S. No	Topic	Class No	Date
1	Introduction	1 2	27/1 29/1
2	Fundamentals of Immunology • Definitions and basic terms • Types of immunity • Organs of immune system • Cells of immune system	3 4	3/2 5/2
	Innate immunity • PAMPs • PRRs • Phagocytosis	5 6	10/2 12/2
3	Antigens • Characteristic features of antigens • Types of antigens • Super antigens	7 8	17/2 19/2
4	Humoral Immunity • Antibody – structure and functions	9 10	24/2 26/2
5	Ig Biosynthesis • Monoclonal antibody production	11 12	3/3 5/3
6	Complement system • 3 pathways of complement system	13 14 15	10/3 12/3 17/3
	Reserve	15	19/3
	First mid term (25 marks)	16	17/3 or 19/3
7	Cell mediated immunity • Macrophages • T cells • Th1 and Th2 response	17 18	24/3 26/3
8	MHC and transplantation immunity	19 20	31/3 2/4
9	Disorders of Immune system • Hypersensitivity • Immunodeficiency	21 22	7/4 9/4
10	Tumor immunology • Tumor specific antigens • TIL	23 24	14/4 16/4
11	Tolerance and autoimmunity	25	21/4
12	Antigen and Antibody reactions	26	23/4
	Reserve	27 28	28/4 30/4
	Second mid term(25 marks) (submit literature review – 10 marks)	27/28	27/4 or 28/4
	Final (40 marks)		

Major Histocompatability complex

Transplantation Immunology

By
Dr. Gouse Mohiddin Shaik

Major Histocompatibility Complex

- We will learn…….
  - MHC history
  - Role in Transplantation
    - GVHD and HVGD
  - Structure of MHC
  - Diversity of MHC
  - Important features of MHC

Major Histocompatibility Complex

- History
  - Transplantation : Graft rejection
  - Immnune response differences : antibody formation against specific Ag
    - Studies in mice gave clues
- Highly polymorphic
- Bind peptides recognized by T cells
- Class I and Class II

