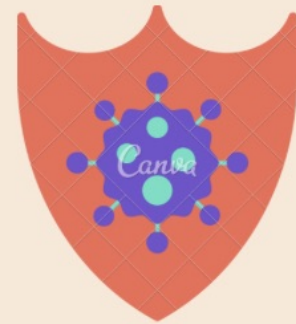


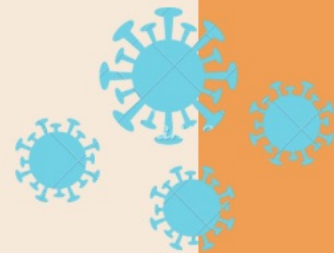
2nd year



Immunology notes

Molecules of the immune
system:

- complement
- cytokines
- MHC molecules



TALA IYAD



3) MHC MOLECULES :

• Introduction :

• Definition of the MHC

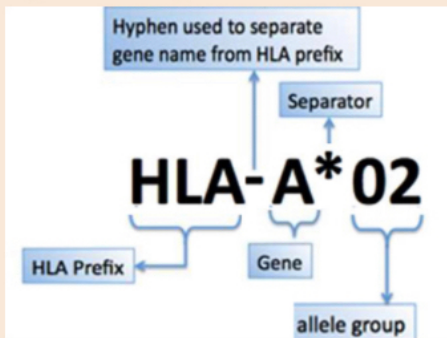
Is a set of cell surface proteins expressed on the surface of all nucleated cells and encoded by a large gene family which controls a major part of the immune system in all vertebrates

• MHC molecules play a major role in three lines



• MHC nomenclature :

MHC were formerly called Human Leukocyte Antigens (HLA) or major histocompatibility complex (MHC) because they were discovered at first on the human leukocytes (WBCs). Later on they called MHC molecules because of their important function in tissue compatibility

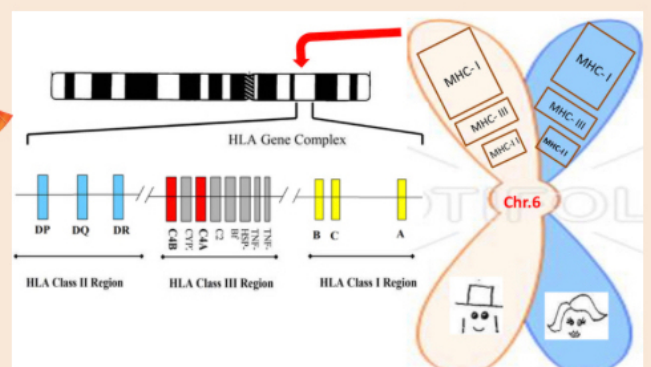


MHC genes in humans are found on the short arm of chromosome 6 and are divided into three categories or classes.

- Class I molecules are coded for at three different locations or loci, termed A, B, and C. with multiple alleles, expressed by all tissue cells
- Class II genes are situated in the D region, and there are several different loci, known as DR, DQ, and DP. with multiple alleles. Expressed mainly by APC
- Class III genes, which code for complement and TNF proteins. (C4, Bf, C2)

Inheritance of MHC genes

Multiple allele are present at each of MHC gene (a single base or a segment of bases)



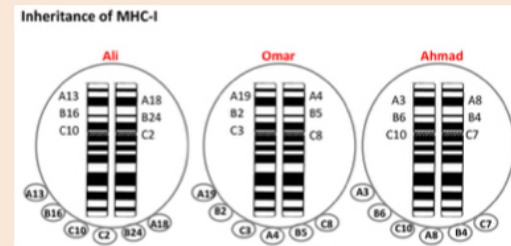
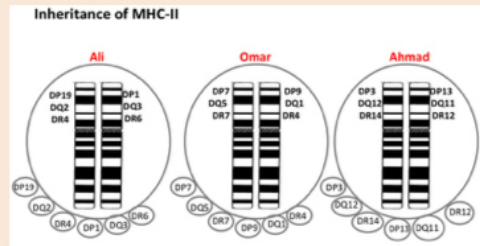
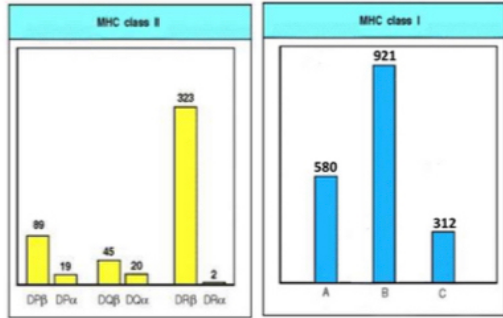
3) MHC MOLECULES :

- **Human MHC Class 1 and 2 genes are highly polymorphic :**

Each MHC locus has many alleles.

