

Major Histocompatibility Complex (MHC)

**Dr.Eman Albataineh,
Associate Prof. Immunology
College of Medicine, Mutah university**

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 human being

MHC restriction: in thymus T lymphocytes are selected to recognize self MHC molecules through positive selection

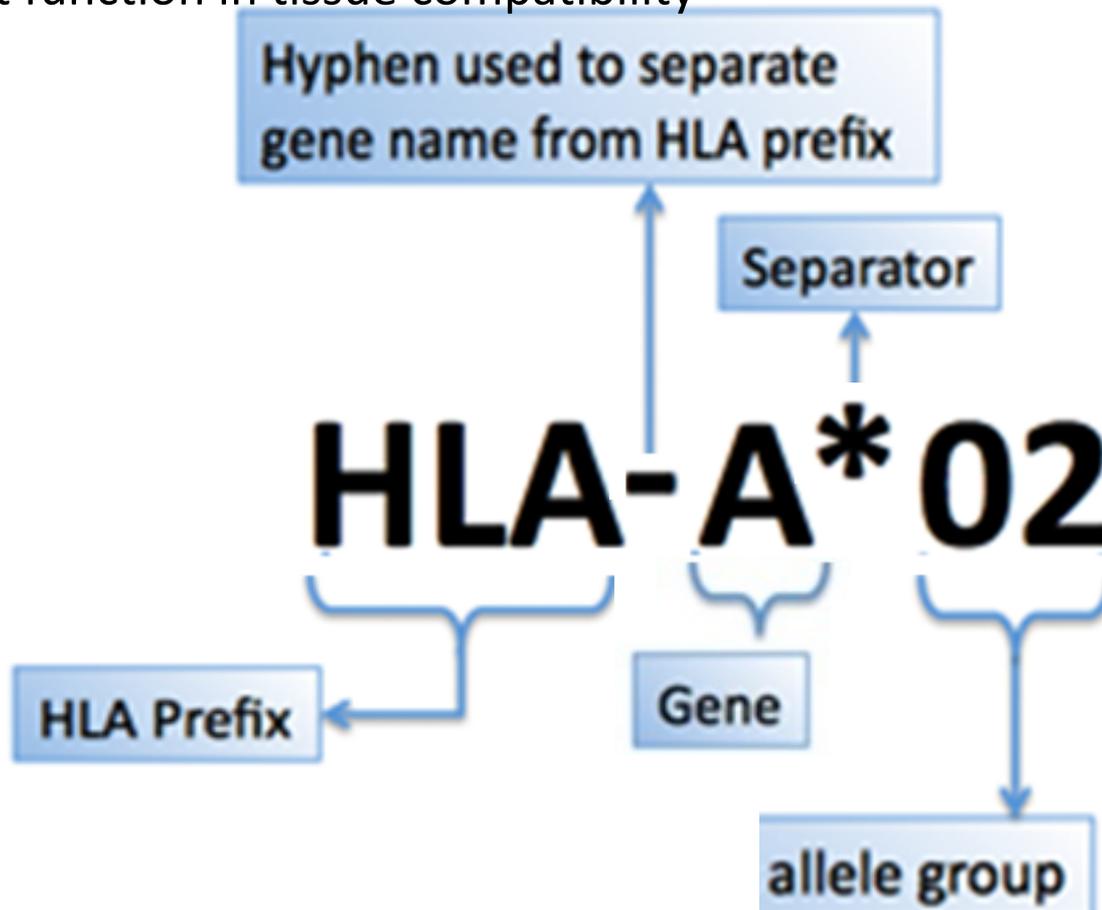
MHC molecules play a major role in three lines



MHC molecules

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 Molecules

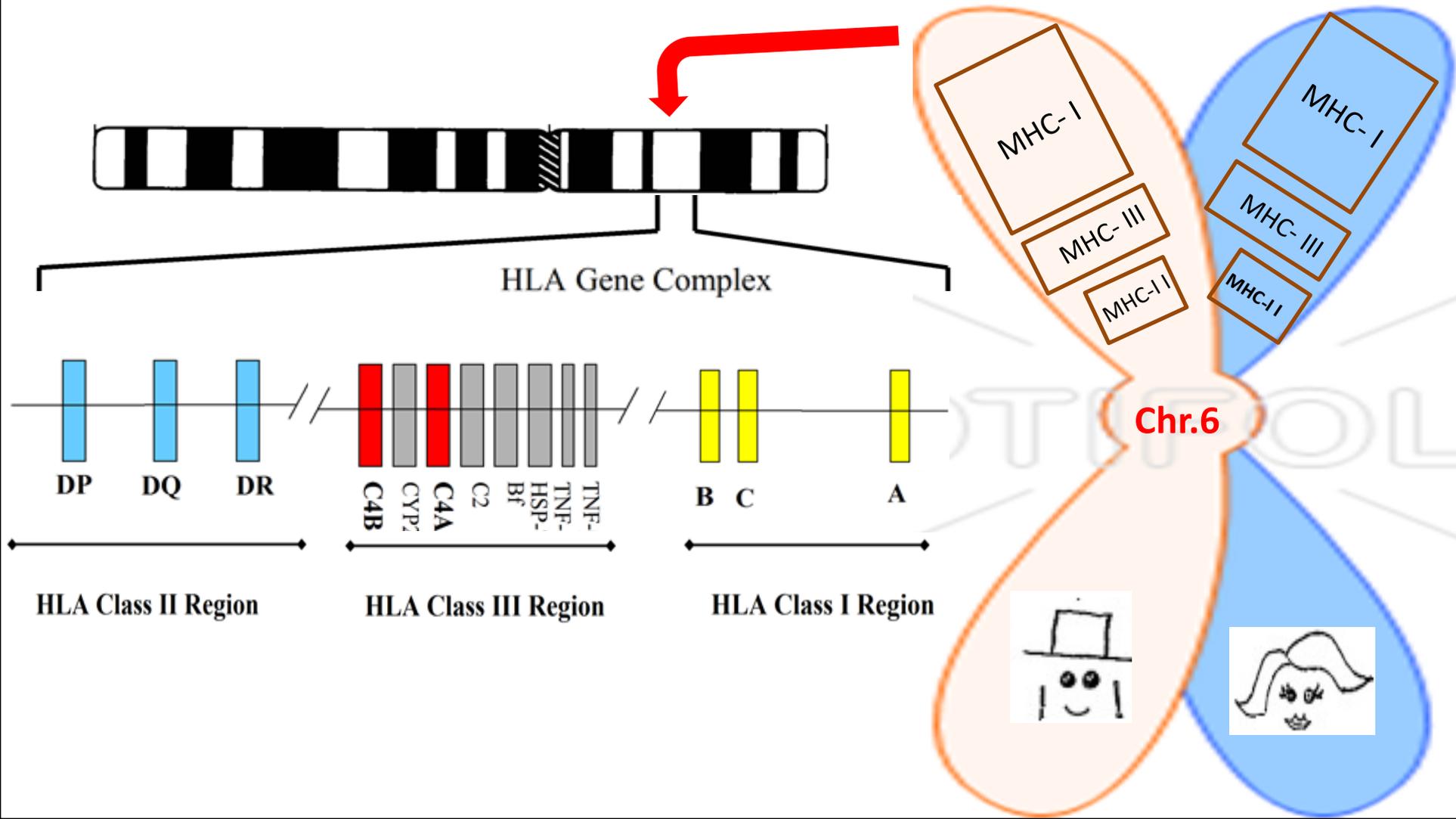
MHC genes in humans are found on the short arm of **chromosome 6** and are divided into three categories or classes.

