

# Major Histocompatibility Complex (MHC)

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

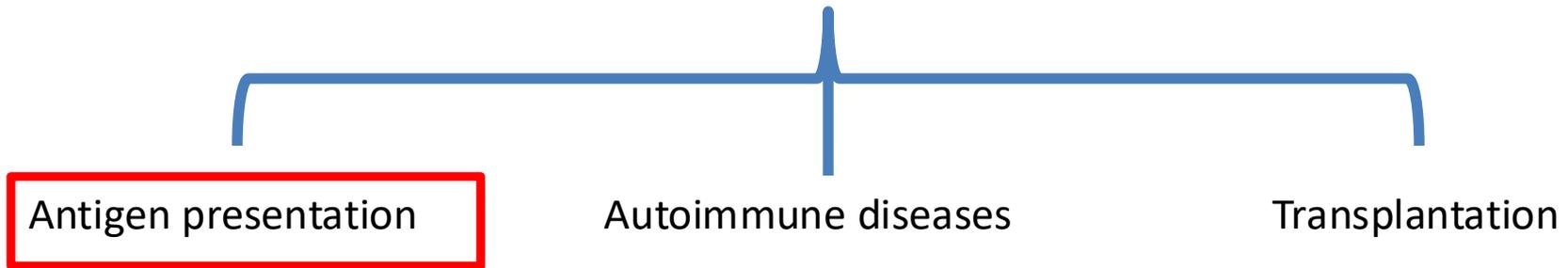
# Introduction

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## 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

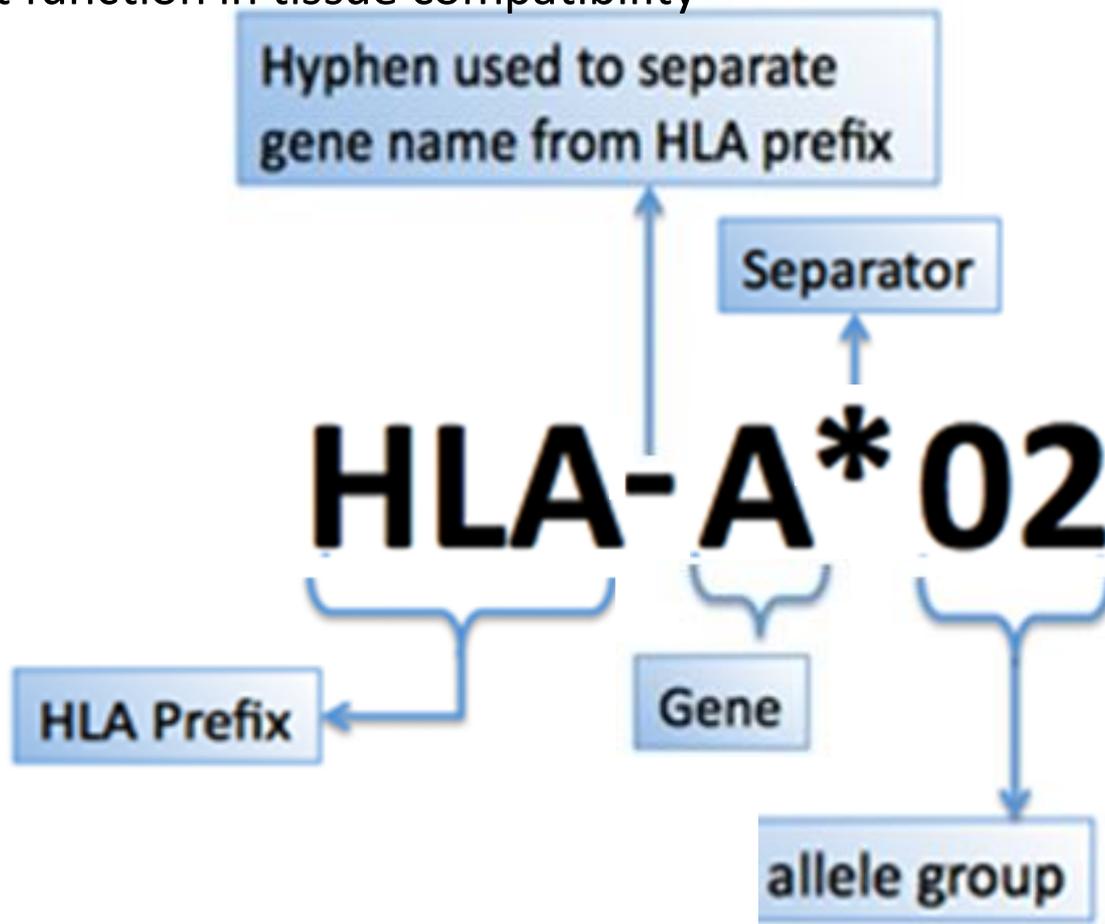
**MHC molecules play a major role in three lines**