- The difference in the inheritance of MHC molecules among individuals is due to the presence of a big number of MHC alleles

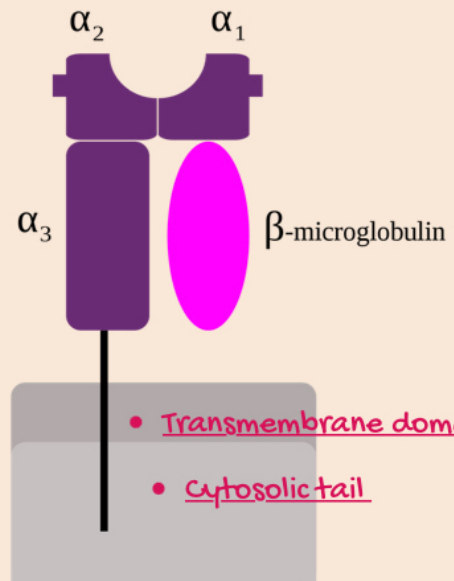
- Each person take one allele or each locus from each parent. So for class 1 MHC we inherited 6 alleles give 6 different MHC1, and 6 MHC2 alleles give 6 different MHC2



• MHC MOLECULE class 1 :

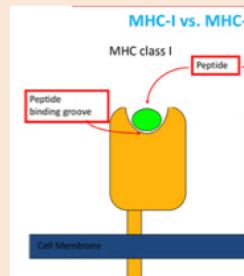
- In All nucleated cells express MHC1
- four domains; heavy chain (α1, α2, α3) β2 microglobulin, transmembrane and cytoplasmic tail
- hypervariable parts are α1, α2 :
- Thus are peptide binding regions.
- α3 is the constant region bind

• Structure:

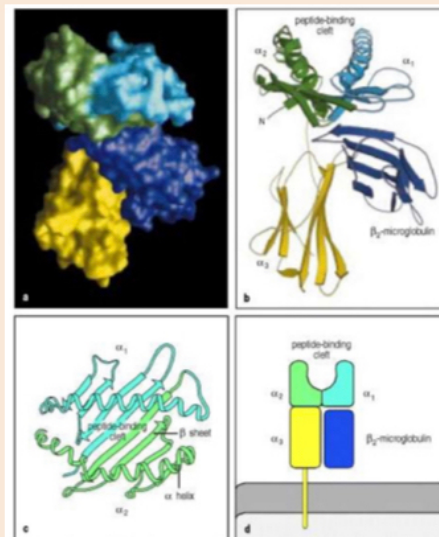


CD8

- Remember:
- Th CD4 bind MHC 1
- TC CD8 bind MHC 2



- Function :
- Glycoproteins expressed on all nucleated cells
- Major function to present processed Ags to TC

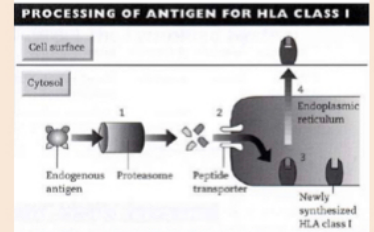


- B2 microglobulin :
- encoded on ch.15
- bind non covalently
- no transmembrane
- region

3) MHC MOLECULES :