1. **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**
2. **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**
3. **Class III genes**, which code for complement and TNF proteins

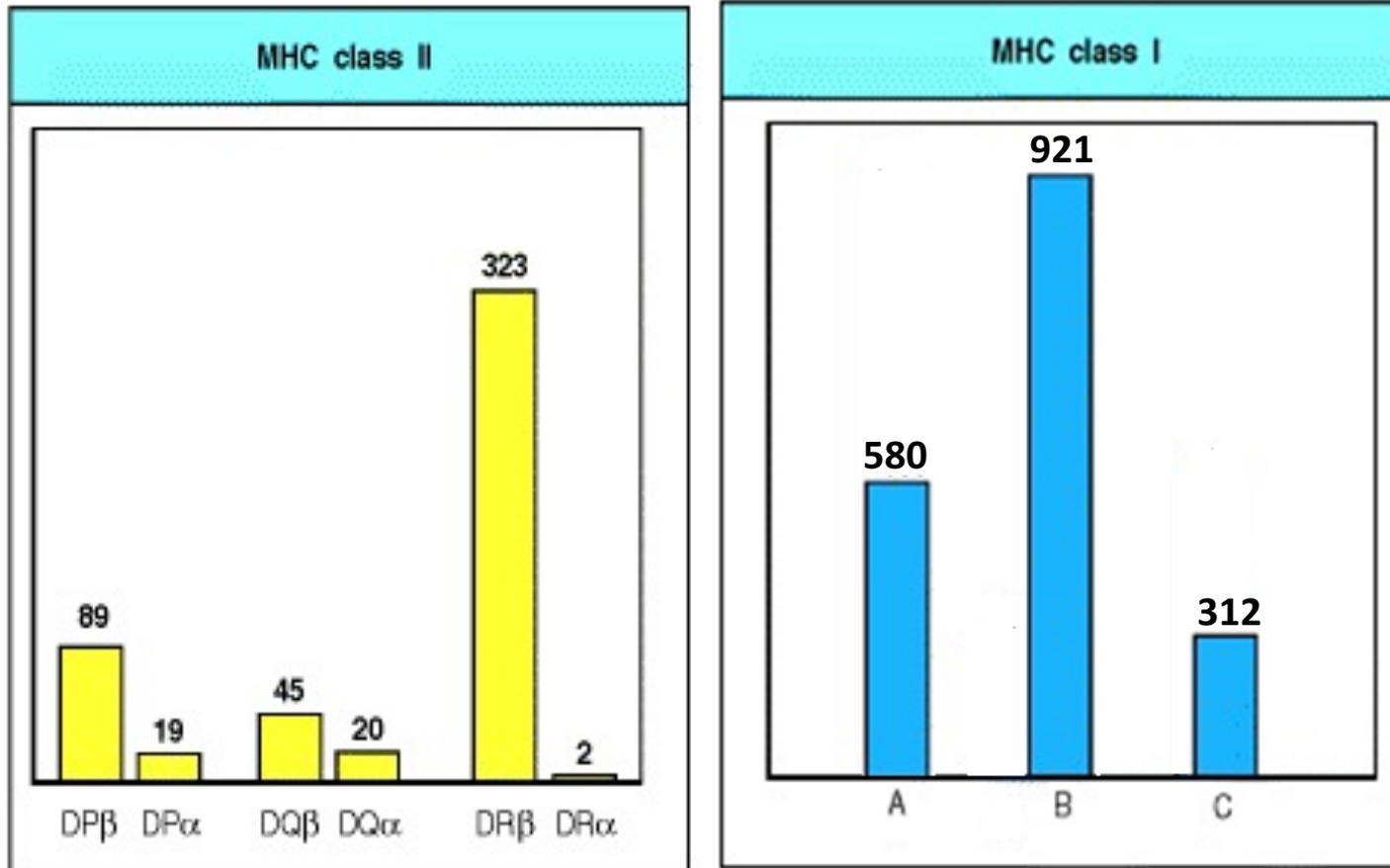
MHC genes (alleles)

Inheritance of MHC genes

- ✓ Multiple allele are present at each of MHC gene



Human MHC Class 1 and 2 genes are highly polymorphic

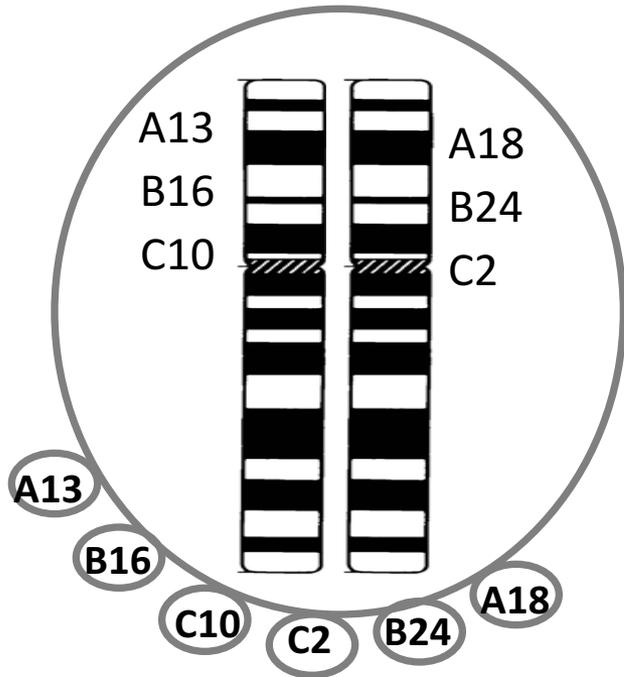


- Each MHC locus has many alleles.
- The difference in the inheritance of MHC molecules among individuals is due to the presence of a big number of MHC alleles
- Each person carries 2 alleles of each of the 3 class-I and class 2 genes, (A, B and C) (DP, DQ, DR), and so can express six different types of MHC-I and 6 different MHC2