# MHC 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

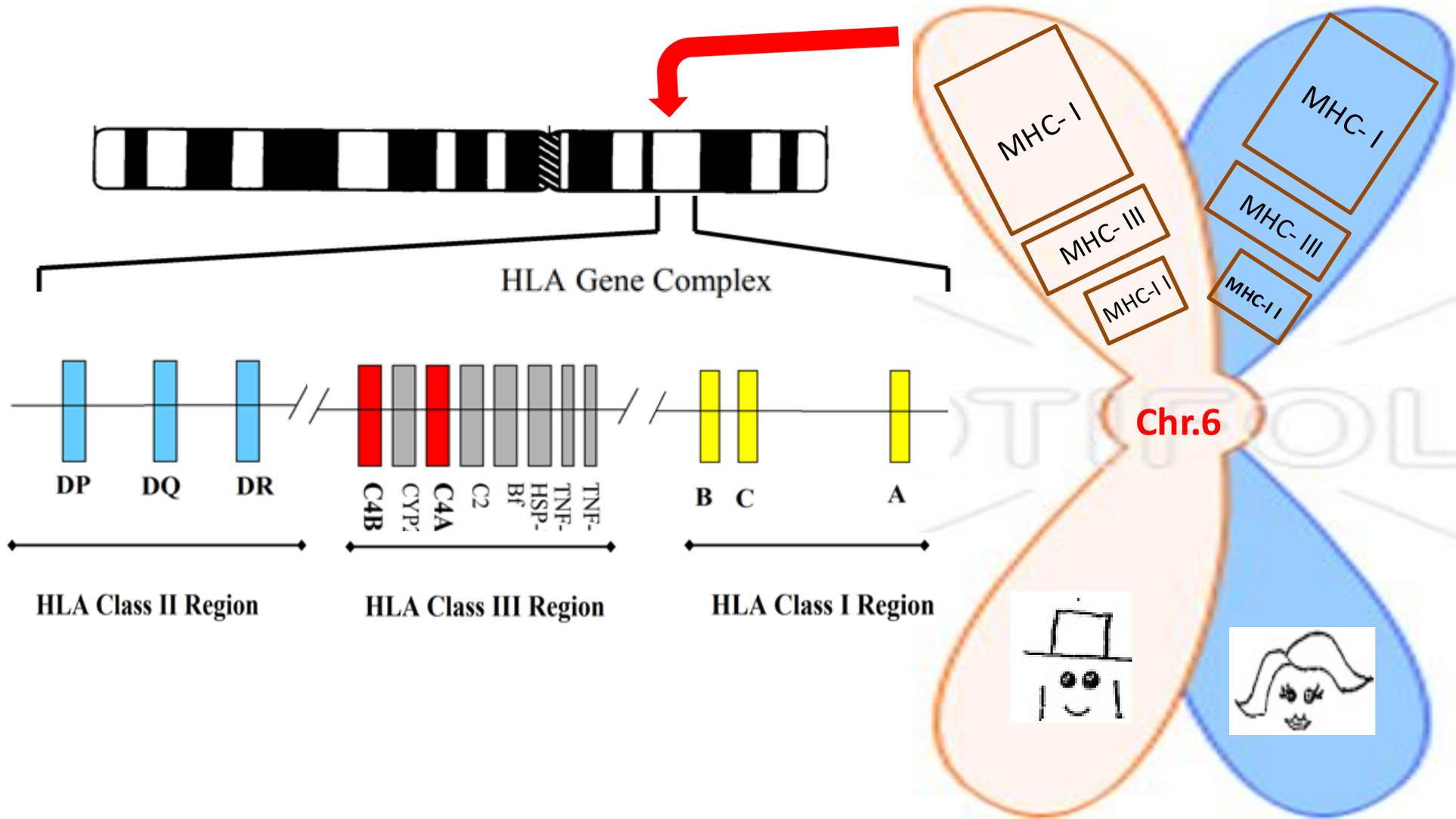
MHC genes in humans are found on the short arm of **chromosome 6** and are divided into three categories or classes.

