

Lecture Outline

MHC Restriction

Jan. 31, 2001

I. Definition of self MHC restriction;

MHC restriction is the requirement that APC or target cells express MHC molecules that the T cell recognizes as self in order for T cell to respond to the antigen presented by that APC or target cell. (T cells will only recognize antigens presented by their own MHC molecules.)

CD8 T cells bind class I MHC which are expressed on most cells in the body.

CD4 T cells bind class II MHC which are only expressed on specialized APCs.

APCs primarily reside in 2 ° lymphoid tissue (lymph nodes, spleen) but can be found in most tissues.

II. MHC Genetics

Mouse MHC gene complex called H-2. Human MHC gene complex called HLA.

MHC Molecules	Mouse H-2	Human HLA
Class I	K,D,L	A, B, C
Class II	I-A, I-E	DR, DQ, DP

Definitions:

Alleles functional forms of the same genes.

Heterozygous different allele at each locus.

Homozygous same allele at each locus.

Haplotype is the total set of MHC alleles present on one chromosome.

For each MHC gene locus you have 2 copies which can be denoted by their allele classification. Most humans will be heterozygous and will have different alleles for each of the different HLA loci. (e.g. A2/A12, B17/B83, C3/C37, DR3/DR4 etc).

Syngeneic identical at all MHC loci same allele on both chromosomes. (inbred mice or identical twins).

Allogeneic --genetically different at MHC different alleles. Every person gets a chromosome from each biological parent which contains an MHC molecule at each locus.

Polymorphic -presence of multiple functional forms of same gene.

The MHC is highly polymorphic -meaning a great deal of variety of MHCs can potentially be at any one given locus as many as 100 alleles possible.

III. MHC Polymorphism and Disease

MHC diversity provides a greater ability to present a wider variety antigens which is helpful when trying to fight disease on an individual basis and for a population.

In an **individual** there are multiple MHC molecules with heterozygosity with different alleles thus a wide variety of peptides will be presented.

In a **population** there are many different individuals with varied MHC alleles which have different capacities to bind peptides in an epidemic. Some individuals will probably be able to present peptides, develop immune response, and survive. Provides for long term protection of population.

IV. Tissue Typing

Transplantation

MHC are the proteins that are used to match donor organs with transplant recipients.

Tissue typing is used to determine which MHC molecules are expressed on donor tissue in order to match the person receiving the transplanted organ. The closer the MHC the less likely the transplanted organ will be rejected.

What causes transplant rejection?

Self T cells can bind to foreign MHC cells and kill the foreign cells because they are seen as non-self.

This is called an **alloimmune** response.

V. Structure of MHC Molecules

Class I MHC

1. Heavy chain- encoded by HLA- A, B, C or mouse H-2 K, D, L. All Class I MHC Heavy chains combine with the invariable β -2 microglobulin.
2. Class I MHC is expressed on most cell type. Presents antigen to CD8⁺ T cells.
3. Presents endogenously derived ags. Peptides bound to class I MHC are sampling of intracellular environment.

Class II MHC

1. α and β chains both encoded in MHC.
Cleft of Class II MHC formed by both chains.
2. Found only on APCs present to CD4⁺ T_{helper} cells.
3. Binds peptides from endocytic pathway which are from exogenously derived proteins. Samples extracellular environment.

VI. Antigen binding of MHC

Cleft of the MHC. The cleft or groove of the MHC molecule is usually defined as the peptide binding site where contact is made with MHC but still allows for the peptide to be recognized by the TCR.

MHC molecules and peptides have affinities for each other.

MHC molecules are promiscuous --they will bind many different peptides--this is in contrast to TCR and Ab bind only one. But they do not bind all peptides. Different alleles and different MHC genes bind different sets of peptides.

- VI. Thus your MHC molecules will determine what part of a protein antigen (which peptides) will be recognized as foreign.