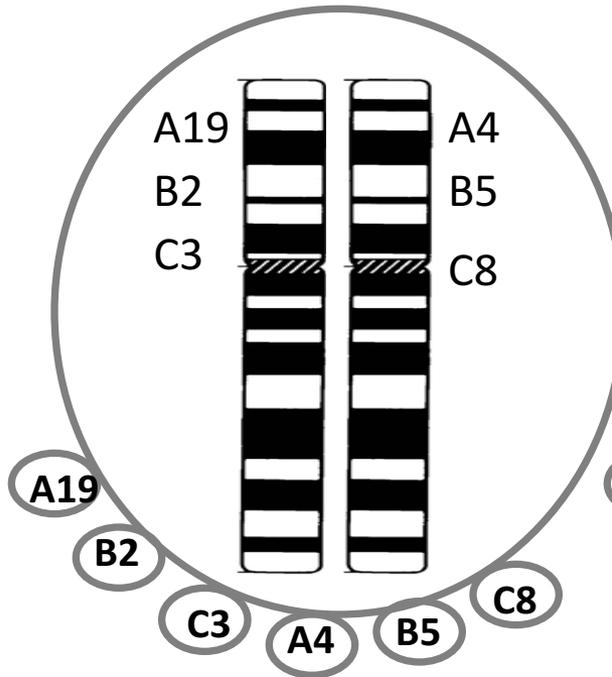
MHC-I

Inheritance of MHC-I

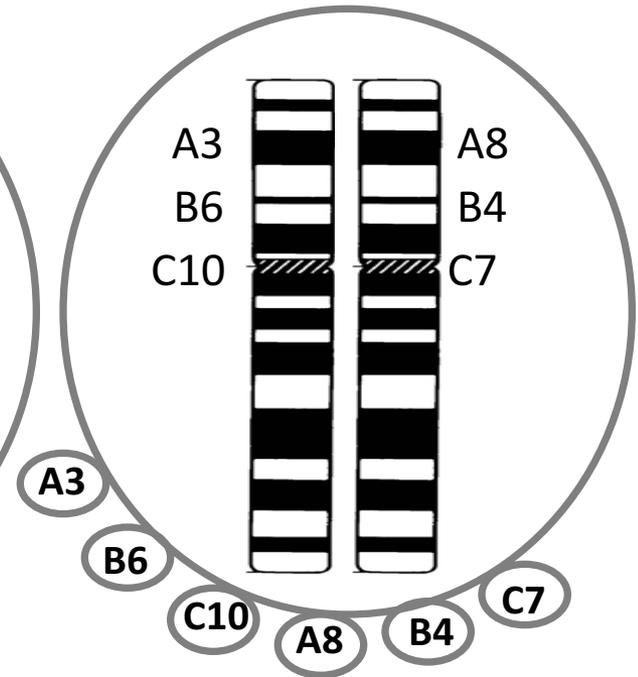
Ali



Omar



Ahmad



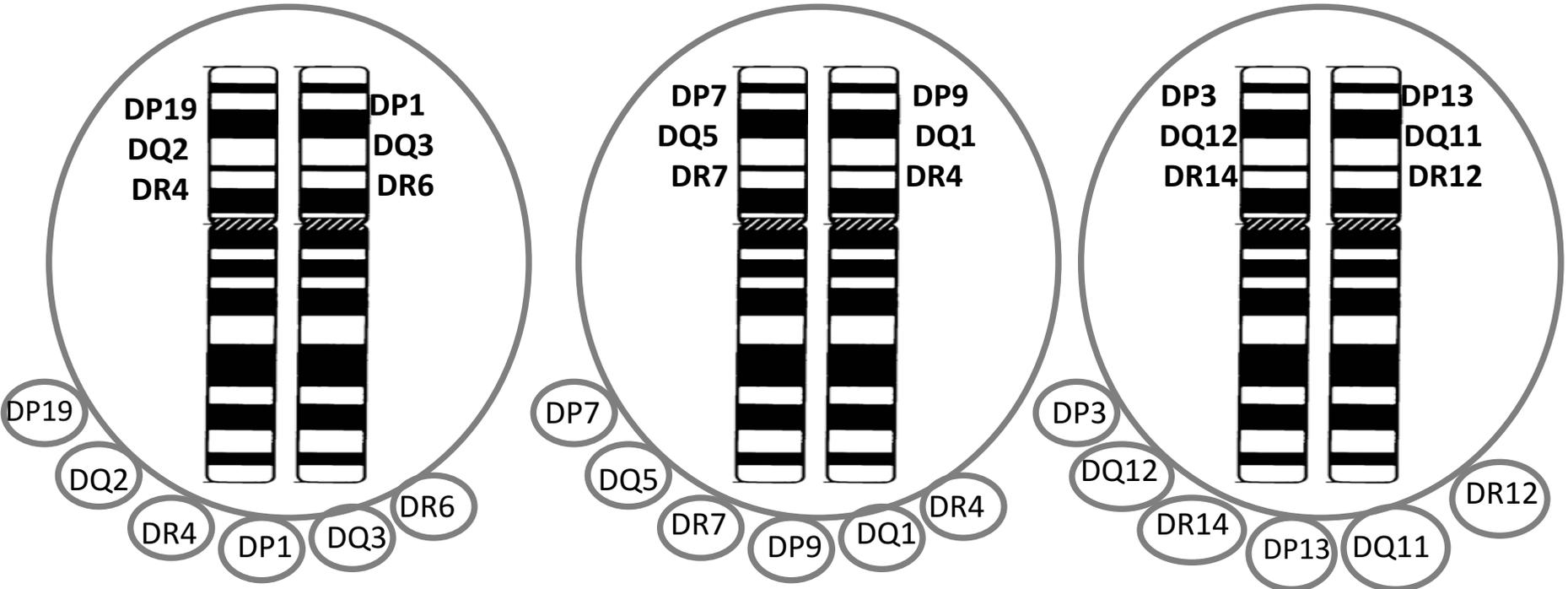
MHC-II

Inheritance of MHC-II

Ali

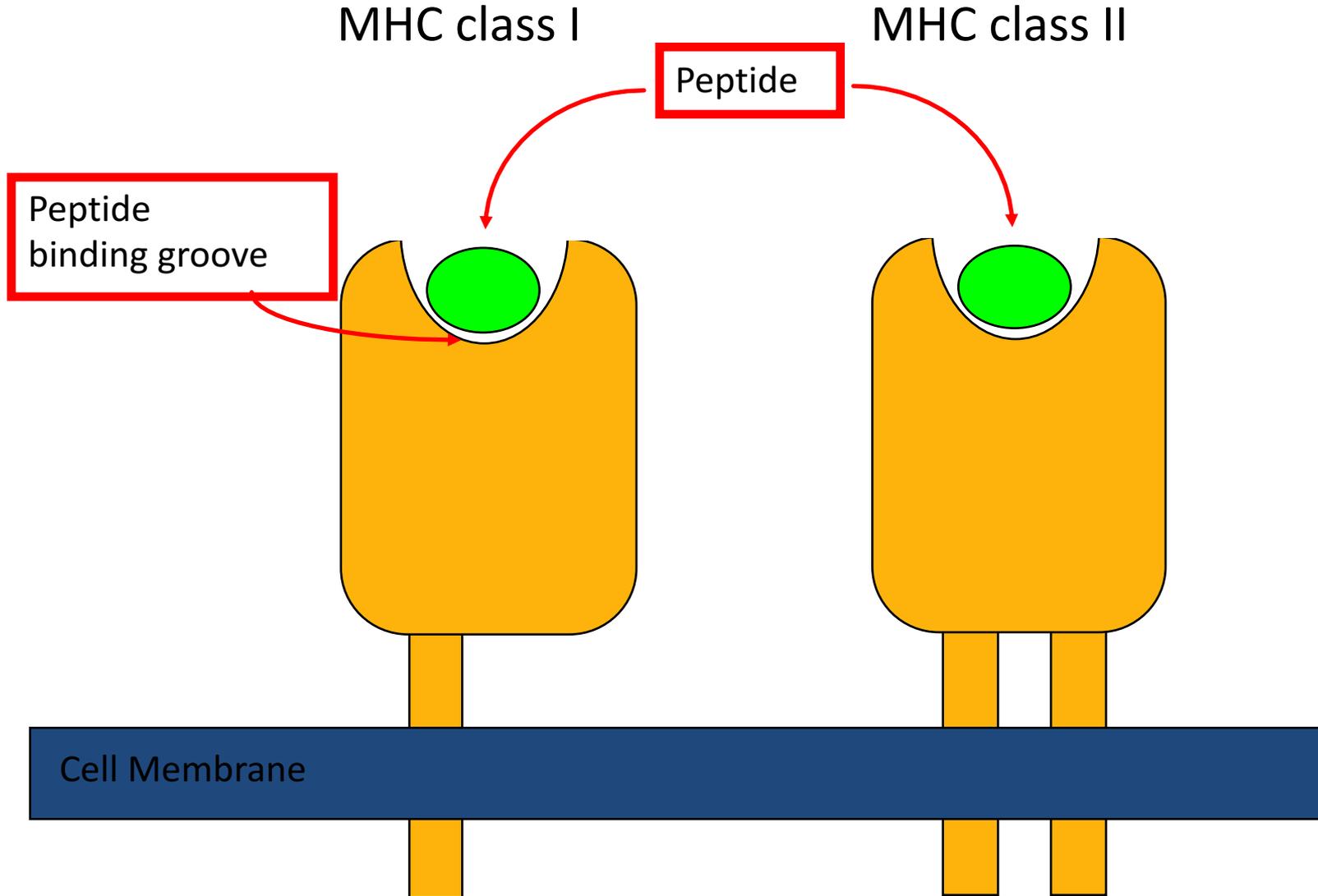
Omar

Ahmad



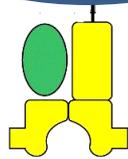
MHC-II

MHC-I vs. MHC-II

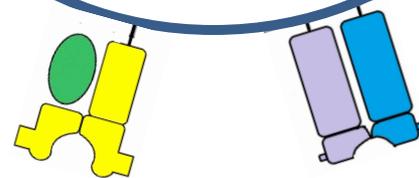


Expression of MHC molecules

All nucleated cells
express MHC1

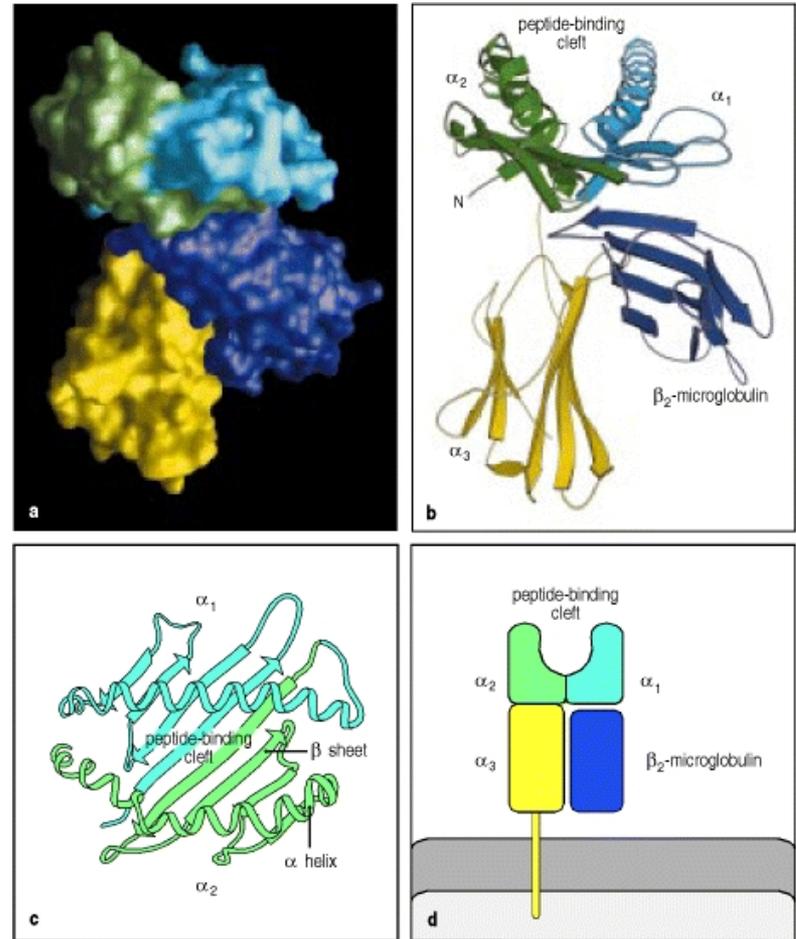


APC can express both
MHC1 & MHC2



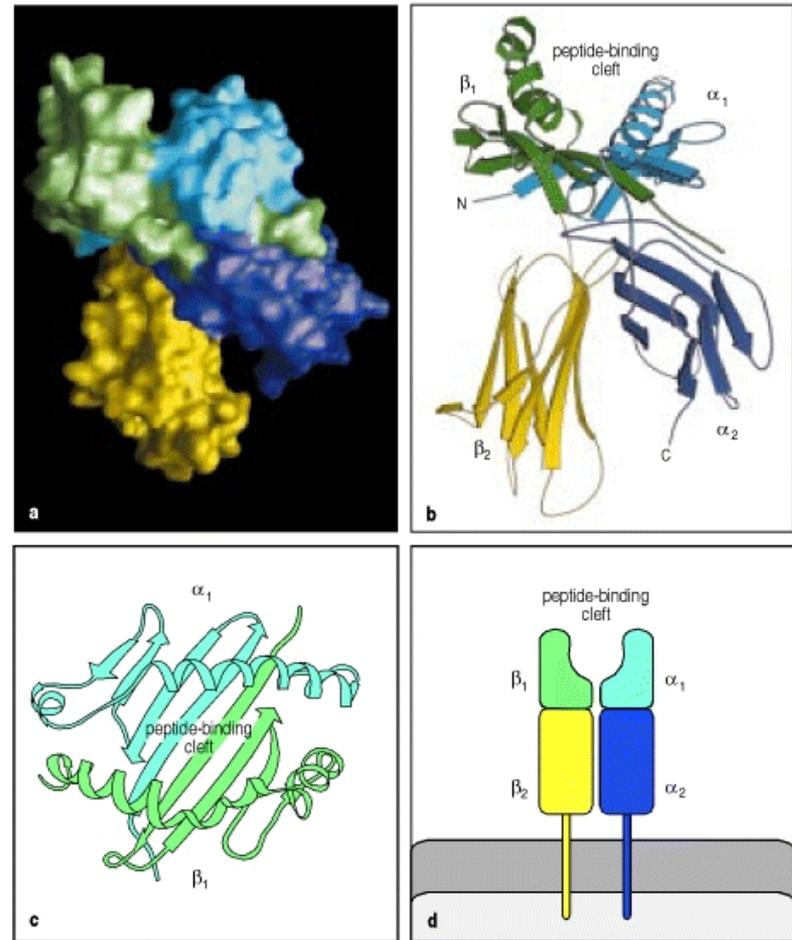
MHC 1 protein structure

- four domains; Heavy chain (α_1 , α_2 , α_3) β_2 microglobulin, transmembrane and cytoplasmic tail
- Hypervariable parts are α_1 , α_2 .
- α_3 is the constant region bind CD8



MHC 2 protein structure

- Four domains; $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$
- Hypervariable parts are $\alpha 1$, $\beta 1$.
- $\beta 2$ is the constant region bind CD4
- transmembrane and cytoplasmic tail



Functions of MHC molecules

- I. Their products play role in discriminating self/non-self
- II. Participate in both humoral and cell-mediated immunity
- III. MHC Act As Antigen Presenting Structures
- IV. Genes Of MHC Organized In 3 Classes
 - Class I MHC genes
 - Glycoproteins expressed on all nucleated cells
