MAJOR HISTOCOMPATIBILITY COMPLEX

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MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) INTRODUCTION

- Confer the ability of self and non-self to immune system.
- Most polymorphic loci known in vertebrates and span about four million base pairs in humans.
- Encode cell surface proteins (**class I and II MHC molecules**)
- Have a pivotal role in directing immunological self/non-self recognition.
- Responsible for graft rejection, autoimmune disorders, and immune responses to infectious.
- Are called human leukocyte antigen (HLA) in Humans; SLA in swine;, OLA in ovine ; ELA in equine; DLA in dogs; BoLA in bovine.

THE HISTORY OF MHC RESEARCH

1916, Little and Tyzzer found that tumours could be transplanted only among same strains of mice.

1927, Bover found there was histocompatibility ('histo' means 'tissue') among identical twins

1930s, Gorer found that the tumour growth or rejection is linked to expression of a particular antigen.

1933, Haldane found similar immune response for both transplanted tumours and normal cellular antigens

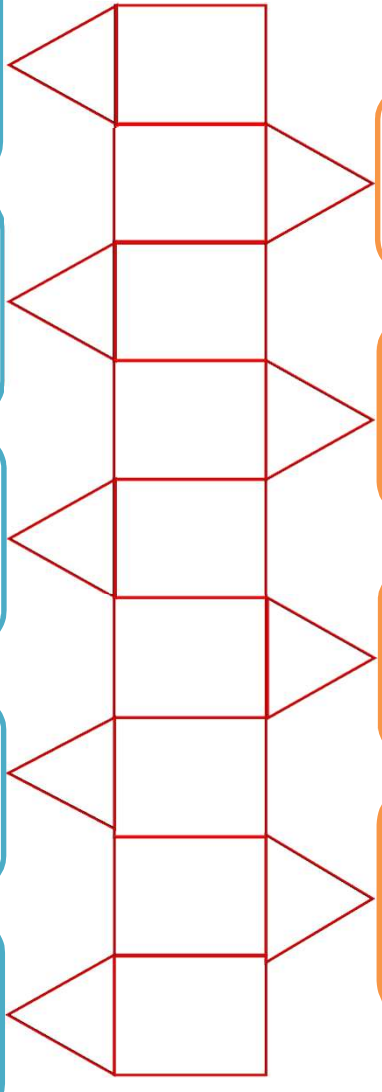
1940s, Medawar attributed graft rejection to immune attack on foreign graft.

Snell and his colleagues discovered genes controlling tissue rejection, the MHC.

1970 immune responses were shown to be under control of interactions between MHC and T -cells.

1975, Zinkernagel demonstrated that MHC and were also involved in humoral, as well as cellular responses.

1980s and 1990s, X-ray crystallographic structure of MHC molecules was revealed.



Snell and Colleagues worked to find out the reason behind destruction of tissue when introduced from one individual to another individual of same species

What they found out was very interesting!

They found that a group of genes controlled rejection

This was named as Major Histocompatibility (MHC)

Histocompatibility: histo means tissues and compatible means agreeable or getting along

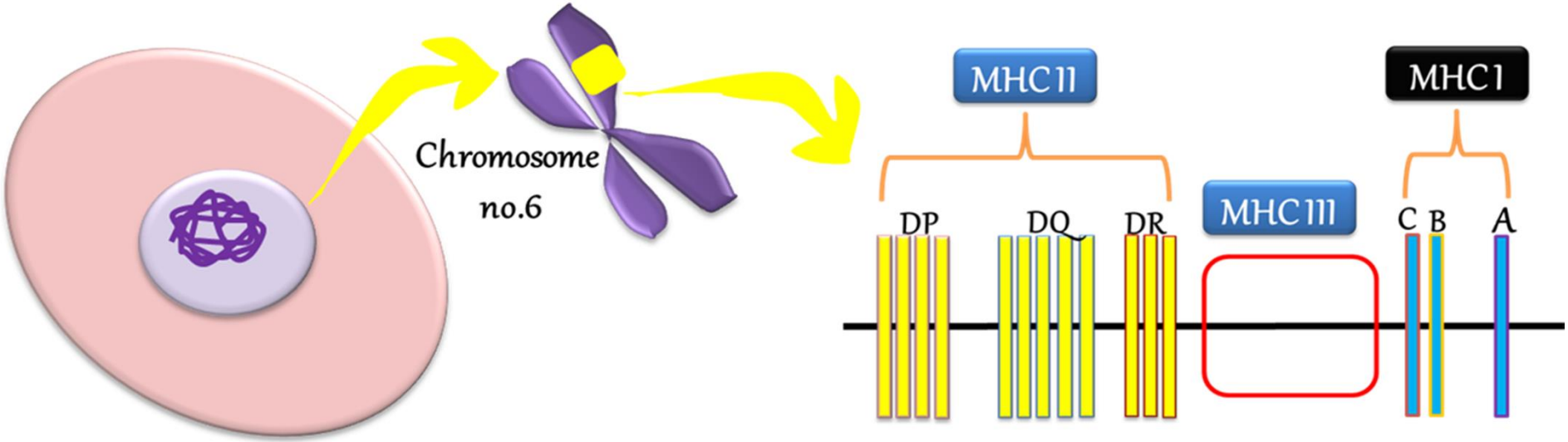
Complex: a large genetic region having several loci

