Major Histocompatibility Complex

Prepared By

Assist. Prof. Dr. Batool Al-Ghurabei

MHC

MHC - The Major Histocompatibility Complex

In all vertebrates there is a genetic region that has a major effect on graft survival. This region is referred to as the MHC.

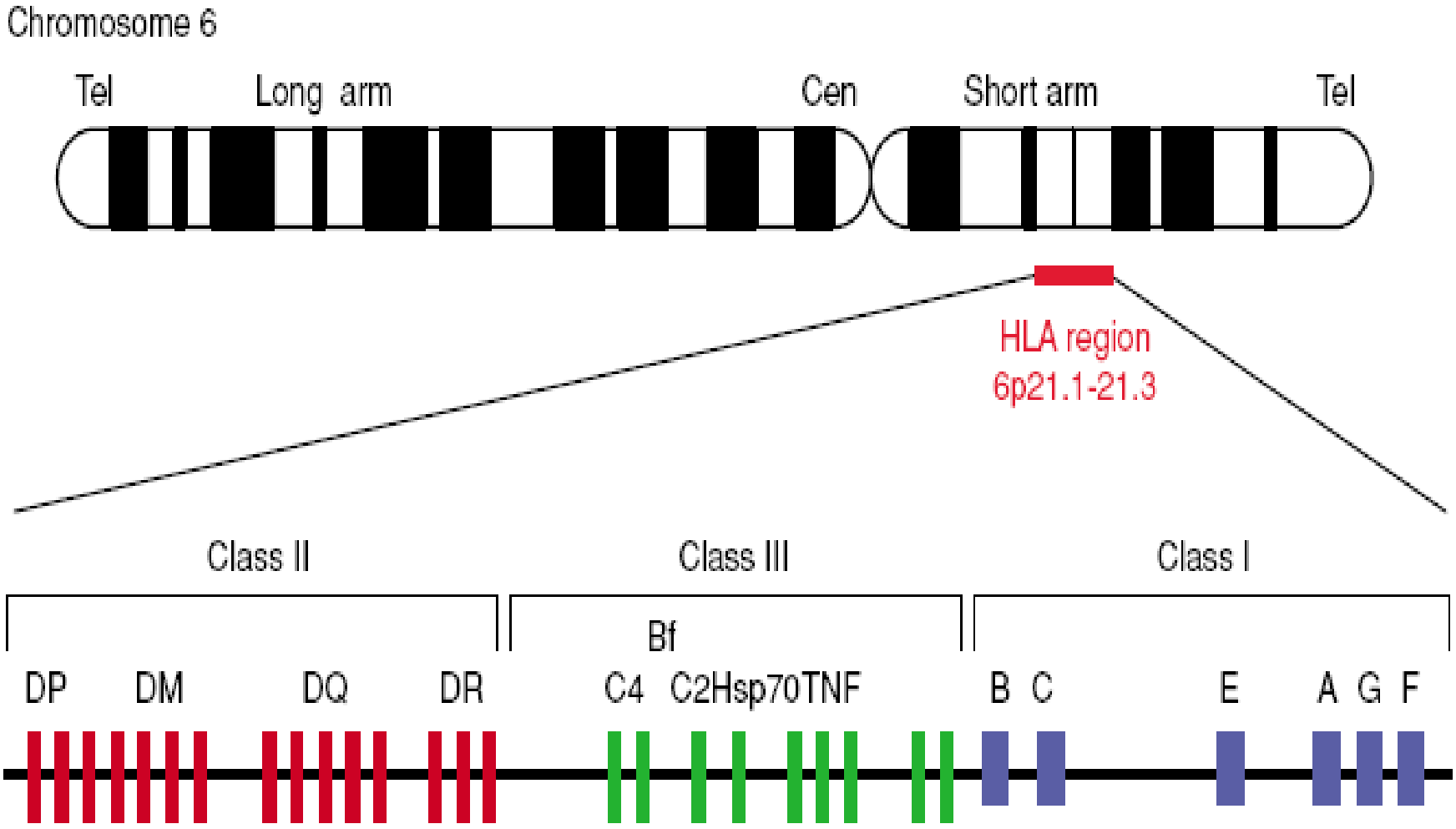
Nomenclature

- **MHC = Major Histocompatibiliy Complex**
- **HLA = Human Leucocyte Antigen.**

In human MHC is called human leukocyte antigen is a cluster of genes located on the short arm of chromosome 6, and encoding cell-surface molecules (class I and class II) that are involved in interactions with T-cells. HLA genes are the most polymorphic genes in man.