 - Major function to present processed Antigens to T_C CTL triggers the cell to undergo programmed cell death ,cell mediated immunity
 - Class II MHC genes
 - Glycoproteins expressed on APC such as Macrophages, B-cells, DCs
 - Major function to present processed Antigens to T_H then Th polarize to either type 1 (Th1), type 2 (Th2), type 17 (Th17), or regulatory/suppressor (Treg),depending on APC and cytokine environment
 - Class III MHC genes
 - Products that include secreted proteins that have immune functions.
Ex. Complement system, inflammatory molecules

Functions of MHC-I molecules

Express all Types of endogenous proteins synthesized, live and multiply in the human cells including:

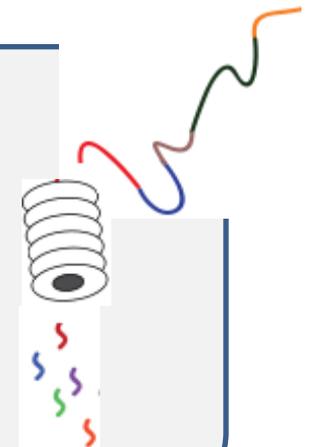
1. Intracellular bacteria
2. The mutated cellular proteins
3. The viral proteins (antigens)

A small amount of proteins in cytosol, mostly self peptides derived from protein turnover and defective ribosomal products in cancer or during viral infection, intracellular microorganism infection, are directed to the proteasome in which these proteins are degraded into short peptides in order to be transferred to endoplasmic reticulum (ER) by transporter proteins (TAP) 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)