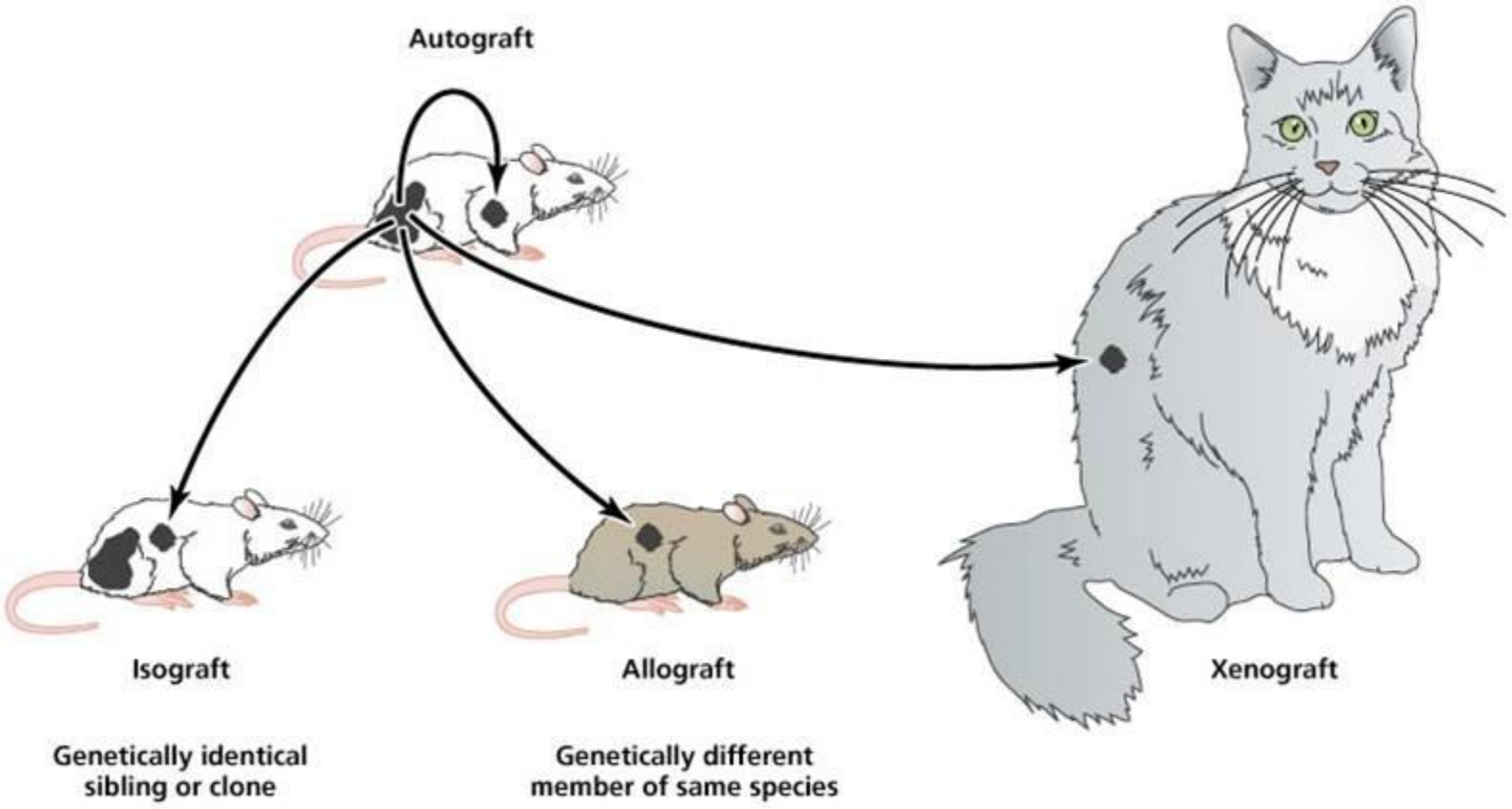
Major Histocompatibility Complex

- What is MHC
  - HLA – humans
  - H2 – mice
  - Minor histocompatibility antigens

  - Play role in immune response
  - Play role in antigen presentation
  - Play major role in graft transplantation
  - Role in predisposition to disease