These genes code for proteins which decide whether tissue being transplanted in an individual will be accepted or rejected

MHC (HLA) GENETIC ARCHITECTURE

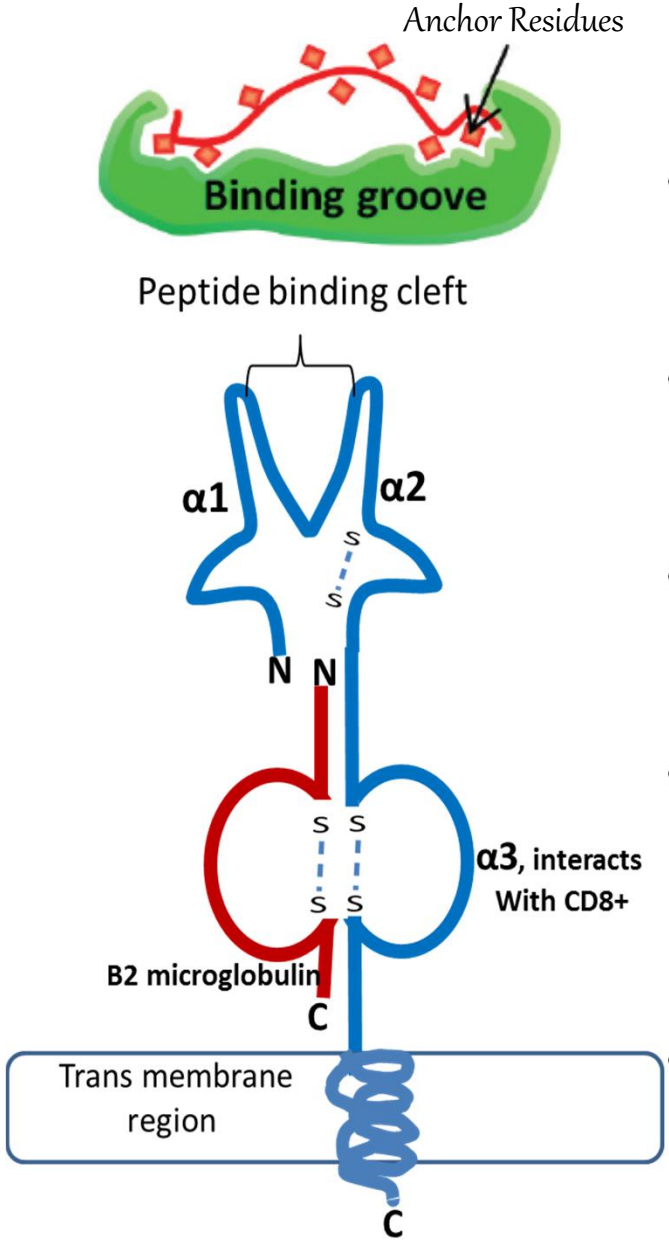
- A large region on chromosome 6 with over 200 coding loci.
- Highly polymorphic; contains class I, class II and III genes, with other genes for growth, development, reproduction, odour and olfaction.
- MHC class I has six loci (e.g. A, B and C) and MHC class II has eight loci (e.g. DP, DQ and DR) in humans.
- Each MHC class II locus has several genes.
- The polymorphism at each locus varies from single to more than 100 alleles.