Intarcellular bacteria →

Mutated self protein →

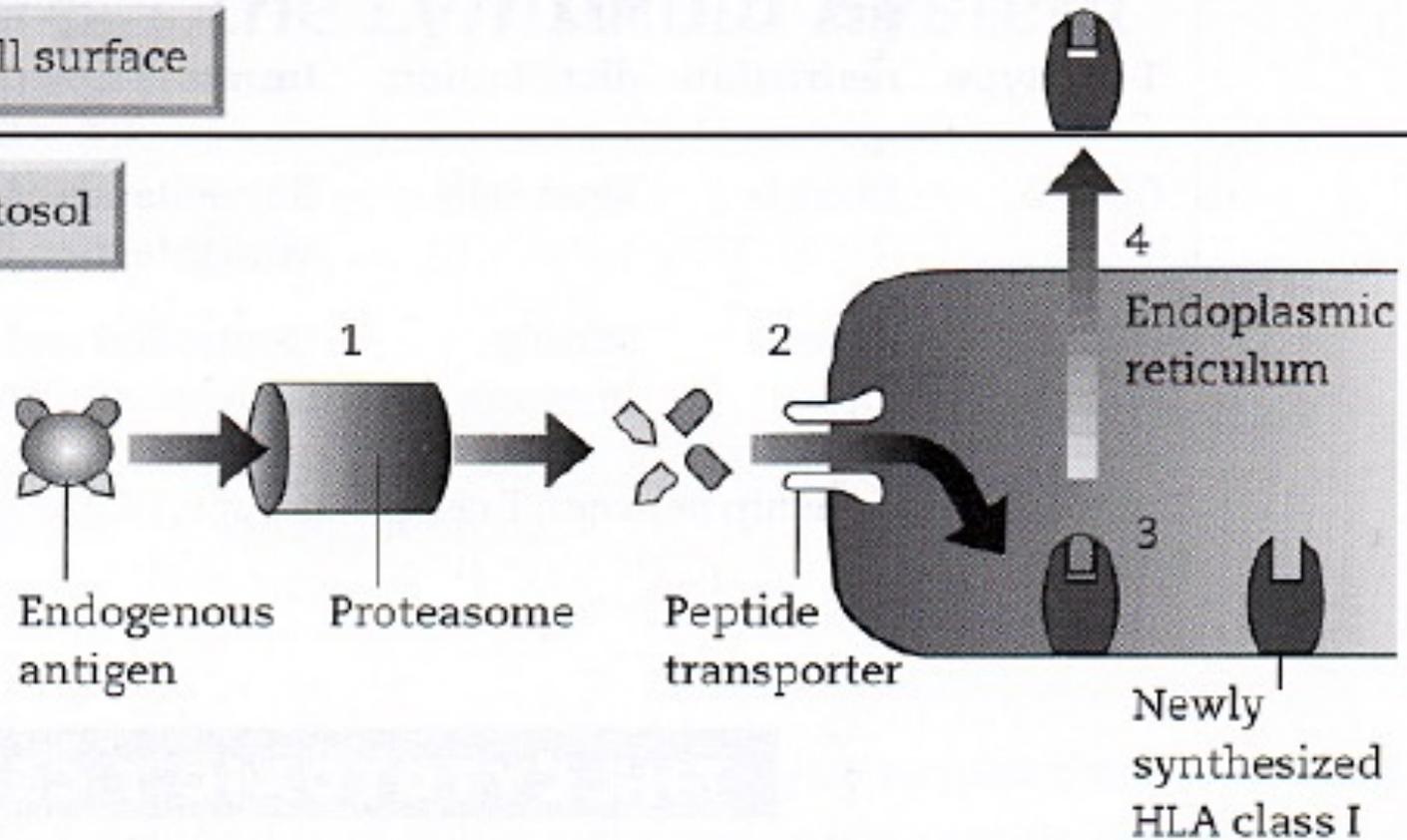
Viral protein →



PROCESSING OF ANTIGEN FOR HLA CLASS I

Cell surface

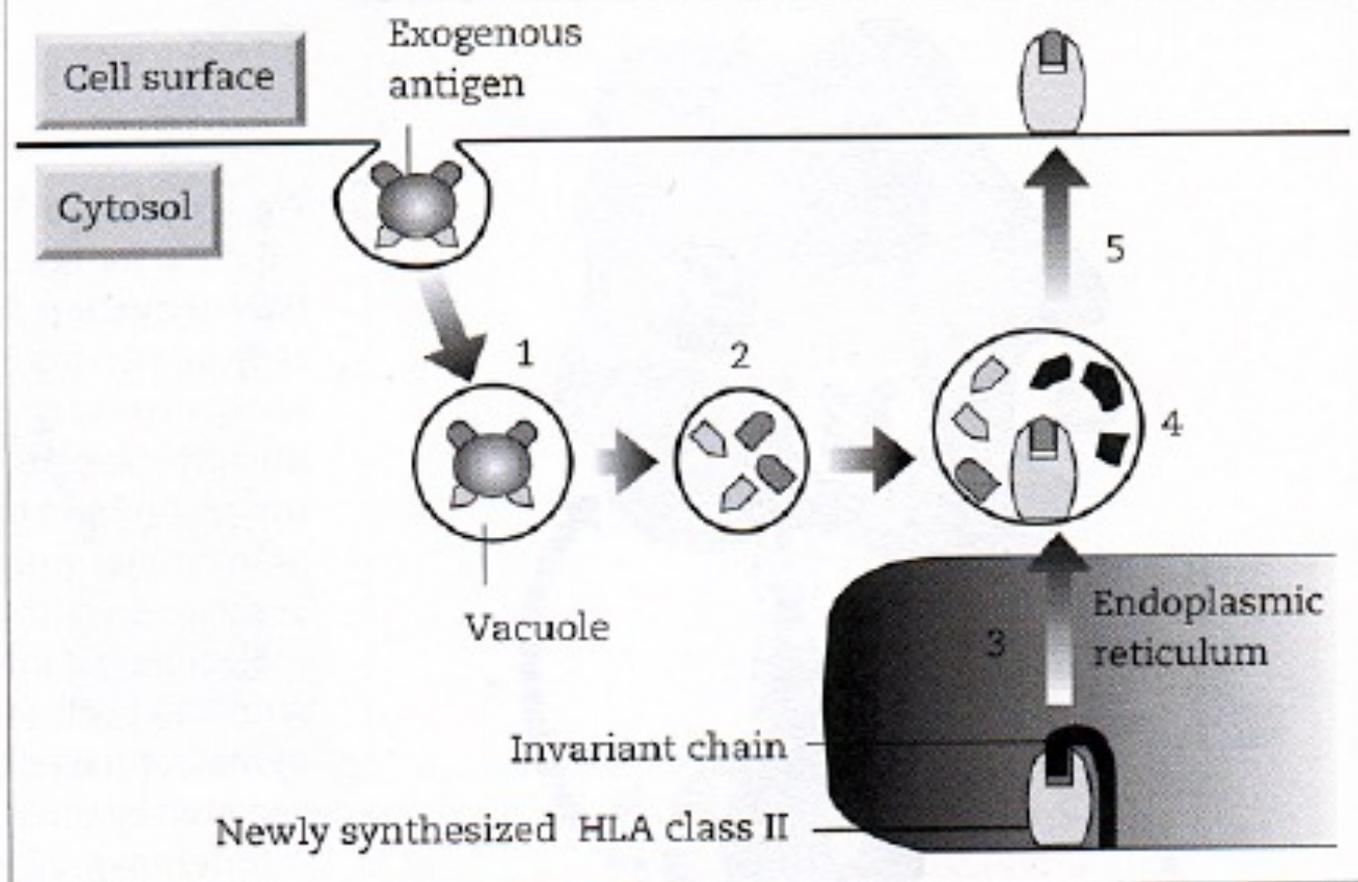
Cytosol



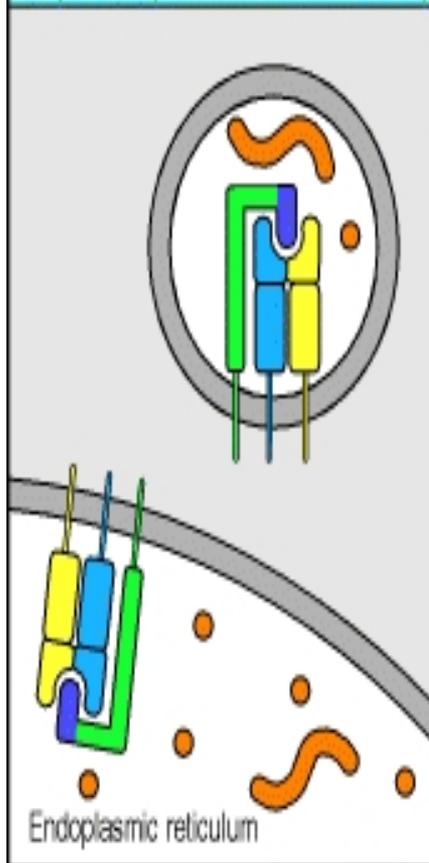
MHC2

- 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 Li 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.