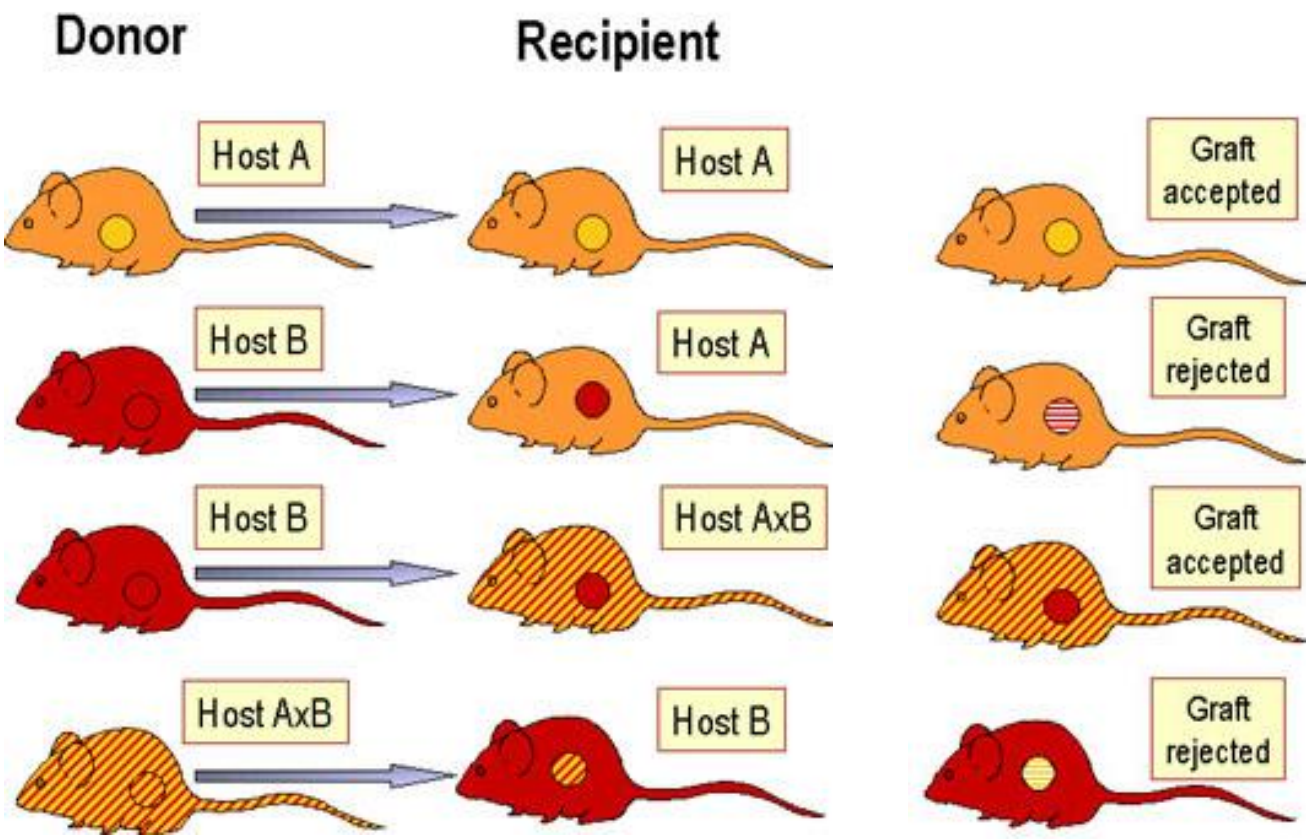
Transplantation

- Graft



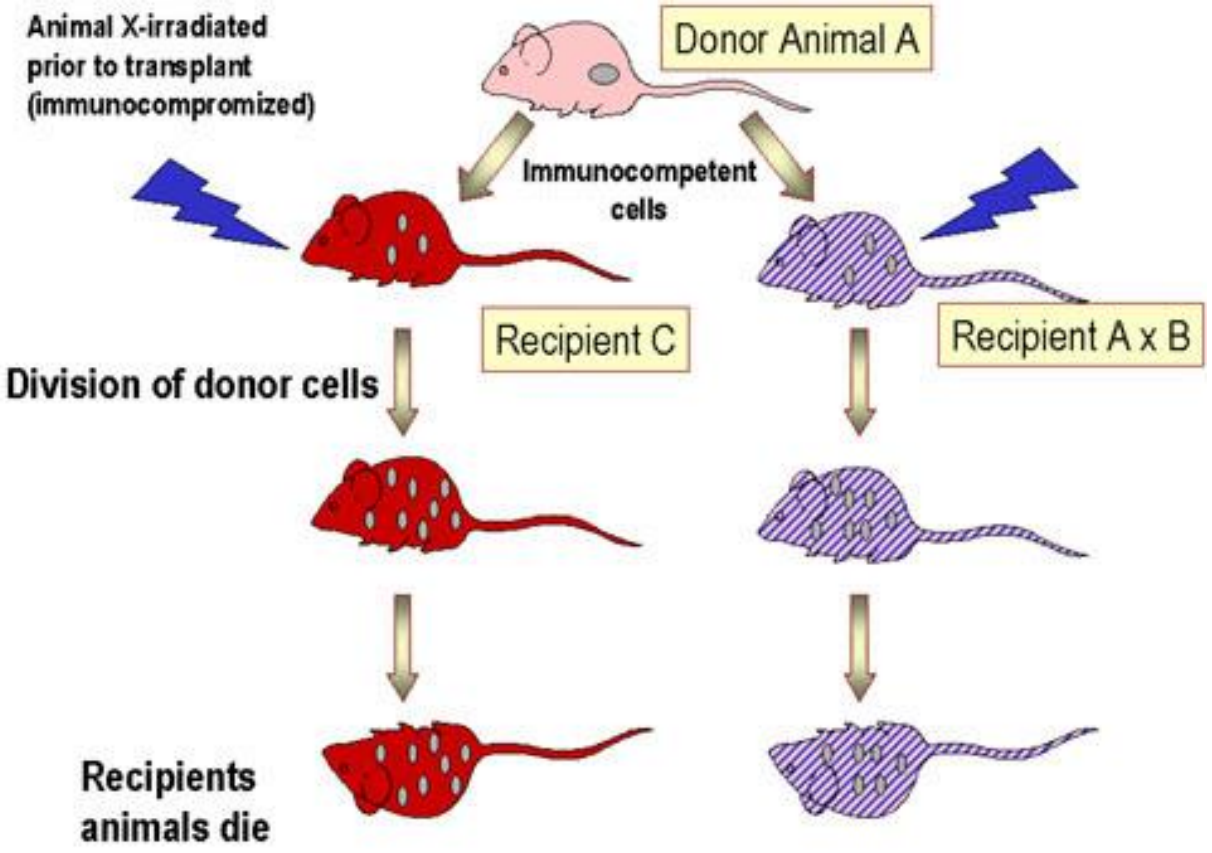
- Auto, Iso, Allo and xeno

