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Major Histocompatibility Complex

INTRODUCTION:

Every mammalian species studied till date possess a tightly linked cluster of genes, the major histocompatibility complex (MHC) whose products are associated with intercellular recognition and self / non-self discrimination. The MHC is a region of multiple loci that play major roles in determining whether a transplanted tissue will be accepted as histocompatible or rejected as histoincompatible. The concept that the rejection of foreign tissue is the result of an immune response to a cell-surface molecules (histocompatibility antigens) came from the work of R.A.Gorer and G.D.Snell in mid 1930s.

CLASSIFICATION:

The MHC genes are organized into regions encoding three classes of molecules:-

A. **Class I MHC gene** encodes glycoproteins expressed on the surface of nearly all nucleated cells; these glycoproteins present peptide antigens on CD-8^+altered-self cells necessary for activation of T_C cells.

B. **Class II MHC gene** encodes glycoproteins expressed primarily on the APC (Antigen Presenting Cell) like dendritic cell, macrophage, B-cell; these glycoproteins present processed peptide antigens on CD-4^+ APC necessary for activation of T_H cells.

C. **Class III MHC gene** encodes secretory proteins associated with immune processes; they include soluble serum proteins, components of complement system, tumour necrosis factor, etc.

MHC HAPLOTYPES:

- The loci constituting the MHC are highly polymorphic; many alternate forms of the genes or alleles exist for each locus.
- The MHC loci are closely linked i.e. the recombination frequency within the MHC complex is very low.
- As such the an individual inherits the alleles encoded by these closely linked loci as two sets, one from each parent.
- Each set of alleles is referred to as a *haplotype*.
- An individual inherits one haplotype from the mother and one haplotype from the father.
- In an outbred population the offsprings are generally heterozygous at many loci and will express both maternal and paternal MHC alleles; these alleles are therefore codominantly expressed i.e. both maternal and paternal genes are expressed in the same cells.
- In inbred strains , each locus is homozygous as maternal and paternal haplotypes are identical.

1. STRUCTURE OF CLASS I MHC MOLECULE:

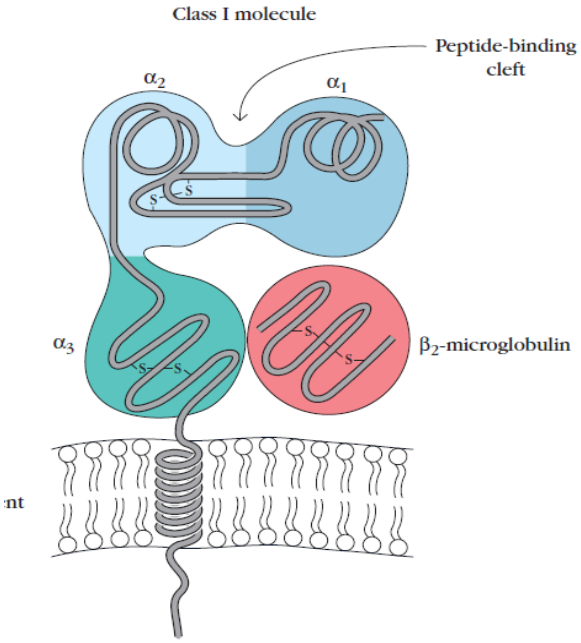

Fig. Diagram of Class I MHC molecule

- Class I MHC molecule contain a large α-chain associated noncovalently with the smaller β_2-microglobulin molecule.
- The α-chain is a 45 Kda polymorphic transmembrane glycoprotein encoded by the genes A, B and C of human HLA complex and by K and D/L regions of mouse H-2 complex.
- β_2- microglobulin is a 12 Kda protein located in a separate chromosome; α and β_2- microglobulin association is necessary for Class I MHC activation.
- The α-chain is anchored in the plasma membrane by its hydrophobic transmembrane segment and hydrophilic cytoplasmic tail.
- A peptide-binding cleft is located on the top surface of ClassI MHC molecule having a size sufficient to bind 8-10 amino acids.

2. STRUCTURE OF CLASS II MHC MOLECULE:

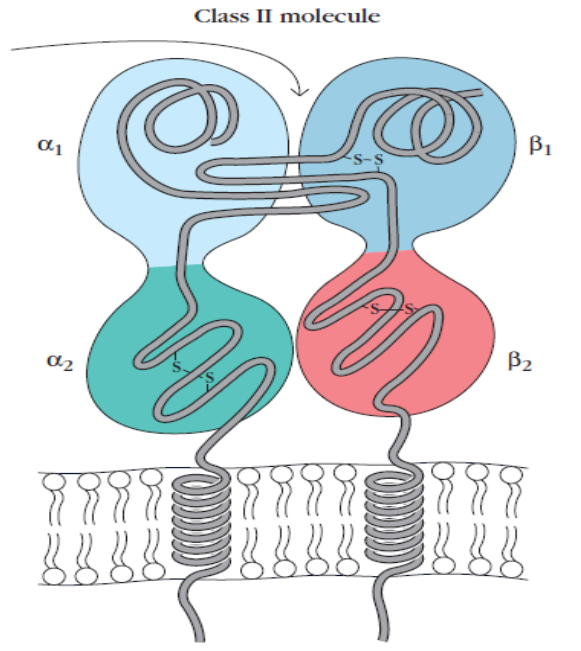

Fig. Diagram of Class II MHC molecule

- Class II MHC molecules contain two different Polypeptide chains: a 33 Kda α-chain and a 28KDa β chain.
- α and β chains are connected by noncovalent association.
- Both α and β chains are anchored to plasma membrane by a hydrophobic transmembrane segment and a hydrophilic cytoplasmic tail.
- Class II MHC molecules exist as a dimmer of the αβ heterodimer --- a dimmer of dimmers.

Remarks:

- ☼ The peptide binding cleft in Class I MHC molecule is blocked at both ends whereas the cleft is open on Class II MHC molecules.
- ☼ Class I MHC molecules bind peptides and present them to CD-8^+ T_C cells.
- ☼ Class II MHC molecules bind peptides and present them to CD-4^+ T_H cells.

☼ Homology with the constant region of Ig molecule has placed MHC Class I and Class II molecules in the broad group of immunoglobulin superfamily.

3. STRUCTURE OF CLASS III MHC MOLECULE:

- Class III MHC molecule is a non-membrane protein.
- Diversity in structure has resulted in great difficulty to give them a generalised structure.
- Exact function of Class III MHC molecule is still to be understood.
- It is thought that they play a major role in complement activation as they include many complement components ------ C2, C4a, C4b, factor B; besides TNF-α, TNF- β, 21-hydroxylase enzymes (21-OHA, 21-OHB) are considered to be a part of it.

Remarks:

MHC molecules play a vital role in processing and presentation of non-self atigenic peptide molecules by antigen presenting cells (APC).

CHEETAHS : MHC AND SUSCEPTIBILITY TO DISEASES

Cheetahs have been shown to be far more susceptible to viral diseases than other big cats. As the present cheetah population arose from a limited breeding stock, the species suffers from a loss of MHC diversity due to frequent inbreeding. The increased susceptibility to cheetahs to various viral diseases may result from a reduction in the number in different MHC molecules available to the species as a whole and a corresponding limitation on the range of processed antigens with which these MHC molecules can interact. Thus the high level of MHC polymorphism that has been observed in various species may be advantageous by providing a broad range of antigen presenting MHC molecules.

Reference:
Immunology by J. Kuby