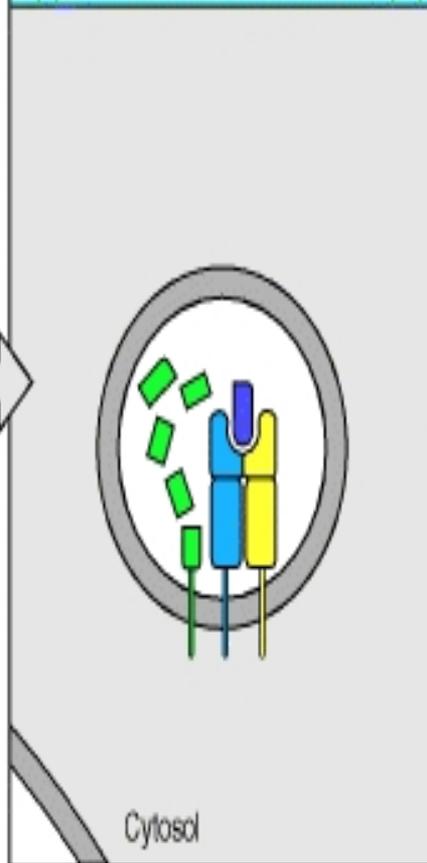
PROCESSING OF ANTIGEN FOR HLA CLASS II



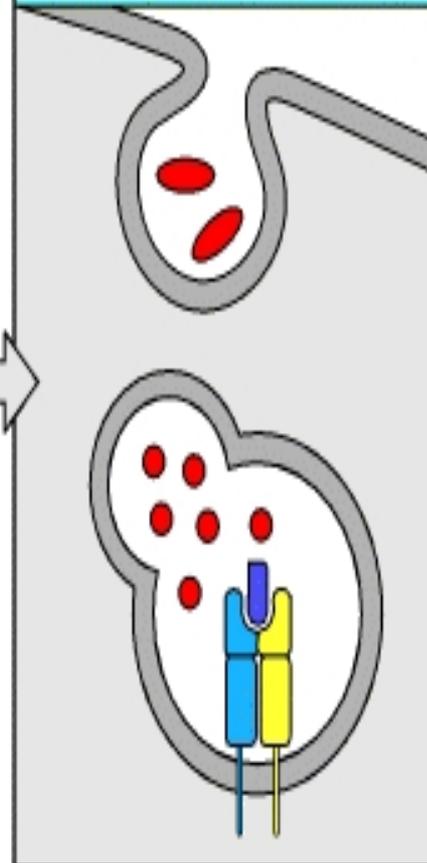
Invariant chain (Ii) forms a complex with MHC class II, blocking the binding of peptides and misfolded proteins



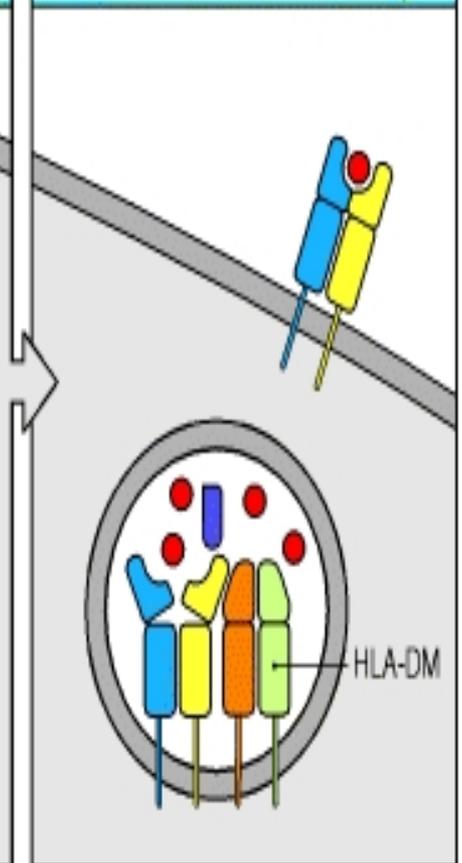
Ii is cleaved in an acidified endosome, leaving a short peptide fragment, CLIP, still bound to the MHC class II molecule



Endocytosed antigens are degraded to peptides in endosomes, but the CLIP peptide blocks the binding of peptides to MHC class II molecules



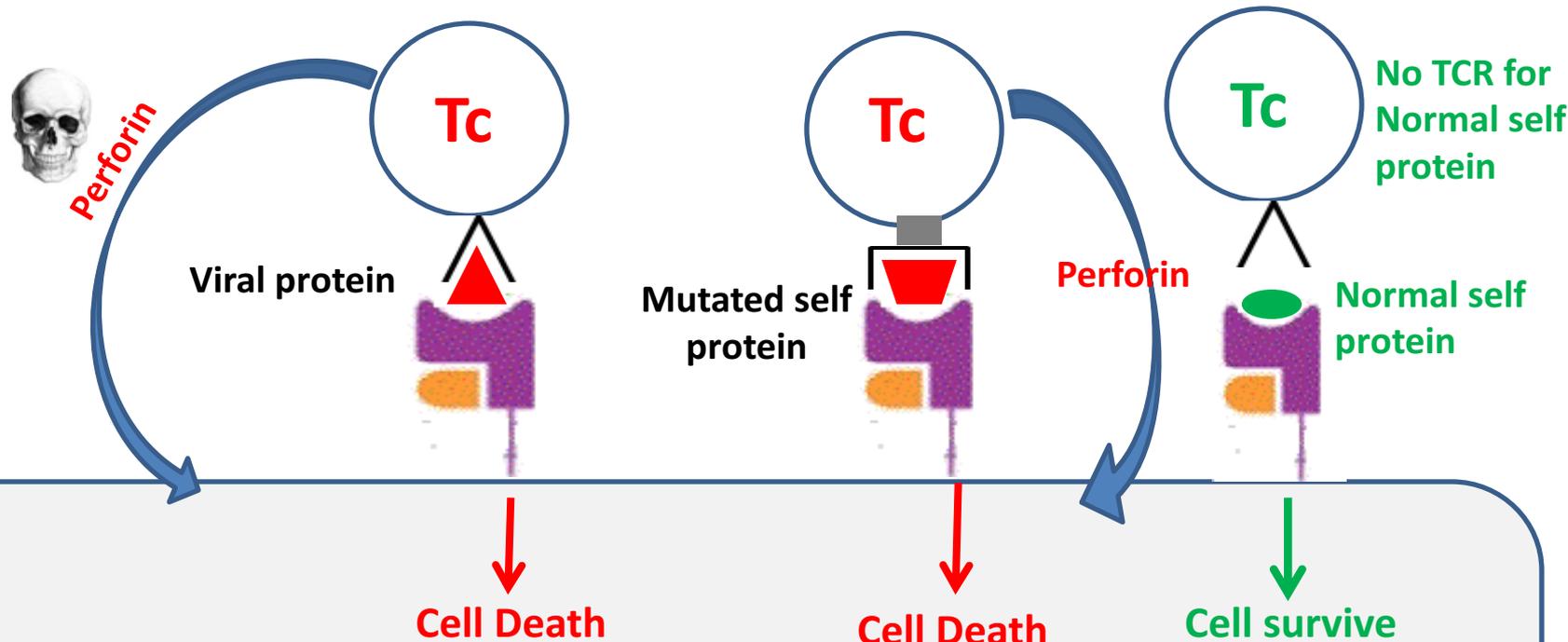
HLA-DM binds to the MHC class II molecule, releasing CLIP and allowing other peptides to bind. The MHC class II molecule then travels to the cell surface