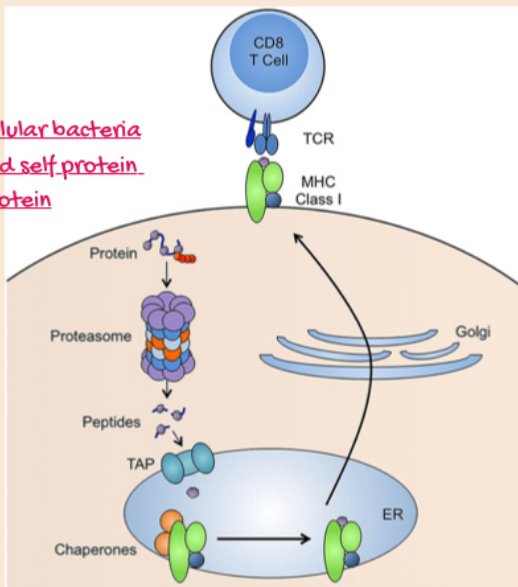
• MHC MOLECULE class 1 :

- Express all Types of endogenous proteins synthesized, live and multiply in the human cells including:
- 1. Intracellular bacteria
- 2. The mutated cellular proteins
- 3. The viral proteins (antigens)



• Mechanism :

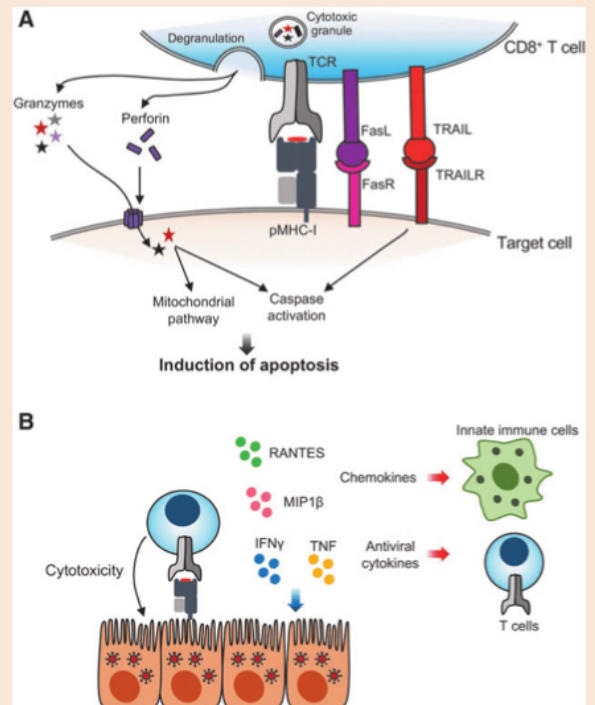
- Intracellular bacteria
- Mutated self protein
- Viral protein



• 1)

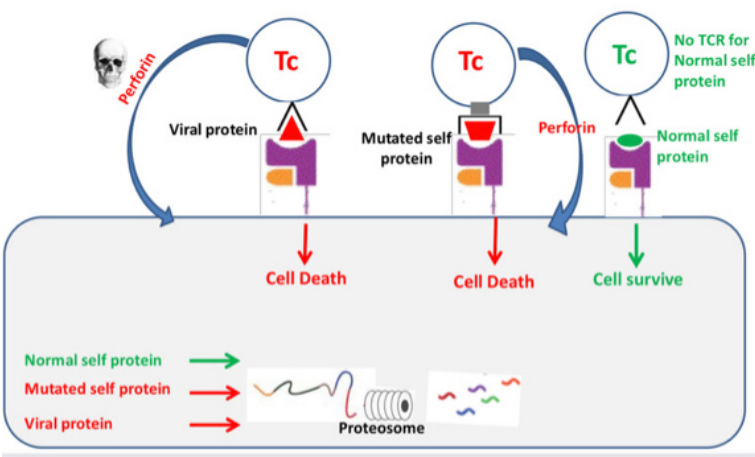
- A small amount of these proteins are directed to the proteasome
- in which these proteins are degraded into short peptides in order to be transferred to endoplasmic reticulum (ER)
- where they complexed with the MHC-I molecules. Then these proteins with MHC-I
- are expressed on the surface of the cell
- to be presented to the cytotoxic T-cells (CTLs)

• 3)



• 2)

MHC-I molecules
1. Antigen presentation to CTL to check the normal expression of cellular proteins