Principles of Transplantation



Host vs Graft Disease

Principles of Transplantation

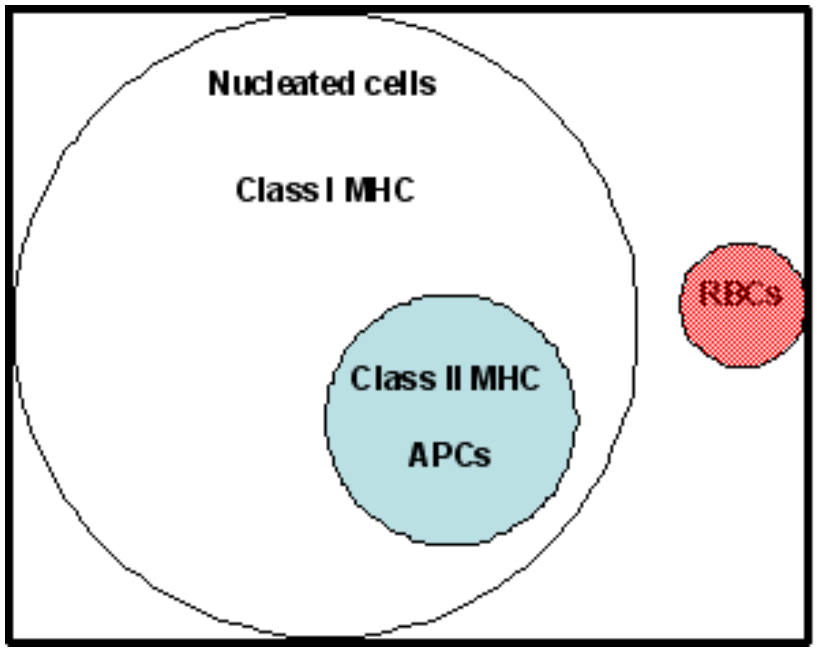


Graft vs Host Disease (GVHD)