Significance of the MHC

- role in immune response
- role in organ transplantation
- role in predisposition to disease



Gene map of the human leukocyte antigen (HLA) region

The HLA genes

The HLA genes are divided into 3 regions, one encode for class I, other encode class II, the last encode for class III .

Class I region: encodes to class I molecules: HLA-A, -B and –C molecules.

Class II region: previously known as immune response (Ir) genes. This encodes to class II molecules HLA-DR and DQ molecules which control the immune response to various antigens.

The HLA **class III region** located between class I and class II genes and encodes components of the C system(C2, C4 and factor B).

The HLA molecules

Three types of molecules referred to as class I, II and III antigens are expressed by this gene complex.

The HLA-class I molecule

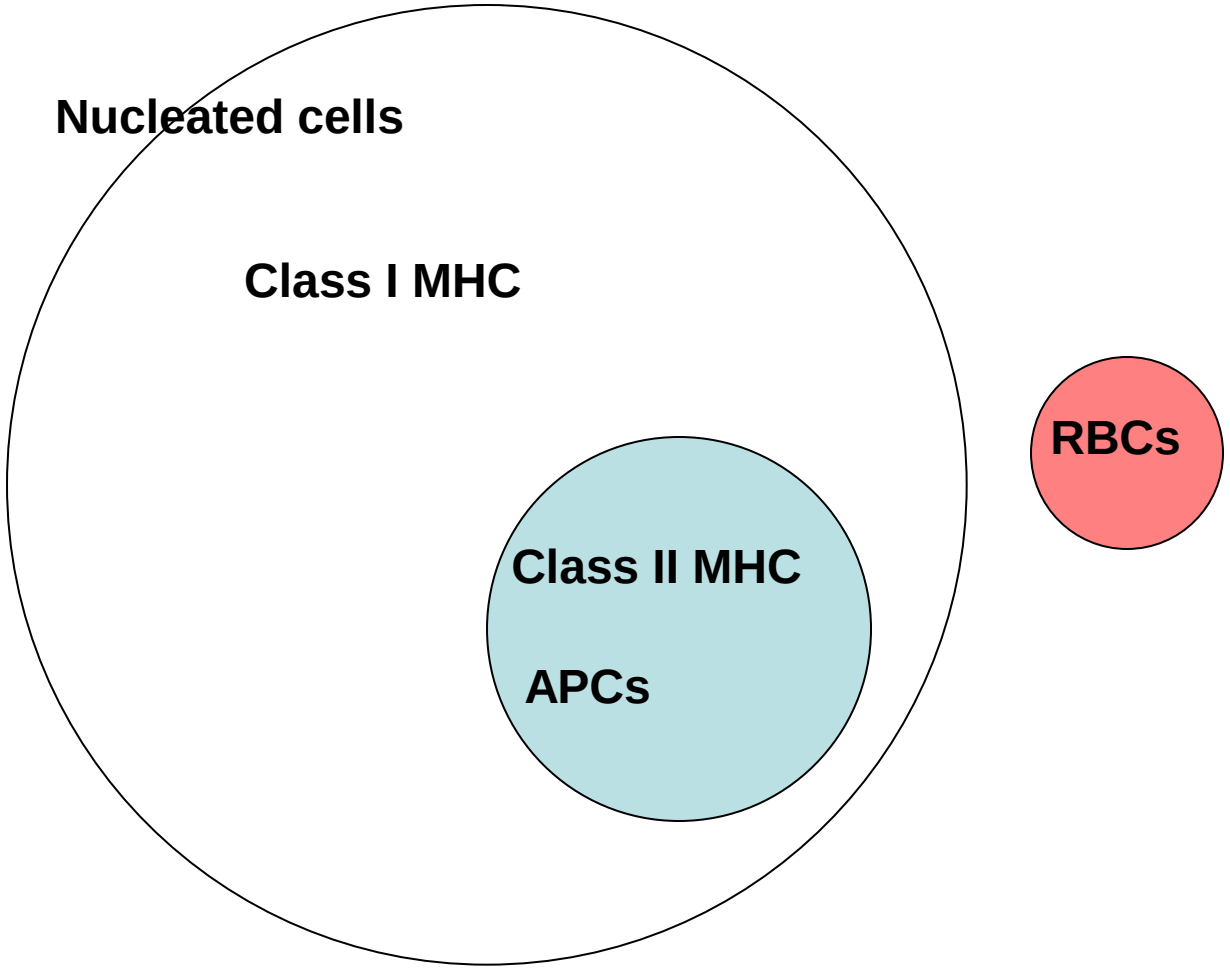
The HLA class I molecules are expressed on most nucleated cells (but not RBCs), and play a central role in the activation of cytotoxic T-lymphocytes (CD8) by presenting short peptides of Ag to these cells.