MHC (HLA) GENETIC ARCHITECTURE



The HLA complex has approximately 4 Mb on chromosome 6 and with three major regions having more than 260 loci, coding for more than 160 protein.

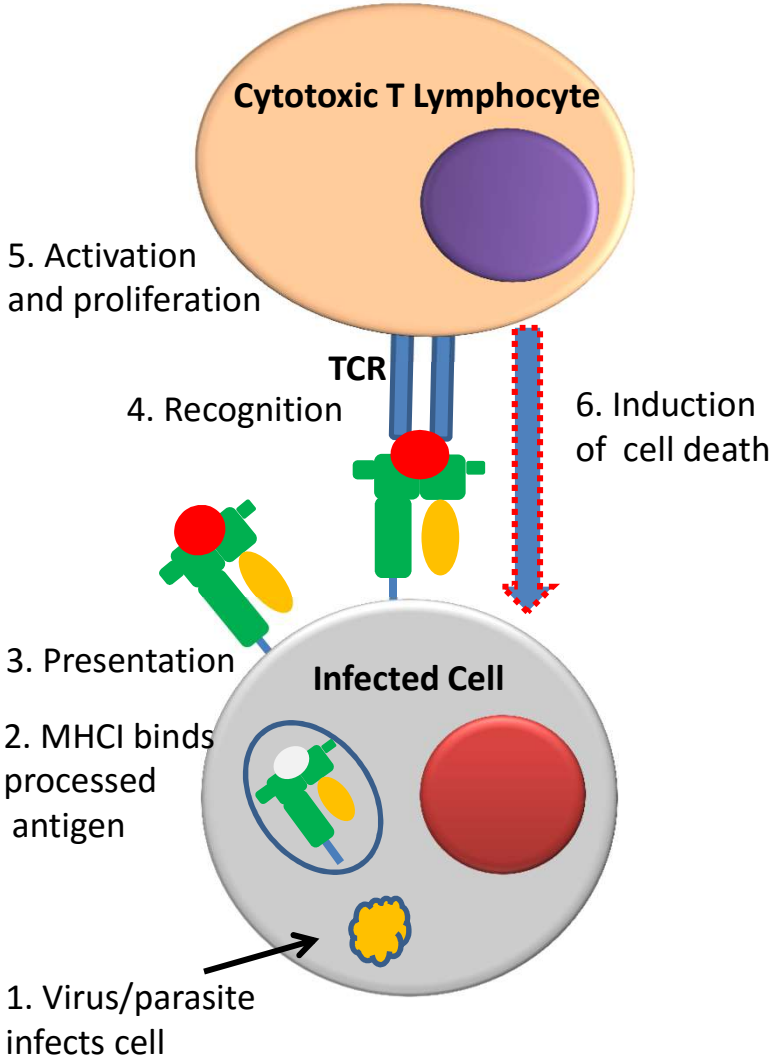
MHC Class 1



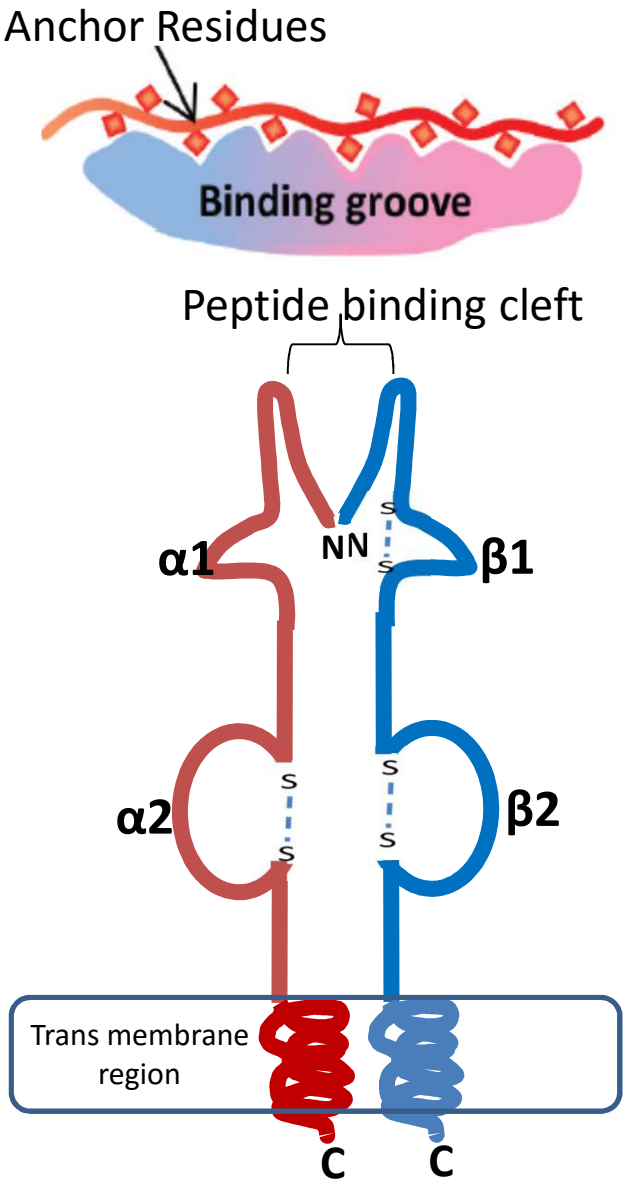
- Is a heterodimer of trans membrane α chain with β2-microglobulin (β2m).
- α chain (43 kDa) has α1, α2, and α3: three extracellular globular domains .
- α1 and α2 domains form a groove that fits an 8- to 10-mer antigenic peptide.
- α3 highly conserved; interacts with CD8+ Cytotoxic cells.
- β 2 microglobulin is a 12 kDa (encoded by single gene on chromosome 15); non-covalently bound to alpha chain.
- Has a well defined peptide binding motif depending on type of the allelic variant of MHC.

FUNCTION OF MHC CLASS I MOLECULES

- Present processed self peptides or foreign peptides from intracellular virus/parasite to Cytotoxic T Lymphocytes (CTLs).
- T-cell receptor (TCR) of CTL binds to MHC–antigen complexes.
- CD8 adhesion molecules on CTL stabilizes the with the APC through interaction with MHC I.
- On recognising the antigen as foreign, there is activation of CTL which proliferates and destroys other infected cells.