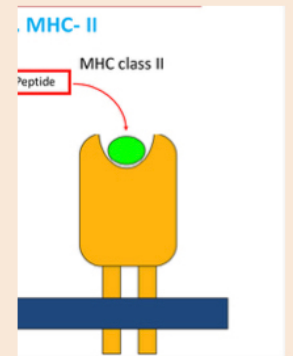
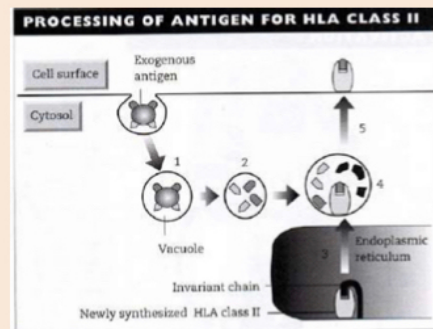
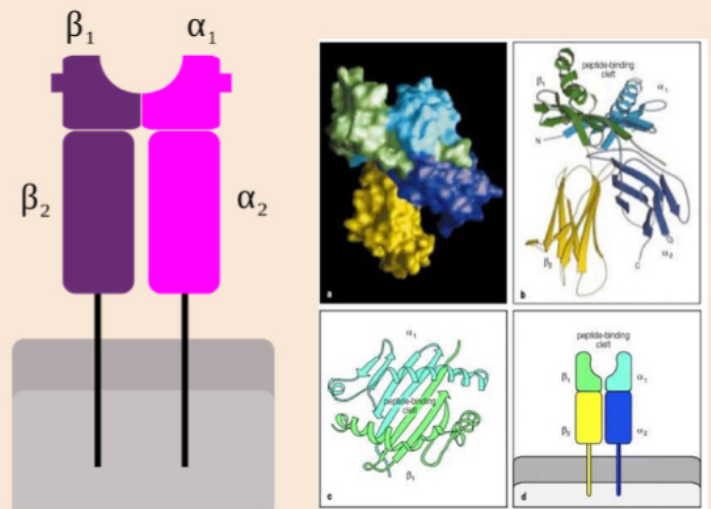


- killing mechanism : Fas L on Tc surface bind Fas L receptor on infected cell surface (one of change that occur due to infection) .
- lead to secrete perforin and granzymes which enter the cell through pores formed by perforin and induce apoptosis..

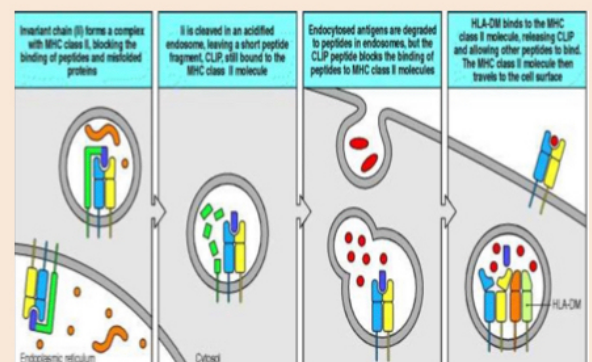
3) MHC MOLECULES :

• MHC MOLECULE class 2 :

- APC can express both MHC1 & MHC2 .
- Four-domains; $\alpha_1, \alpha_2, \beta_1, \beta_2$
- Hypervariable parts are α_1, β_1 .
- Thus are peptide binding regions.
- β_2 is the constant region bind CDA
- transmembrane and cytoplasmic tail
- Note : bind longer peptides than class 1 .
- Function :