During Bone marrow transplants

MHC Distribution

- Distribution of MHC molecules in humans

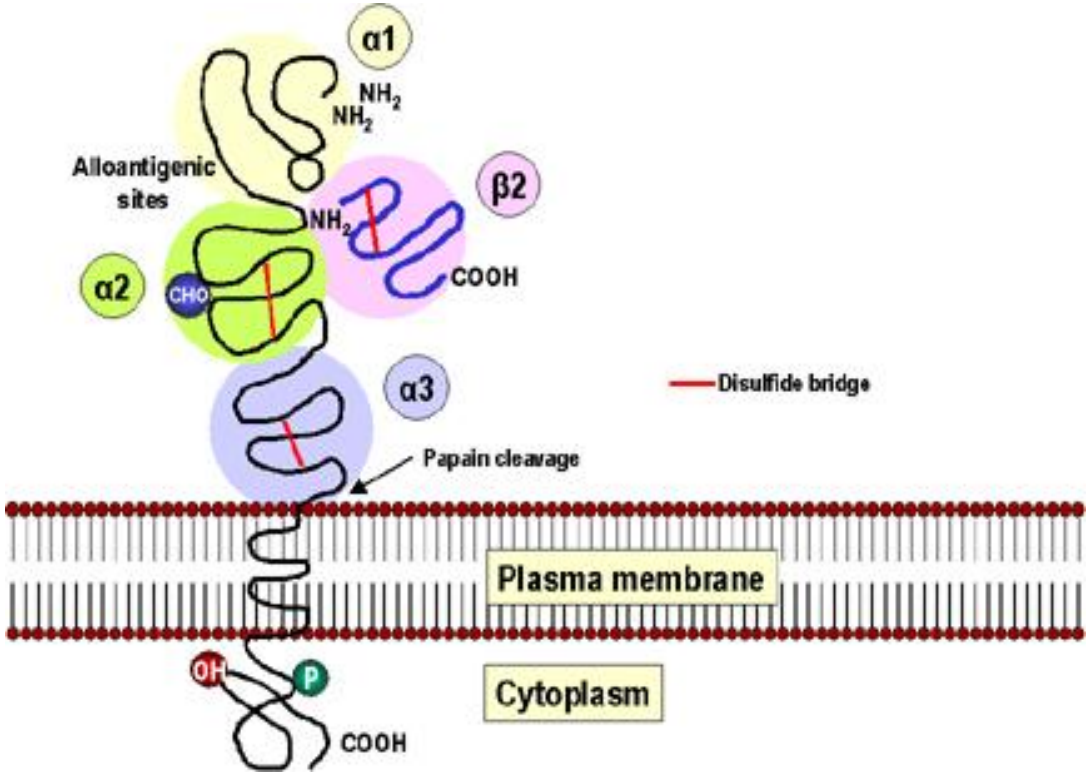


- All cells have MHCI, immune cells have I and II

Structure of MHC class I

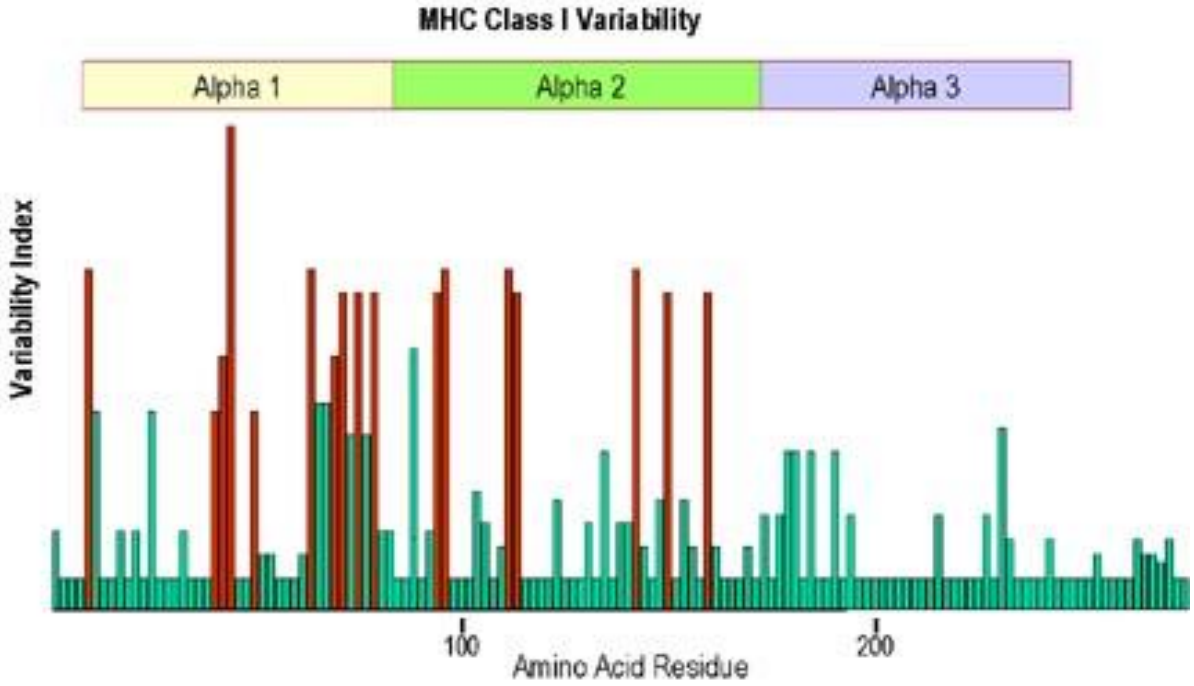
- MHC I molecules are composed of 2 poly peptide chains one long α and a short β chain called β2 microglobulin
- α chain has 4 regions
  - Phosphorylated cytoplasmic region
  - Transmembrane region rich in hydrophobic amino acids
  - Conserved α3 domain binding CD8
  - Highly polymorphic α1 and α2 domains forming peptide binding groove
- β2 microglobulin stabilizes α chain