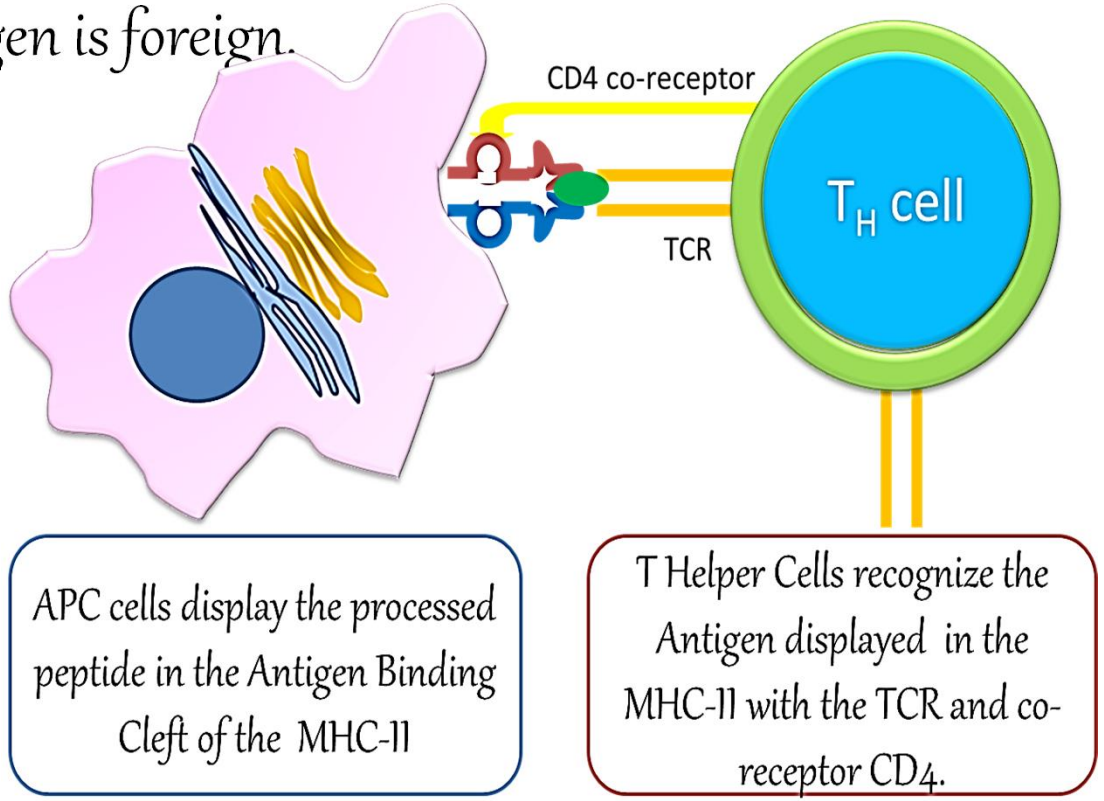
MHC CLASS II



- Is a heterodimer formed of one α (32 to 34 kDa) and one β chain (29-32 kDa) .
- Both α and β chain have one intracellular, one trans membrane, and two extracellular domains.
- α1 and β1 domains come in vicinity to form an antigen-binding cleft/groove which has open ends; and fits a bigger antigenic peptide (14-mer or more) protruding from both sides of the cleft.
- Both α and β encoded by DP, DQ and DR region in the HLA complex.
- β 2 interacts with the CD4 of T-helper cell..
- Have peptide motifs that bind with specific residues in the peptide-binding groove giving a twisted configuration to binding peptide and thus exposing sites for external interactions.

THE FUNCTION OF MHC CLASS II MOLECULES

- Process and present antigens to T helper (T_H) cells.
- The activated T_H cell finds other macrophages to activate them.
- B cells also act as Antigen presenting cell and expresses MHC II.
- B cell is activated, only if it presents the antigen to the activated T_H in order to confirm that antigen is foreign.