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

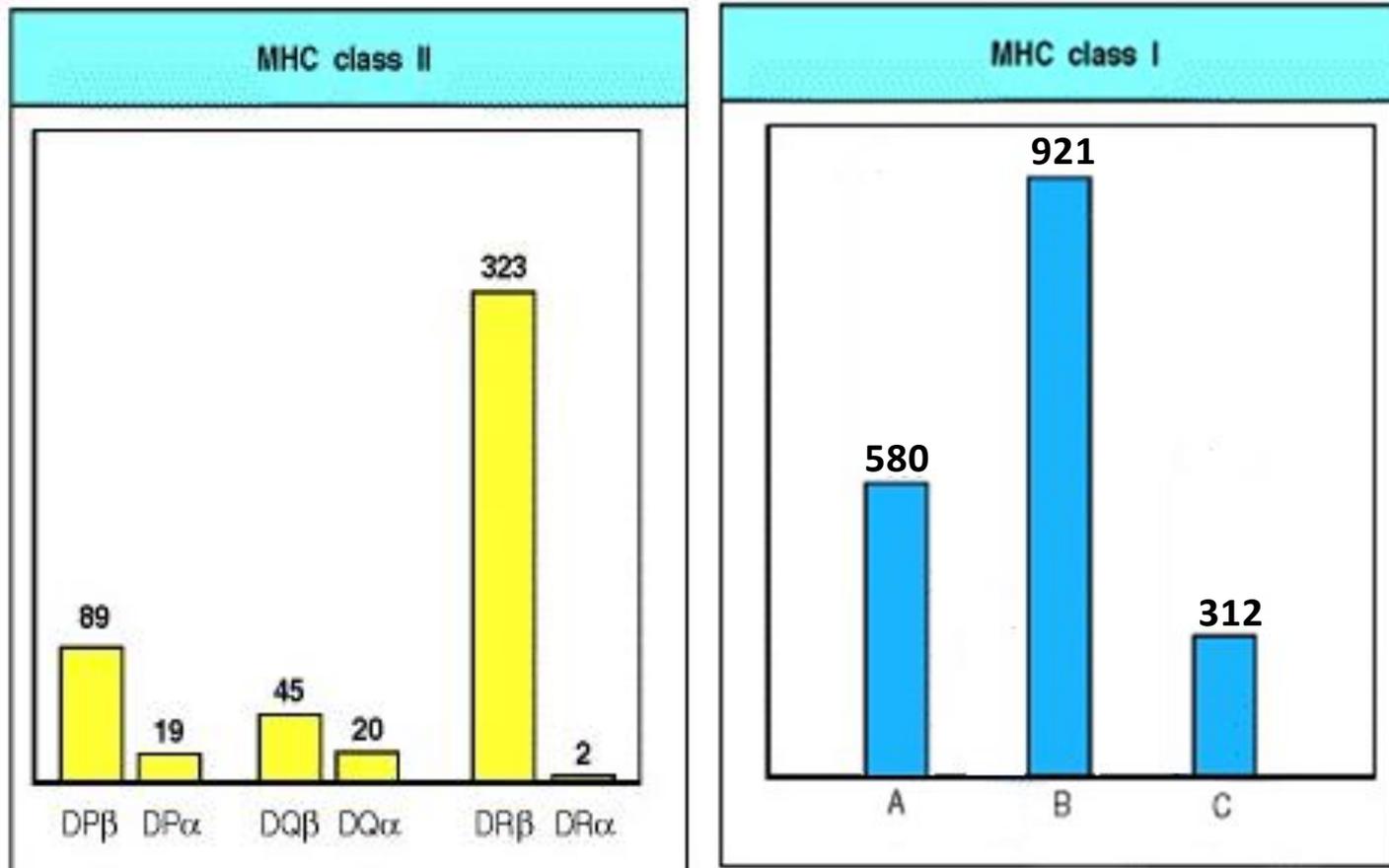
# MHC genes (alleles)