Structure of MHC class I



The MHC class 1 molecule has three globular domains alpha 1 (yellow), alpha 2 (green) and alpha 3 (blue). The alpha 3 domain is closely associated with the non-MHC -encoded beta 2 microglobulin (pink). The latter is stabilized by a disulfide bridge (red) and is similar to an immunoglobulin domain in three-dimensional structure. The alloantigenic sites which carry determinants specific to each individual are found in the alpha 1 and 2 domains. The latter also has a carbohydrate chain (blue, CHO). There is a phosphate in the cytoplasmic domain. Papain cleaves near the outer surface of the plasma membrane

Polymorphic α1 and α2 domains

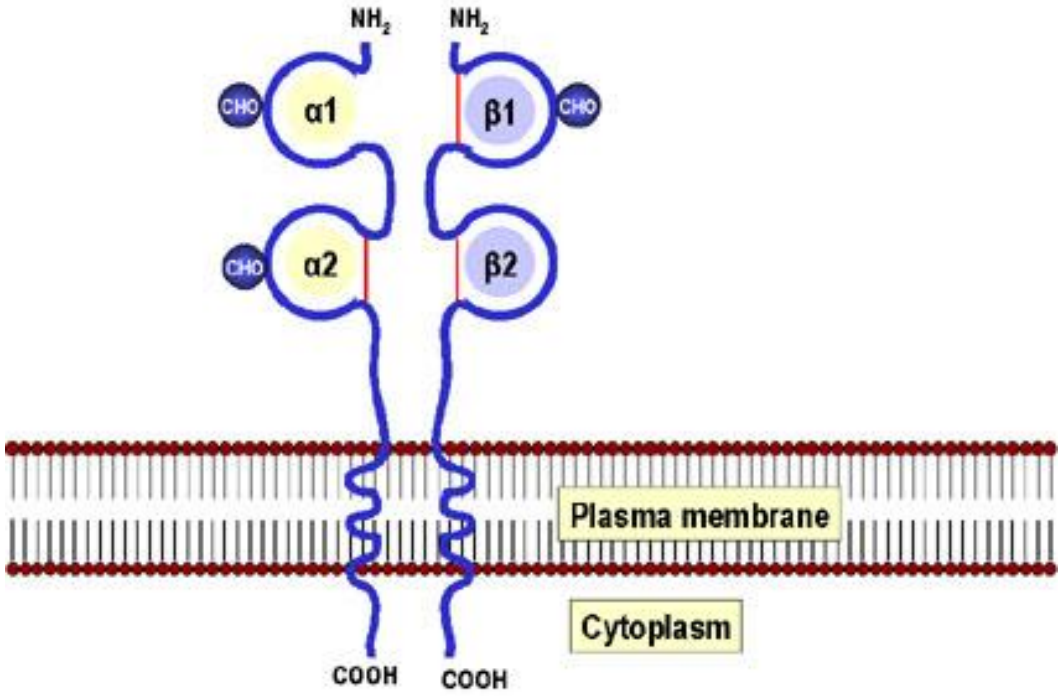


Most variability in amino acids at different positions along the alpha chain of class I MHC molecules occurs in the alpha 1 and alpha 2 regions. The greatest polymorphism is found for amino acids that line the wall and floor of the groove that binds the peptides