MHC CLASS III

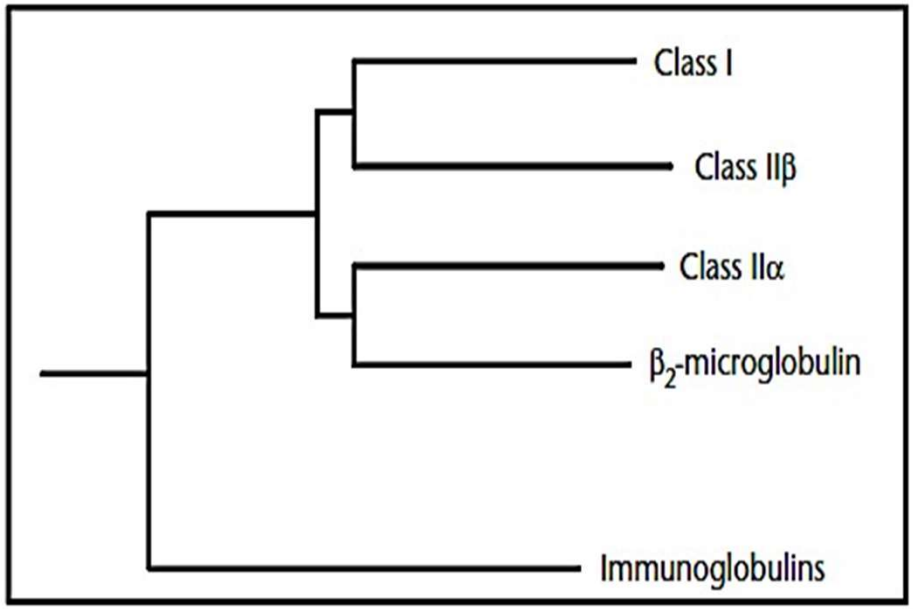
- Lies between the MHC I and MHC II loci, and with approximately 75 genes.
- These genes code different proteins, some of which are constituents of innate immunity.
- Some important ones are:
  - Genes encoding factors C2, C4, and B of the complement system.
  - genes encoding for cytokines involved in various inflammatory pathways such as that for tumour necrosis factor (TNF) superfamily.
  - Several other genes encoding proteins with no link to immune system.

MHC EXPRESSION

- MHC alleles are co-dominantly expressed.
- 2 alleles from each of the three MHC class-I genes, (HLA-A, HLA-B and HLA-C), express six variants of MHC-I in each individual.
- Each MHC molecule binds many similar peptides, thus increasing the diversity of MHC controlled immune responses to infections.
- Polymorphic residues of the antigen-binding cleft of MHC confer different specificities and bind different antigenic peptides.