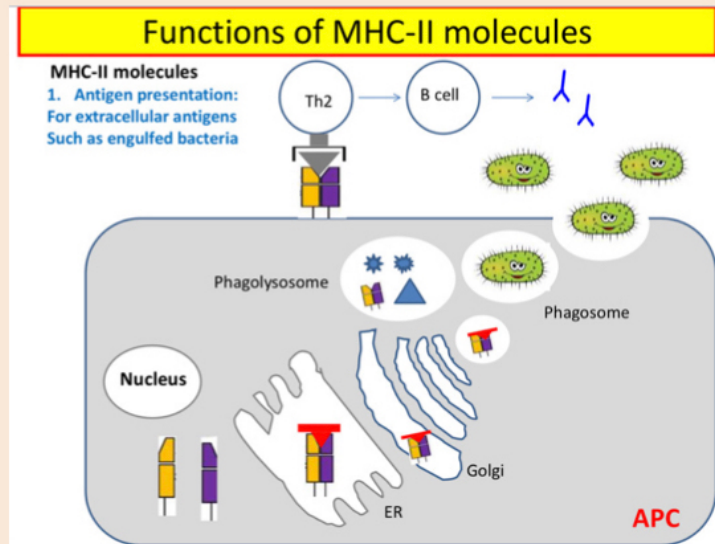
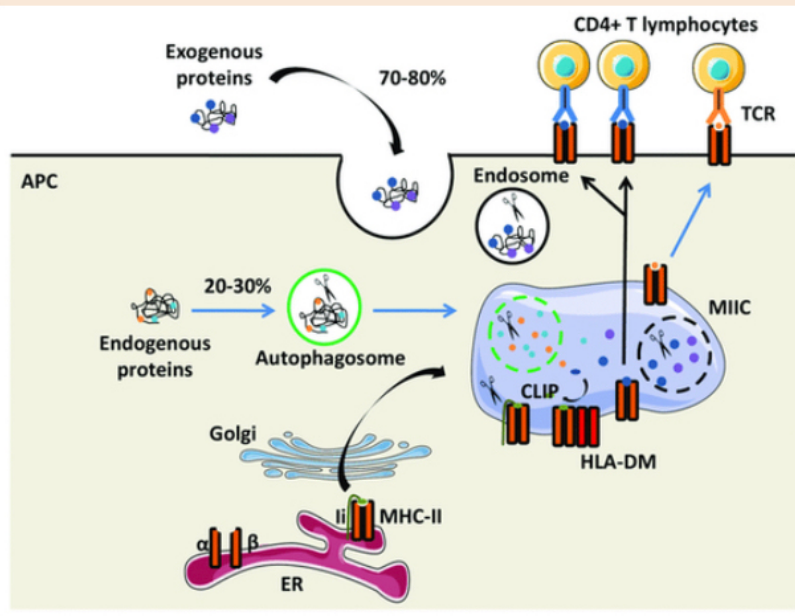
- Class II MHC genes
- Glycoproteins expressed on APC such as M, B-cells, DCs
- Major function to present processed Ags to T_H
- Peptides that bind to MHC class 2 molecules are exogenous peptides that internalized to endosome (vesicle) and lysed there by enzymes
- Newly synthesized MHC class 2 molecules moved from the endoplasmic reticulum to endosome
- MHC2 in ER can not bind endogenous antigen because of the Ii variant that block the binding site, while moving to endosome part this variant will be partly lysed and leave CLIP fragment.
- When high affinity peptides try to bind MHC2, HLA-DM peptide usually bind MHC2 and catalyze CLIP fragment then binding with the peptide occurs and the complex move to the cell surface.



3) MHC MOLECULES :

• MHC MOLECULE class 2 :

• Function :



- Major histocompatibility complex class II (MHC-II) α and β chains, expressed by antigen presenting cells (APCs), are synthesized in the endoplasmic reticulum (ER) where they form a heterotrimer with the invariant chain (Ii)



- After maturation in the Golgi apparatus, the heterotrimer ($\alpha/\beta/Ii$) is delivered to the MHC class II compartment (MIIC) in which endocytosed and exogenous proteins but also Ii are degraded by proteases for generating peptides.



- These so-called MHC class II compartments specialized organelles receive antigenic fragments from endosomes and lysosomes and load them onto class II molecules

- Ii is progressively degraded into the Class II Invariant chain Peptide (CLIP) which binds to the MHC-II groove.



- The chaperone protein HLA-DM induces CLIP replacement by an antigenic peptide. Then, the peptide/MHC-II complexes move to the plasma membrane and are presented to T-cell receptors (TCRs) of CD4 + T lymphocytes.