## Inheritance of MHC genes

- ✓ Multiple alleles are present at each of MHC gene



# Human MHC Class 1 and 2 genes are highly polymorphic

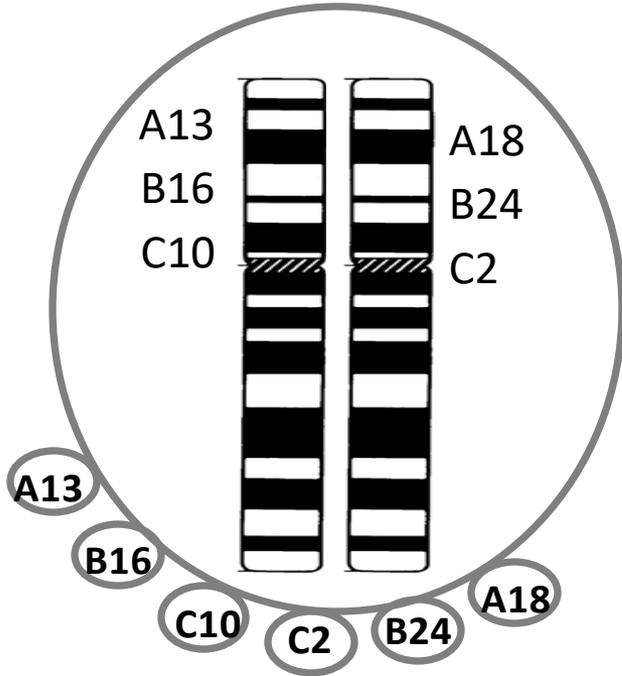


- Each MHC locus has many alleles.
- The difference in the inheritance of MHC molecules among individuals is due to the presence of a big number of MHC alleles. The inheritance is concomitant.
- Each person takes one allele or each locus from each parent. So for class 1 MHC we inherited 6 alleles give 6 different MHC1, and 6-8 MHC2 alleles give 6-8 different MHC2

