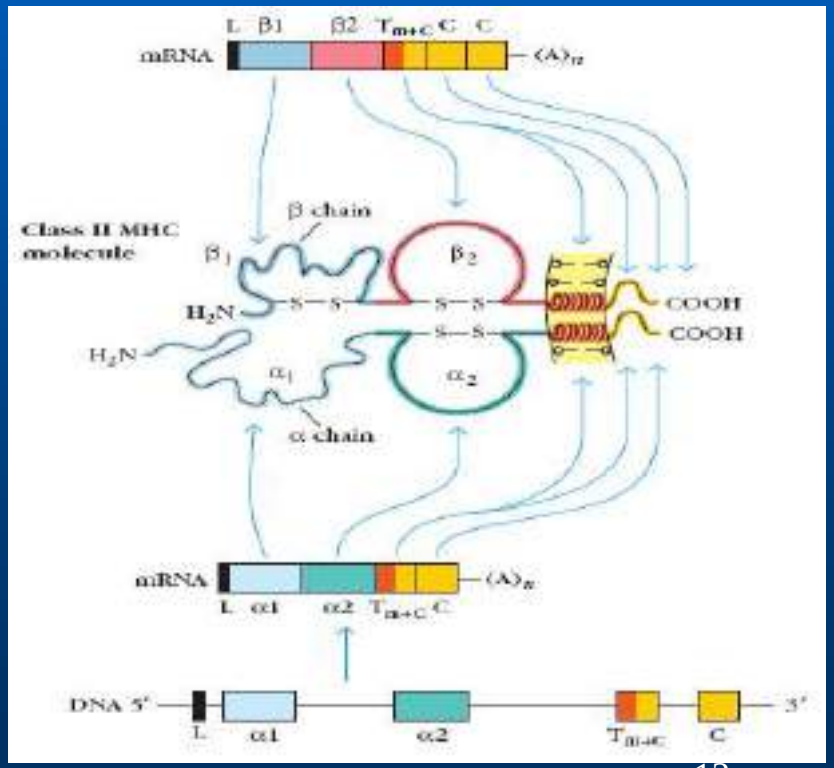


Organization of Class-1 & Class-II genes









PEPTIDE BINDING CLEFT

- **Class I and II MHC molecules exhibit some common peptide-binding features**
  - **In both types of MHC molecules, peptide ligands are held in a largely extended conformation that runs the length of the cleft.**
  - **The peptide-binding cleft in class I molecules is blocked at both ends,**
  - **Class I molecules bind peptides having 8–10 amino acid residues**
  - **Class I binding requires that the peptide contain specific amino acid residues near the N and C termini;**
  - **The peptide-binding cleft in class II is open**
  - **Class II molecules accommodates longer peptides of 13–18 amino acids**
  - **No specific amino acids is required for class II peptide binding**

CLASS I MHC–PEPTIDE INTERACTION

- Class I MHC molecules bind peptides and present them to CD8 T cells.
- Generaly, these peptides are derived from endogenous intracellular proteins that are digested in the cytosol
- Cytosolic peptides are transported into the cisternae of the endoplasmic reticulum, where they interact with class I MHC molecules.
- This process is known as the cytosolic or endogenous antigen processing pathway

A nucleated cell expresses about 10^5 copies of each class I molecule on cell surface and therefore, many different peptides will be expressed simultaneously on the surface of a nucleated cell by class I MHC molecules.

CLASS II MHC–PEPTIDE INTERACTION

- Class II MHC molecules bind peptides and present them to CD4 T cells.
- Generaly, these peptides are derived from exogenous sources
- Exogenous peptides are transported into the cytoplasm, degraded through endocytic pathway
- Digested expgenous proteins are then transported through the cisternae of the endoplasmic reticulum, where they interact with class II MHC molecules.
- This process is known as the endocytic processing pathway.

A nucleated cell expresses about 10^5 copies of each class I molecule on cell surface and therefore, many different peptides will be expressed simultaneously on the surface of a nucleated cell by class II MHC molecules.

Promiscuous behaviour of MHC molecules

- A given MHC molecule can bind numerous different peptides, and some peptides can bind to several different MHC molecules.
- Because of this broad specificity, the binding between a peptide and an MHC molecule is often referred to as “promiscuous.”
- Thus, peptide binding by class I and II molecules does not exhibit the fine specificity characteristic of antigen binding by antibodies and T-cell receptors.