Functions of MHC-I molecules

MHC-I molecules

1. Antigen presentation to Tc to check the normal expression of cellular proteins



Normal self protein



Mutated self protein



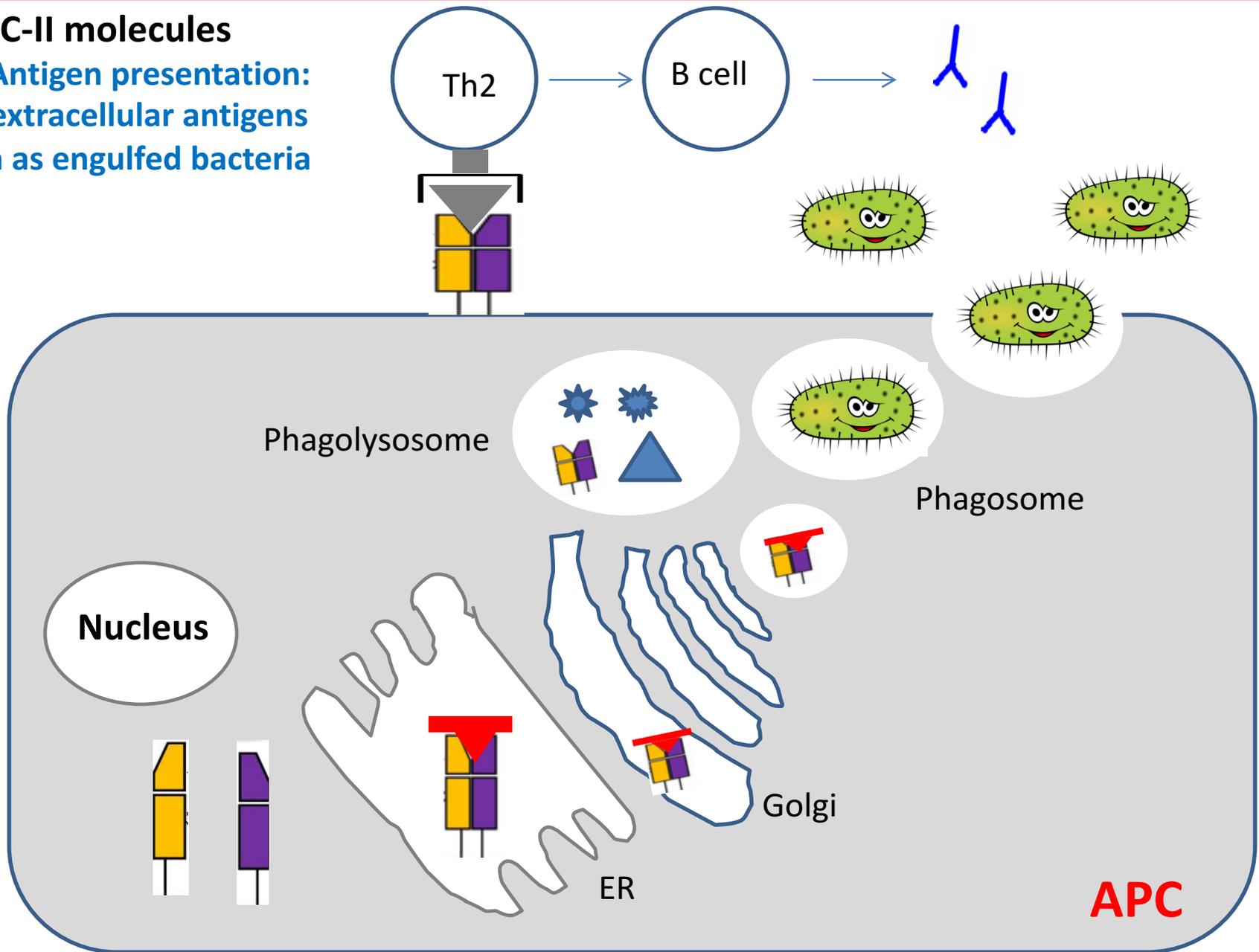
Viral protein



Functions of MHC-II molecules

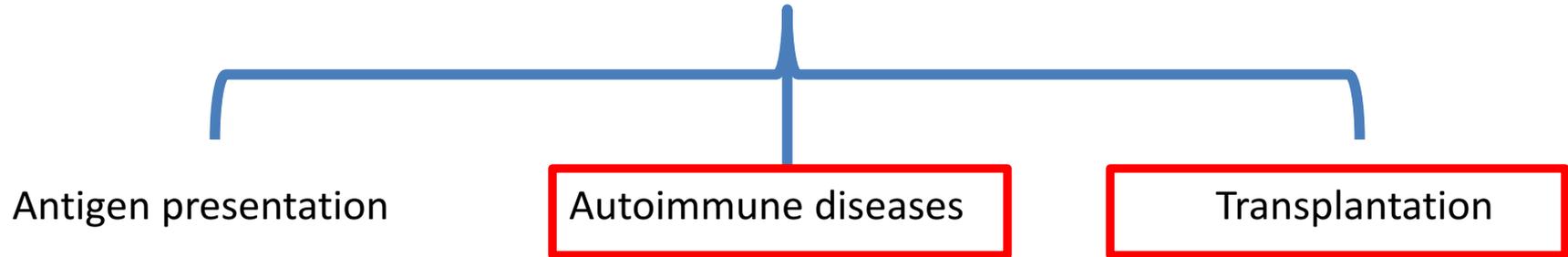
MHC-II molecules

1. Antigen presentation:
For extracellular antigens
Such as engulfed bacteria



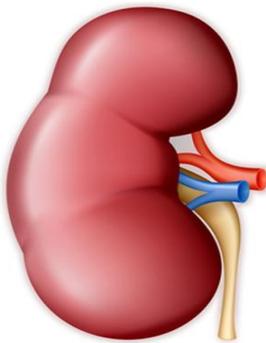
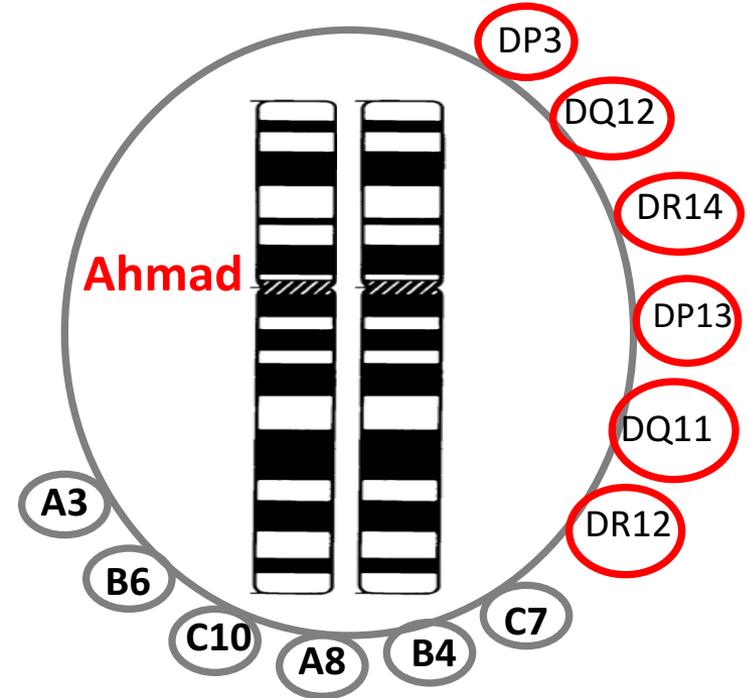
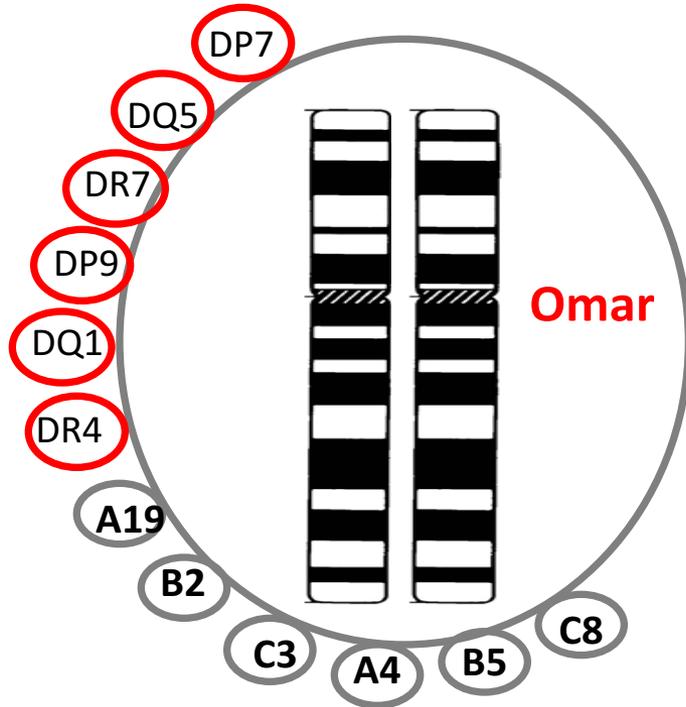
Biological Importance of MHC