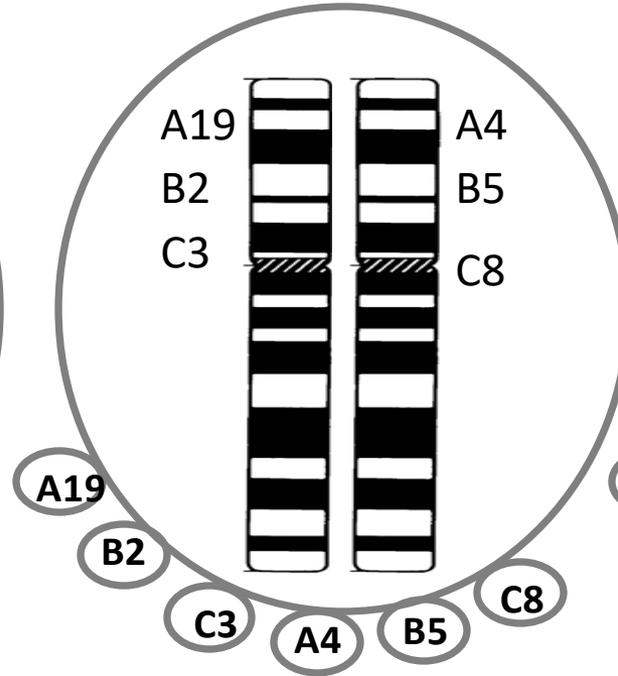
# MHC-I

## Inheritance of MHC-I

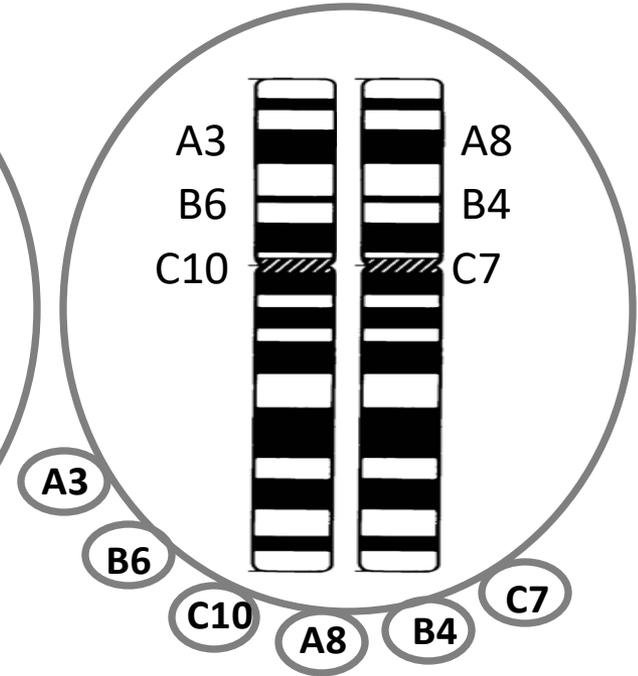
Ali



Omar



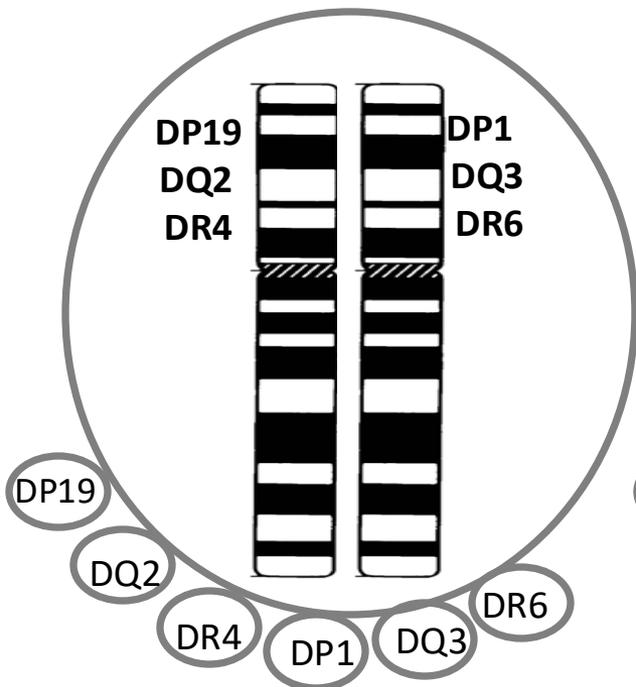
Ahmad



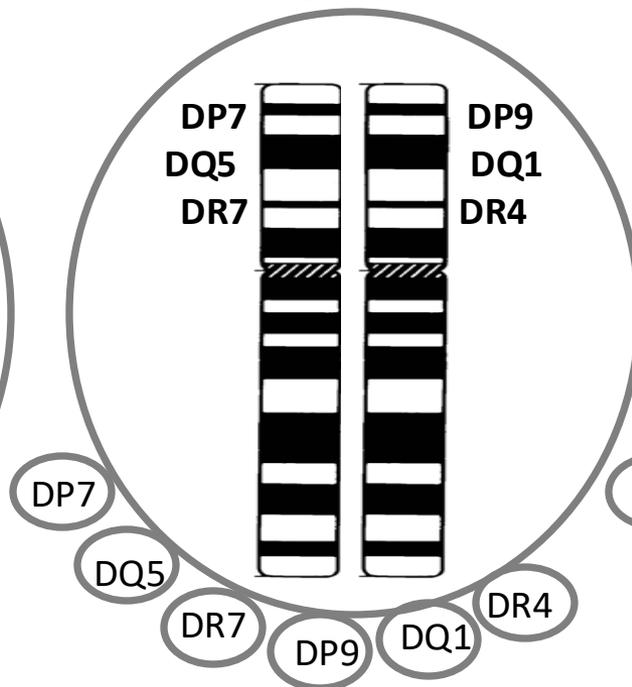