Class I and II Molecules Exhibit Polymorphism

- **Several hundred different allelic variants of class I and II MHC molecules have been identified in humans.**
- **Any one individual, however, expresses only a small number of these molecules— up to 6 different class I molecules and up to 12 different class II molecules.**
- **Yet this limited number of MHC molecules must be able to present an enormous array of different antigenic peptides to T cells, permitting the immune system to respond specifically to a wide variety of antigenic challenges.**

MHC Diversity

- **An enormous diversity is exhibited by the MHC molecules within a species and within individuals.**
- **This variability not from the rearrangement of genes as observed in T and B cells**
- **The diversity of the MHC within a species stems from polymorphism, the presence of multiple alleles at a given genetic locus within the species.**
- **Diversity of MHC molecules in an individual results not only from having different alleles of each gene but also from the presence of duplicated**
- **Genes with similar or overlapping functions**
  - **for example, HLA-A, -B, and -C), the MHC may be said to be polygenic.**

MHC Diversity

- The MHC possesses an extraordinarily large number of different alleles at each locus
- It is one of the most polymorphic genetic complexes known in higher vertebrates.
- These alleles differ in their DNA sequences from one individual to another by 5% to 10%.
- The number of amino acid differences between MHC alleles can be quite significant, with up to 20 amino acid residues contributing to the unique structural nature of each allele.

MHC Diversity

- **Analysis of human HLA class I genes has revealed that there are**
  - **240 A alleles,**
  - **470 B alleles,**
  - **110 C alleles.**
- **The human class II genes are also highly polymorphic and, in some cases, there are different gene numbers in different individuals.**
  - **The number of HLA-DR beta-chain genes may vary from 2 to 9 in different haplotypes,**
  - **350 alleles of DRB genes have been reported.**
  - **DRA chain is relatively conserved and only 2 different alleles reported.**
- **In mice the polymorphism is similarly enormous.**