MHC molecules play a major role in three lines

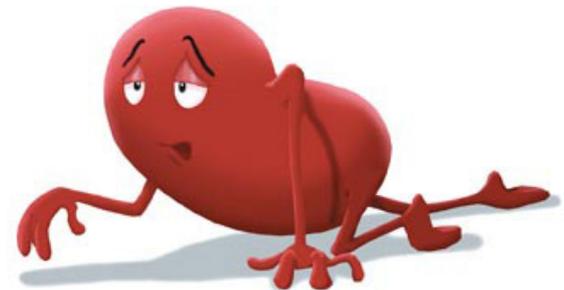


Functions of MHC molecules

2- Transplantation



Kidney from Omar to Ahmad Will be rejected because of MHC molecules incompatibility



Rejected

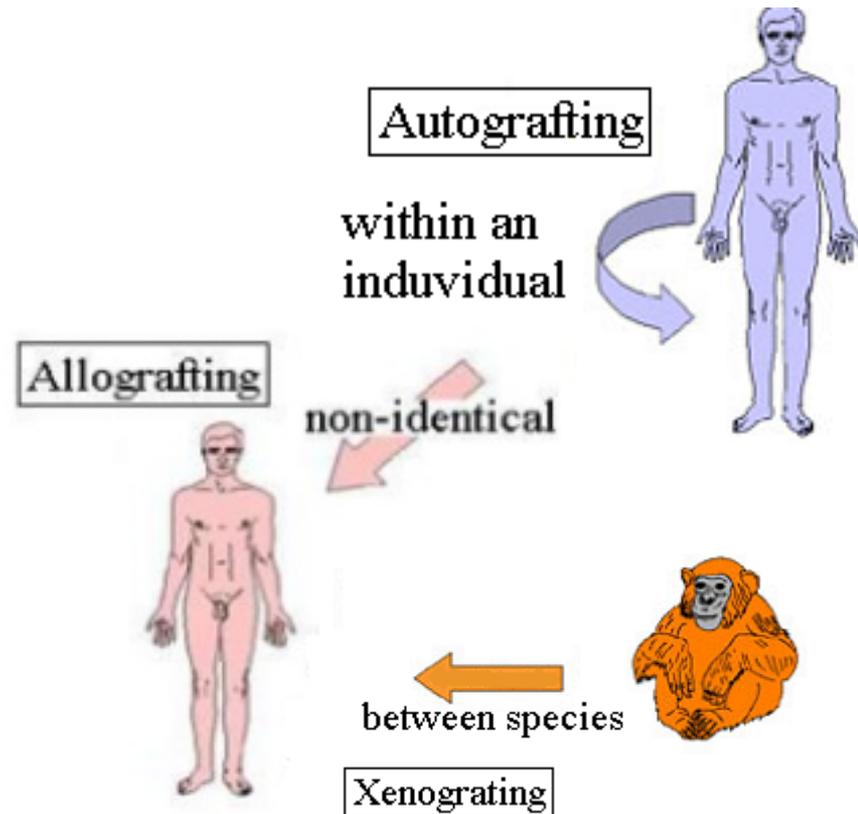
Functions of MHC molecules

2- Transplantation

Methods of Transplantation:

May take place between:

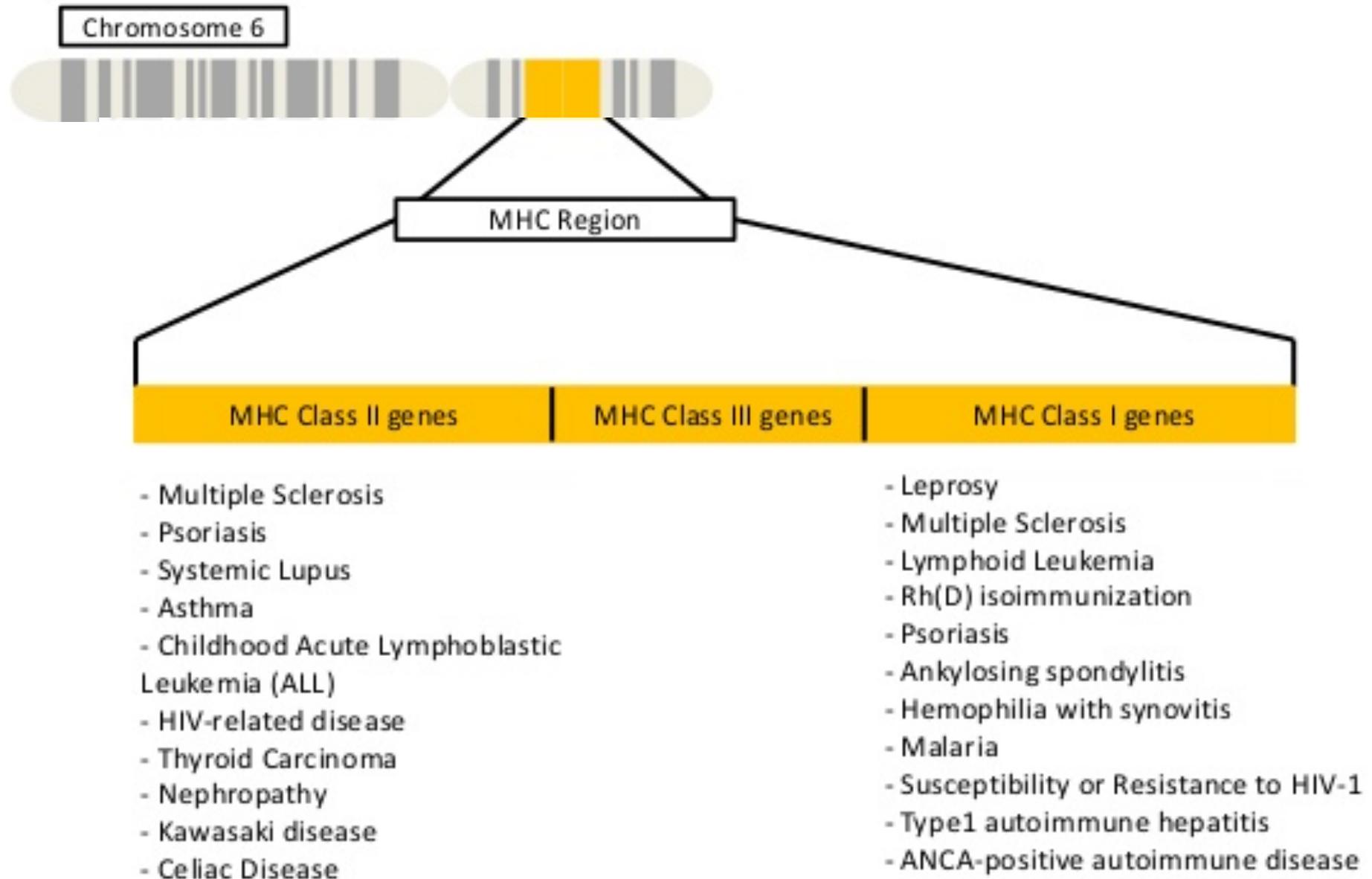
- different parts of the same organism (autografting)
- different organisms of the same species (allografting)
- different species (xenografting)



Matching and cross-matching

- 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

MHC and associated diseases



Association of Human MHC Alleles and Risk for Diseases

<u>Disease</u>	<u>Associated HLA Allele</u>	<u>Relative Risk**</u>
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

Thank You