# MHC-II

## Inheritance of MHC-II

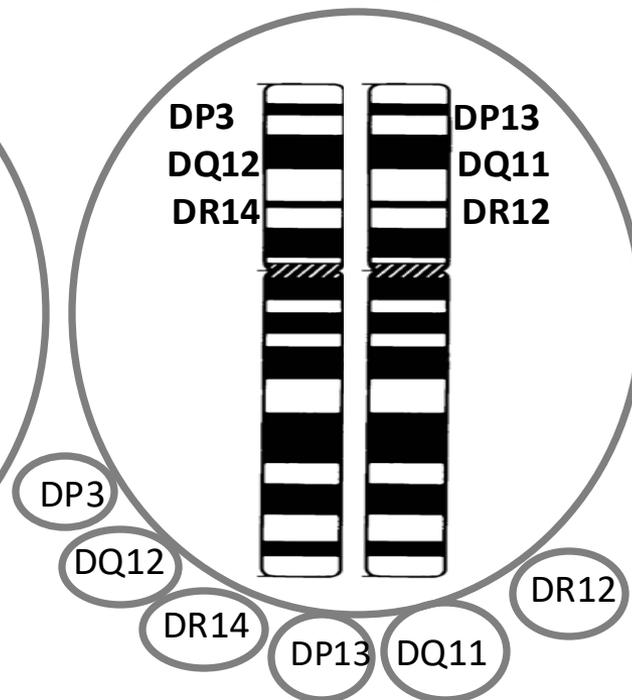
Ali



Omar

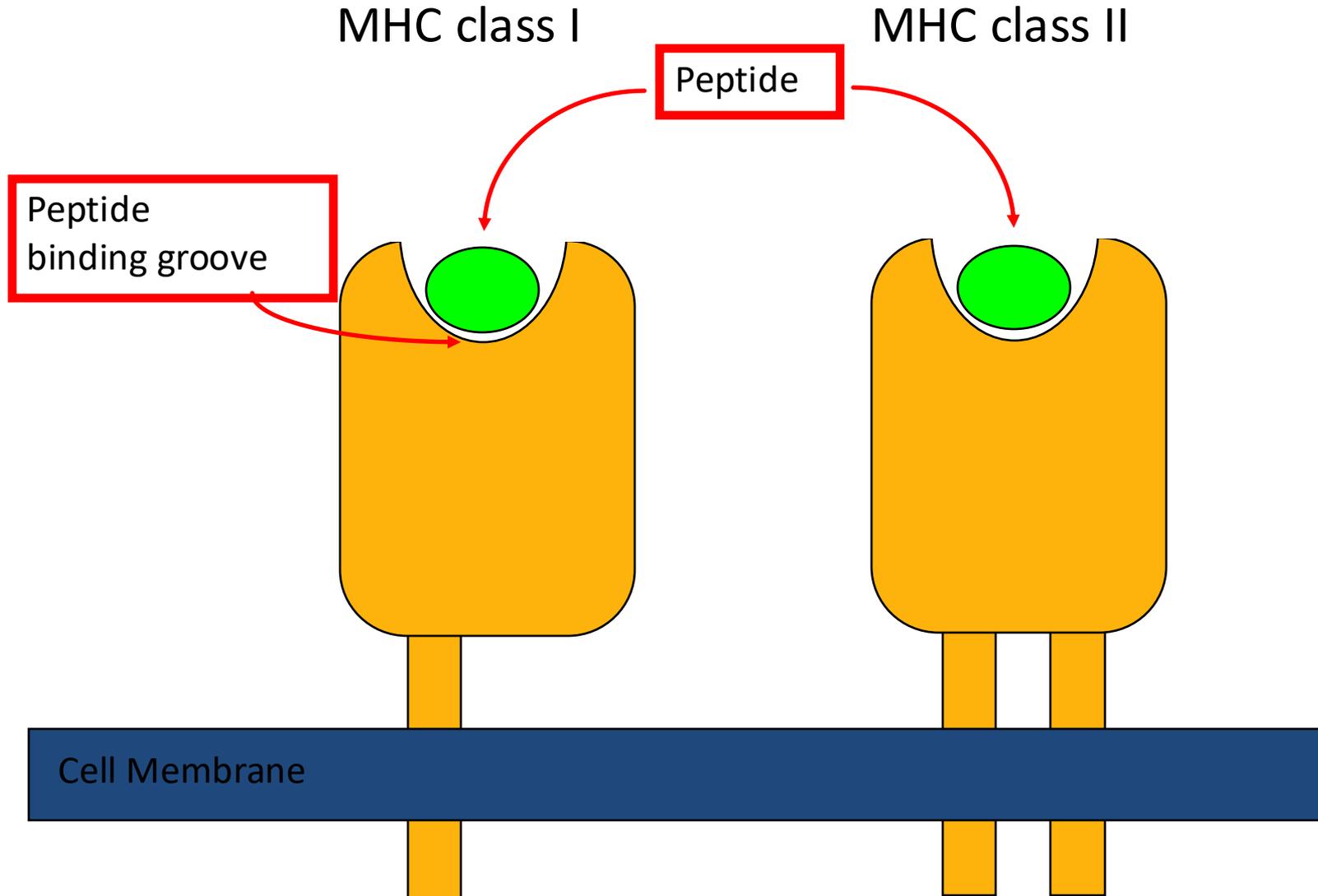


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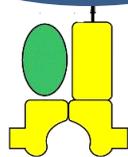