• MHC MOLECULE class 3 :

- Class 3 MHC genes
- Products that include secreted proteins that have immune functions. EX. Complement system, inflammatory molecules

3) MHC MOLECULES :

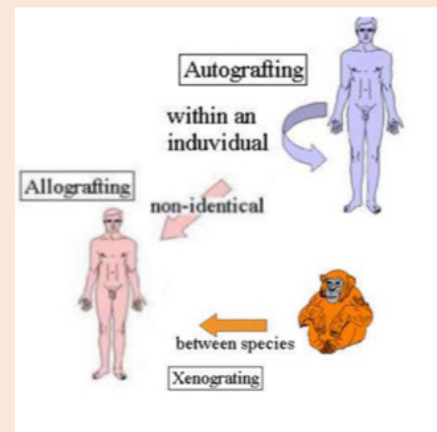
- Function summary :
- Their products play role in discriminating self/non-self
- Participate in both humoral and cell-mediated immunity
- MHC Act As Antigen Presenting Structures
- Genes of MHC Organized In 3 Classes

• MHC molecules play a major role in three lines

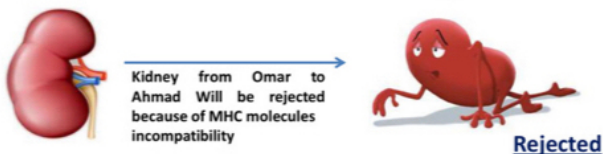
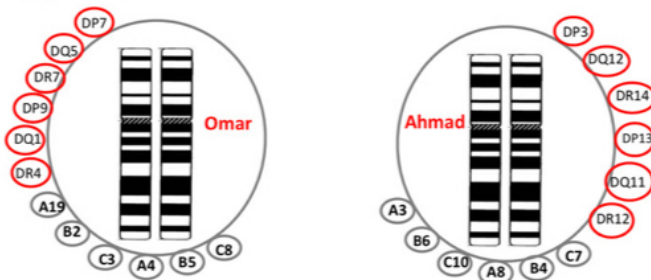


• Transplantation:

- Methods of Transplantation:
- May take place between:
- different parts of the same organism (autografting)
- different organisms of the same species (allografting)
- different species (xenografting)



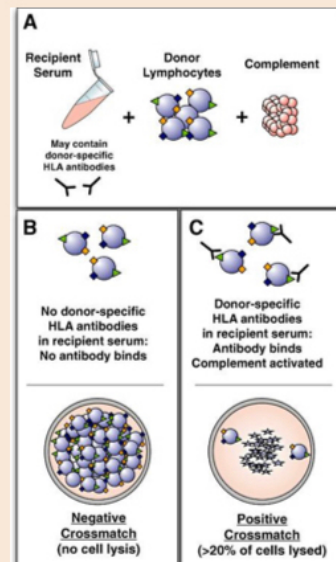
2- Transplantation



- The role of MHC, therefore, is particularly important in organ transplantation, where non-self, normally allogeneic organs from one individual are transplanted into another individual. Antigen presentation by MHC can initiate various types of immunological rejection of transplants

• Matching and cross-matching :

- Methods of Transplantation:
- Matching: finding a donor who shares the HLA antigens of the recipient, to minimize antigen disparities
- — requires donor and recipient antigens to be identified
- Cross-matching: testing the SERUM of the recipient for antibodies against the donor antigens, if present no donation