The HLA-class II molecule

Class II molecules interacts with CD4-T cells, have a helper function. They are expressed on antigen presenting cells (APC): Dendritic cells, Macrophages, B cells.

The HLA-class III molecule

Class III molecules are not *membrane proteins,* but they are *serum proteins* and have no role in antigen presentation; however, they play some role in immune response.


Nucleated cells
Class I MHC
Class II MHC
APCs
RBCs

Functions

***role in recognition of antigens**

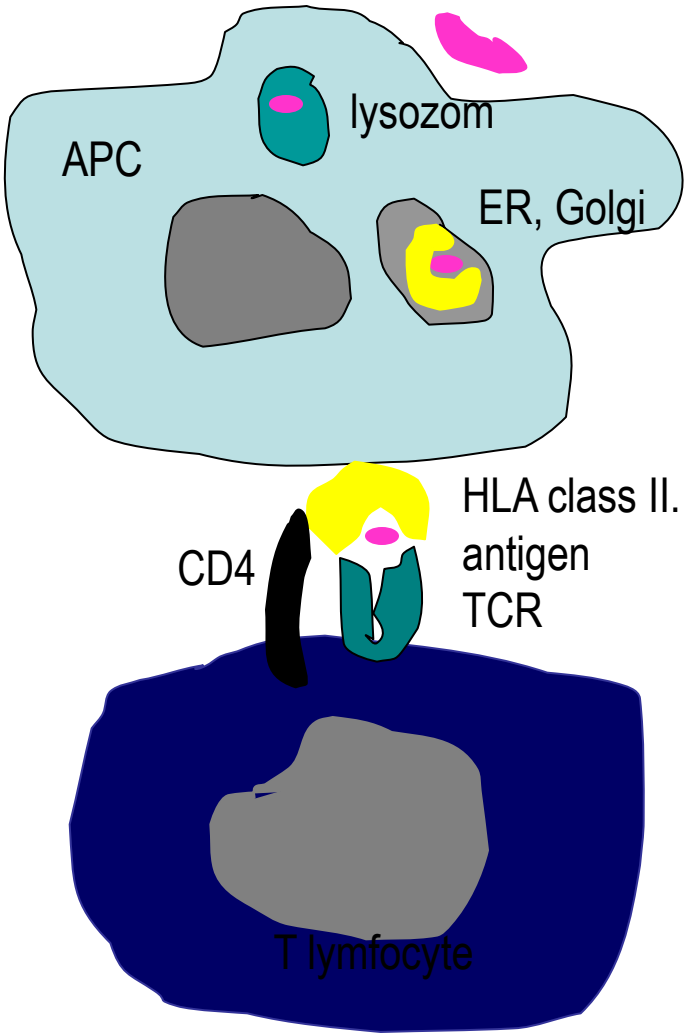
***role in cell-cell interactions in immune system**

The immune system uses the HLA to differentiate self and non-self Ags. TCR (with α and β chains) do not recognize antigen in free or soluble form or as intact protein. But, T-cells recognize portions of protein of antigens that have been fragmented into peptides bond to HLA molecules, so because of the critical role that HLA molecules play in these interactions, T-cell response said to be MHC-restricted.

Function of MHC

- Recognition of antigen by T cells is necessary for induction of the immune response.

  - exogenous antigen presentation



Clinical application of MHC

1-Organ transplantation

2- Paternity testing (forensic medicine).

3- HLA-Ags are used by anthropologist for detections the origins of races and racial admixture.

4-Tissue typing is used to provide more evidence for the diagnosis of the disease. For example, finding the B27 allele can added a clearer diagnostic perspective for an individual with ankylosing spondylitis.

5- detection of genetic predisposing host in special population helps to develop treatment and preventive strategies.

Hypothesis that have been postulated for the association between HLA and diseases:

1- MHC molecules serve as receptors for viruses or bacterial toxins.
2- Molecular mimicry. Protein fragment from a pathogen (or food) sometimes resembles part of a self protein, stimulates the immune system of susceptible individuals (depending on MHC type) to attack the self protein. Can result in auto-immune disease.

3- Defect gene or (disease responsible gene)
4- Defect in complement components that are coded within the HLA region may lead to autoimmune disease due to accumulation of immune complex.

Associations of HLA serotype with susceptibility to autoimmune disease			
Disease	**HLA allele**	**Relative risk**	**Sex ratio (♀:♂)**
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	<0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' disease	DR3	3.7	4–5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematosus	DR3	5.8	10–20
Type I insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	~25	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4–5

Associations of HLA serotype and sex with susceptibility to autoimmune disease.