Structure of MHC class II

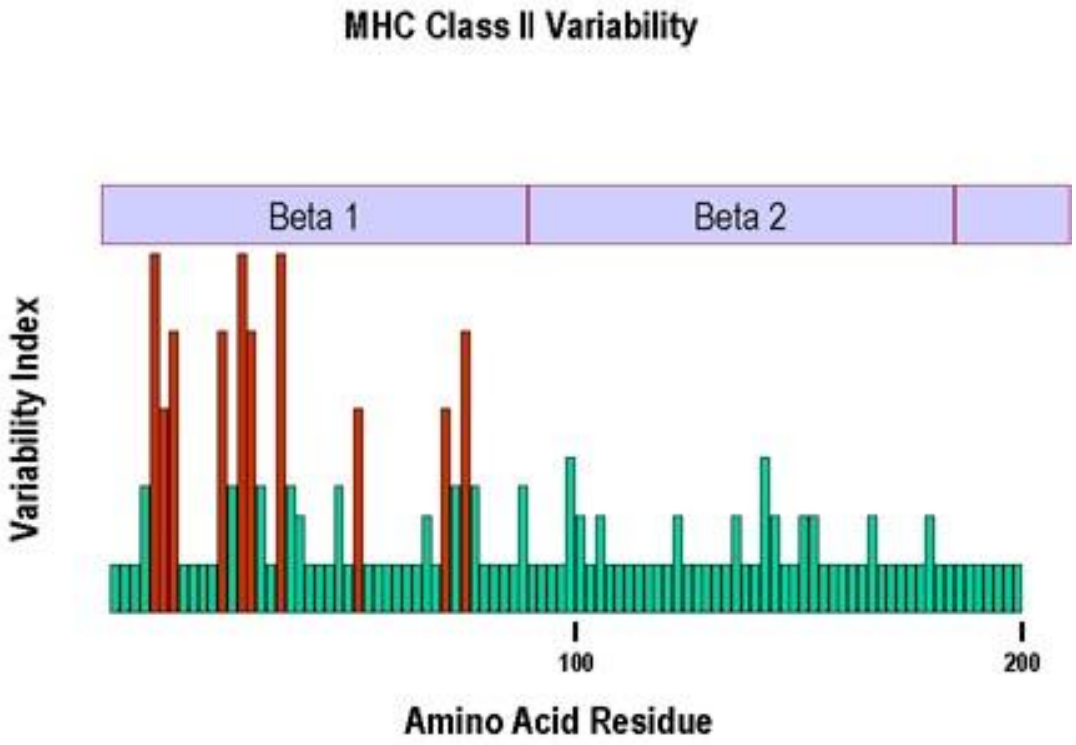
- MHC II molecules are composed of 2 poly peptide chains α and β
- Both α and β chains has 4 regions
  - Phosphorylated cytoplasmic region
  - Transmembrane region rich in hydrophobic amino acids
  - Conserved α2 domain and highly conserved β2 domain binds CD4
  - Highly polymorphic α1 and β1 domains forming peptide binding groove