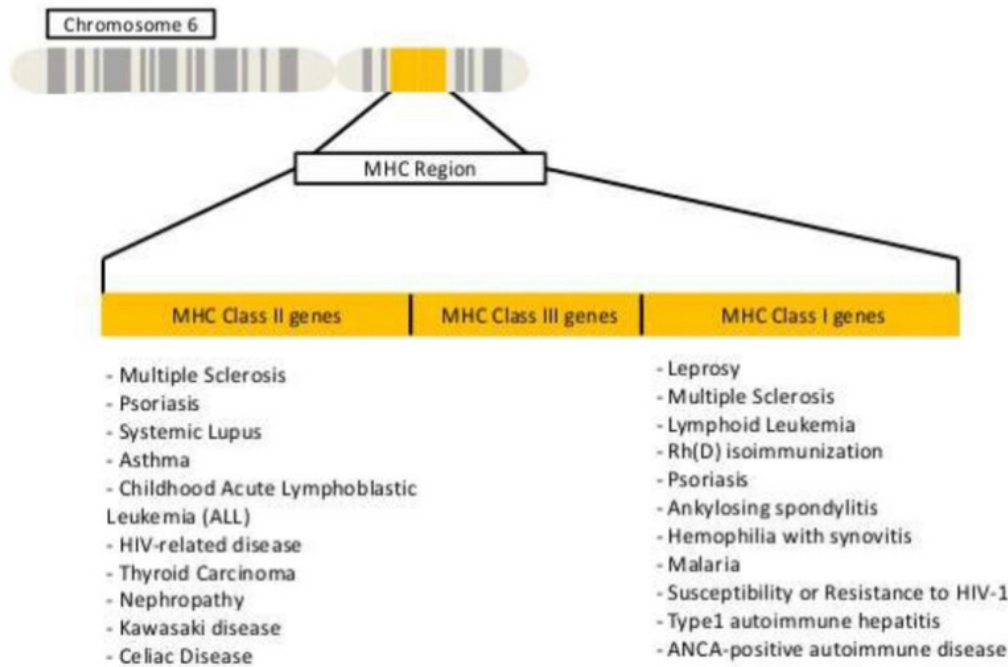
3) MHC MOLECULES :

- MHC molecules play a major role in three lines



- Autoimmune disease :

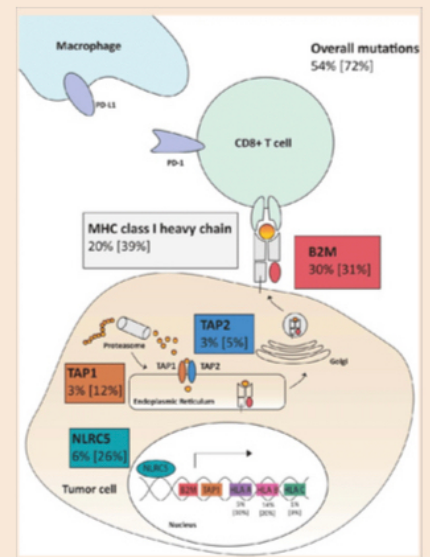
MHC and associated diseases



Association of Human MHC Alleles and Risk for Diseases

Disease	Associated HLA Allele	Relative Risk**
Ankylosing Spondylitis*	B27	90
Hereditary Hemochromatosis	A3/B14	90
Insulin Dependent Diabetes*	DR4/DR3	20
Multiple Sclerosis*	DR2	5
Myasthenia Gravis*	DR3	10
Rheumatoid Arthritis*	DR4	10
Systemic Lupus Erythromatosis*	DR3	5
Narcolepsy	DR2	130

* Autoimmune Disease **Percent of Patients with Allele Divided by Percent of Non-Affected Persons with this Allele



• MCQ :

26) The CD4 protein of T helper cells binds and stabilizes the MHC class II/peptide structure. The subunit that interacts with CD4 cell surface protein is

Select one:

- a) alpha 1 and beta 1 subunit
- b) alpha 2 and beta 2 subunit
- c) alpha 1 and alpha 2 subunit
- d) beta 2 subunit
- e) beta 1 subunit

1) 59) Which of the following gene is not the part of MHC genes

Select one:

- a) DP gene
- b) DR gene
- c) complement gene
- d) TNF gene
- e) IFN genes

47) Regarding processed antigen entering the endoplasmic reticulum and binding to MHC, all are true except

Select one:

- a) the antigen is endogenous antigen
- b) the antigen is viral antigen
- c) it binds just MHC1
- d) can bind MHC2 and MHC1
- e) needs peptide transporter to enter endoplasmic reticulum

18) Viral proteins that are formed inside of an infected cell associate with cell and are presented at the surface of the infected. Select one:

- a) Cytokines
- b) MHC class I molecules
- c) MHC class II molecules
- d) Antibody molecules
- e) complement

THE CLIMB
IS TOUGH,
BUT THE
VIEW
FROM
THE TOP IS
WORTH IT.

Future
DOCTORS