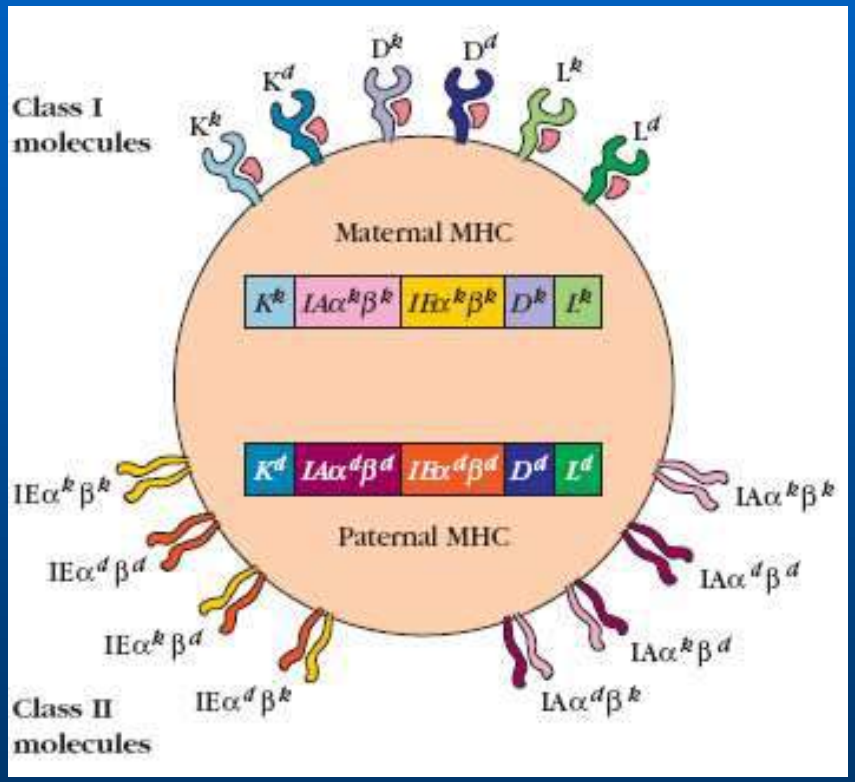
LINKAGE DISEQUILIBRIUM

- **This enormous polymorphism results in a tremendous diversity of MHC molecules within a species.**
- **Given the number of the allelic forms of human HLA-A, -B, and -C, theoretically we can get 240 x 470 x 110, yielding more than 12 million different class I haplotypes**
- **If class II loci are considered, the 5 DRB genes B1 through B5 have 304, 1, 35, 11, and 15 alleles respectively, DQA1 and B1 contribute 22 and 49 alleles, respectively and, DPB1 96 alleles; this allows approximately 1.8×10^{11} different class II combinations.**
- **Because each haplotype contains both class I and class II genes, the numbers are multiplied to give a total of $2.25\ 10^{18}$ possible combinations of these class I and II alleles.**

- However, in reality, the actual diversity is known to be less, because certain allelic combinations occur more frequently in HLA haplotypes than predicted by random combination
- Such state referred to as *linkage disequilibrium.*
- Briefly, linkage disequilibrium is the difference between the frequency observed for a particular combination of alleles and that *expected* from the frequencies of the individual alleles.

Cellular Distribution of MHC Molecules

- The classical class I MHC molecules are expressed on most nucleated cells
- However, the level of expression differs among different cell types.
- The highest levels of class I molecules are expressed by lymphocytes, where they constitute (10^5/cell)
- In contrast, fibroblasts, muscle cells, liver hepatocytes, and neural cells express very low levels of class I MHC molecules.
- The low level on liver cells may contribute to the considerable success of liver transplants by reducing the likelihood of graft recognition



MHC and Immune Responsiveness

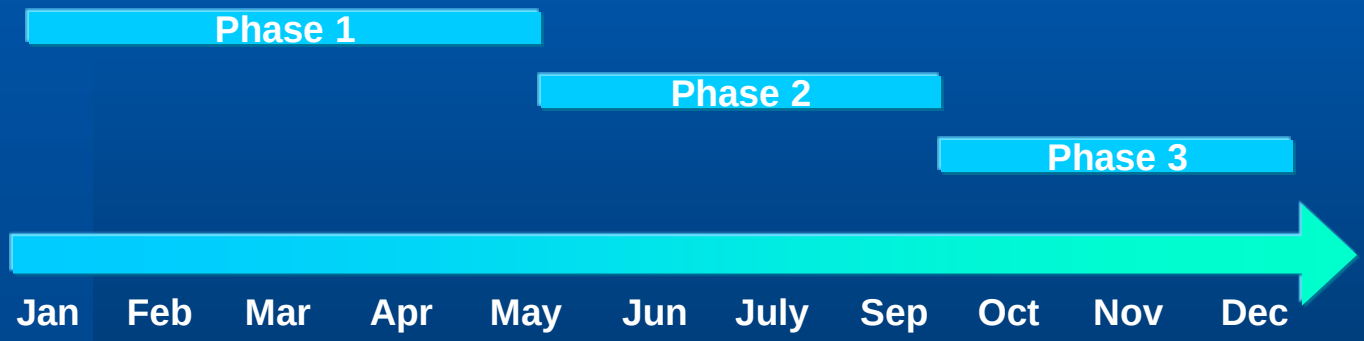
- Benacerraf showed that antibody production against synthetic peptides is is corelated the MHC haplotype
- H.McDevitt, M. Sela, later demonstrated that the MHC-Class II genes are actually responsible for the difference in abtibody production.
- We now know that class II MHC molecules in presenting antigen to T_H cells and is essential for antibody production.

MHC and Disease Susceptibility

- **Some diseases associated with particular MHC alleles and includes autoimmune disorders, certain viral diseases, disorders of the complement system, some neurologic disorders, and several different allergies.**
- **The existence of an association between an MHC allele and a disease should not be interpreted to imply that the expression of the allele has caused the disease—the relationship between MHC alleles and development of disease is complex issue**
- **A number of hypotheses have been offered to account for**
- **the role of the MHC in disease susceptibility**
  - **allelic differences may yield differences in immune responsiveness arising from variation in the ability to present processed antigen or the ability of T cells to recognize presented antigen.**

Schedule

- **Review high-level schedule milestones here**



FOR MORE INFO...

List location or contact for detailed schedule (or other related documents) here