Structure of MHC class II



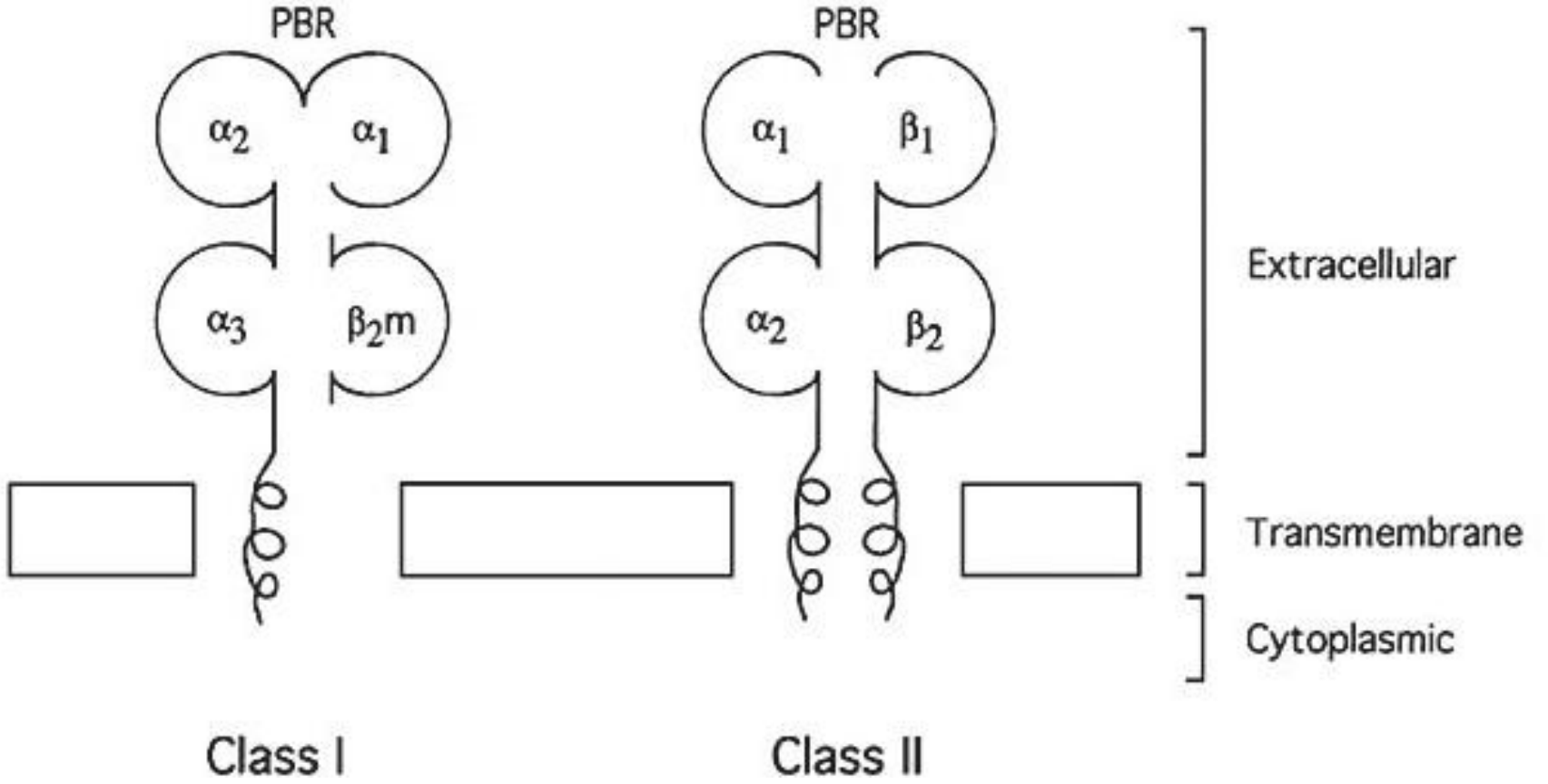
MHC class II molecules comprise two non-identical peptides (alpha and beta) which are non-covalently associated and traverse the plasma membrane with the N terminus to the outside of the cell. The domains closest to the membrane in each chain are structurally related to immunoglobulins. With the exception of the alpha 1 domain, all domains are stabilized by disulfide bridges (red). Both the alpha and beta chains are glycosylated. The beta chain is shorter than the alpha chain (beta mol. wt = 28,000) and contains the alloantigenic sites. There is some polymorphism in the alpha chain of some MHC II molecules

Polymorphic β1 domains



The greatest polymorphism for the beta chain of class II MHC molecules is found for those amino acids in the beta I region that line the wall and floor of the groove that binds the peptide

Comparision of Class I and II



Polymorphism of Class I and II

Table 1. Polymorphism of class I MHC genes

Locus	Number of alleles (allotypes)
HLA-A	218
HLA-B	439
HLA-C	96
HLA-E, HLA-F and HLA-G	Relatively few alleles

Table 2. Polymorphism of class II MHC genes

Locus	Number of alleles (allotypes)
HLA-DPA	12
HLA-DPB	88
HLA-DQA	17
HLA-DQB	42
HLA-DRA	2
HLA-DRB1	269
HLA-DRB3	30
HLA-DRB4	7
HLA-DRB5	12
HLA-DM and HLA-DO	Relatively few alleles

An individual will have a max of 6 Class I and 7-8 class II

Aspects of MHC

- MHC molecules are membrane bound. Recognition by T cells requires cell-cell contact
- Peptide from cytosol associates with class I and is recognized by Tc cells
- Peptides from vesicles associates with calss II and is recognized by Th cells
- A peptide must associate with a given MHC of that individual. Otherwise no immune response will occur

Aspects of MHC

- Mature T cells must have a T cell receptor (TCR) that recognizes the peptide associated with MHC
- Each MHC molecule has one binding site. The different peptides a given MHC can bind all bind to the same site. But only one at a time
- MHC polymorphism is determined only in the germline. There are no recombination mechanisms for generating diversity

Aspects of MHC

- Because each MHC molecule can bind many different peptides, binding is termed degenerate
- Cytokines (INF-γ) increases level of expression of MHC
- MHC alleles are co-dominant
- Why the high degree of polymorphism?
  - Survival of species
- MHC is there to protect humans not to reject transplants

Next class…..

- Tolerance and auto-immunity