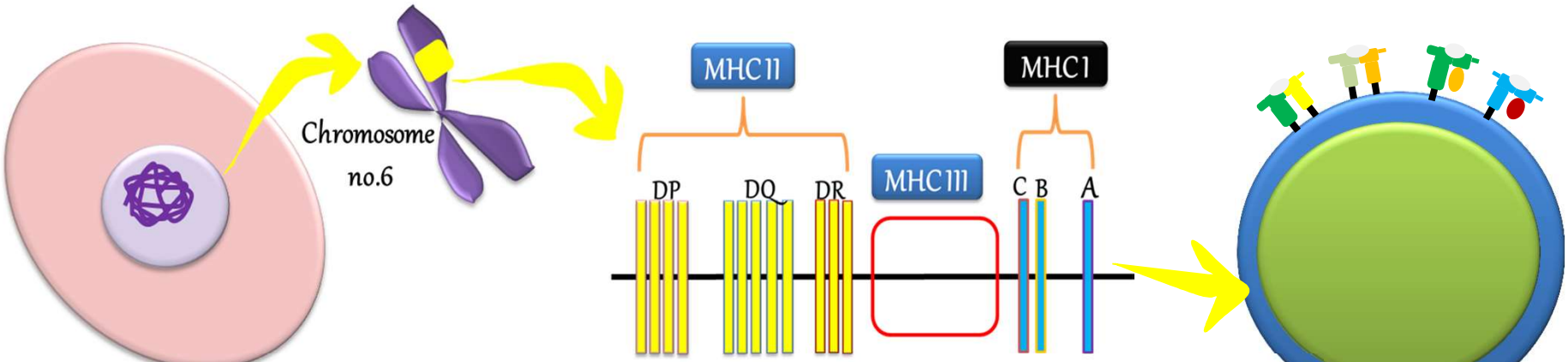
EVOLUTIONARY ORIGINS OF MHC GENES

- Class I and II molecules have similar structure and function which points towards evolution from a common ancestor.
- Both belong to the immunoglobulin multigene superfamily that includes single-gene and multigene families, of antibodies, T-cell receptors and class I and II MHC molecules.

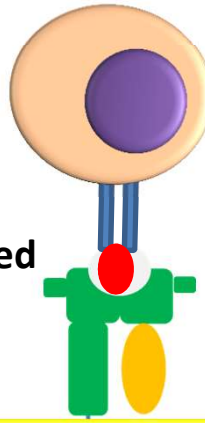


MHC GENES INFLUENCE DISEASE RESISTANCE

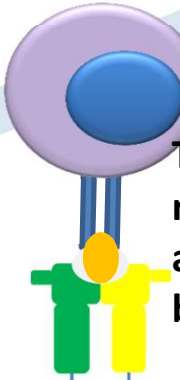
- Different Genetic variants of MHC confer differential resistance and susceptibility to individuals against many infections.
- Many MHC alleles show associations with diseases such as with malaria, hepatitis, and human immunodeficiency virus (HIV).
- Others show association with autoimmune diseases, such as lupus and arthritis, rather than with infectious diseases.
- Differential antigen binding of MHC alleles is the immunological basis of MHC-dependent resistance and the evolution of MHC polymorphisms.



Class I: 3 types HLA-A, HLA-B, HLA-C; Class II 3 types HLA-DP, HLA-DQ, HLA-DR.
3 extra DRβ genes in some individuals can allow 3 extra HLA-DR molecules
Maximum of 9 types of antigen presenting molecules allow
interaction with a wide variety of peptides



Cytotoxic T-cells recognize antigens displayed by MHC I



T Helper Cells recognize antigens displayed by MHC II

MHC Class I is expressed on all nucleated cells and express endogenous antigen

MHC Class II is expressed on all antigen presenting cells such as dendritic cells, macrophages, B--Cells

MHC Class III code for certain inflammatory such as TNF-α and complement

SUMMARY

- MHC plays an important role in control and development of immune system.
- The highly polymorphic nature of MHC genes result in differential immune response and resistance to diseases.
- The antigenic peptides from extracellular pathogens displayed by class II MHCs on APCs is recognised by T Helper Cells.
- The antigenic peptides from intracellular proteins displayed by class I MHCs is recognized by the Cytotoxic T-Cells.
- The class I MHC also induce tolerance to self antigens and immune responses to allo-antigens.

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THANK YOU

To be continued...