# MHC-II

## MHC-I vs. MHC- II

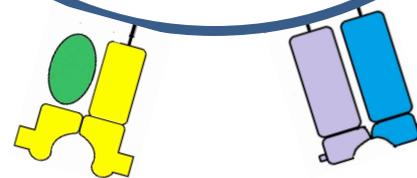


# Expression of MHC molecules

All nucleated cells  
express MHC1

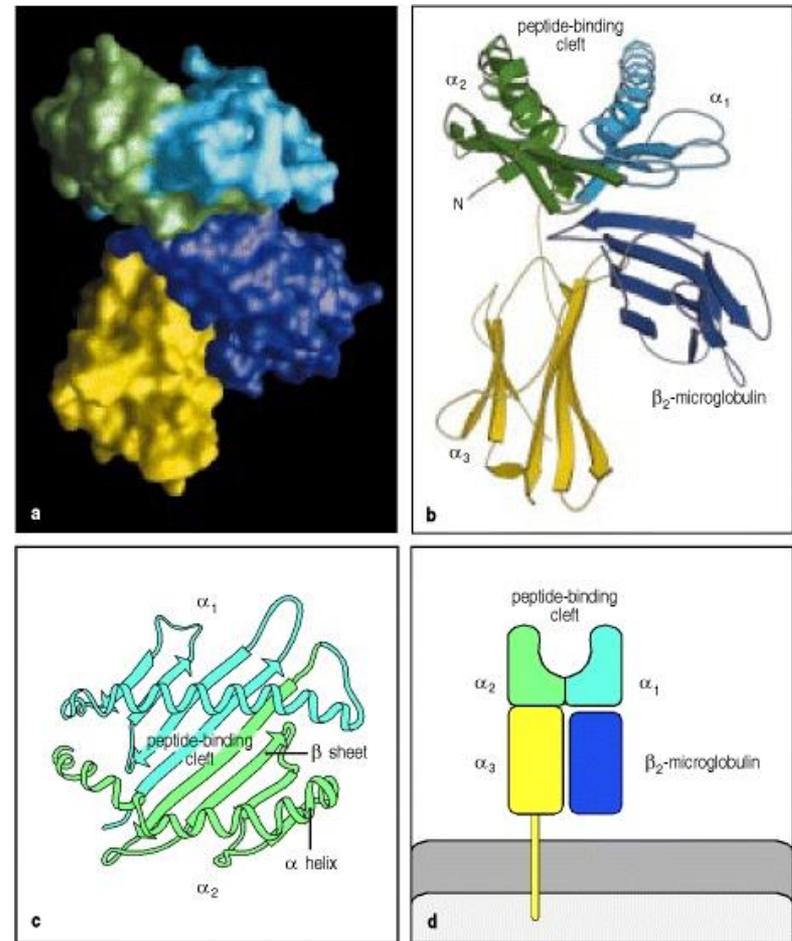


APC can express both  
MHC1 & MHC2



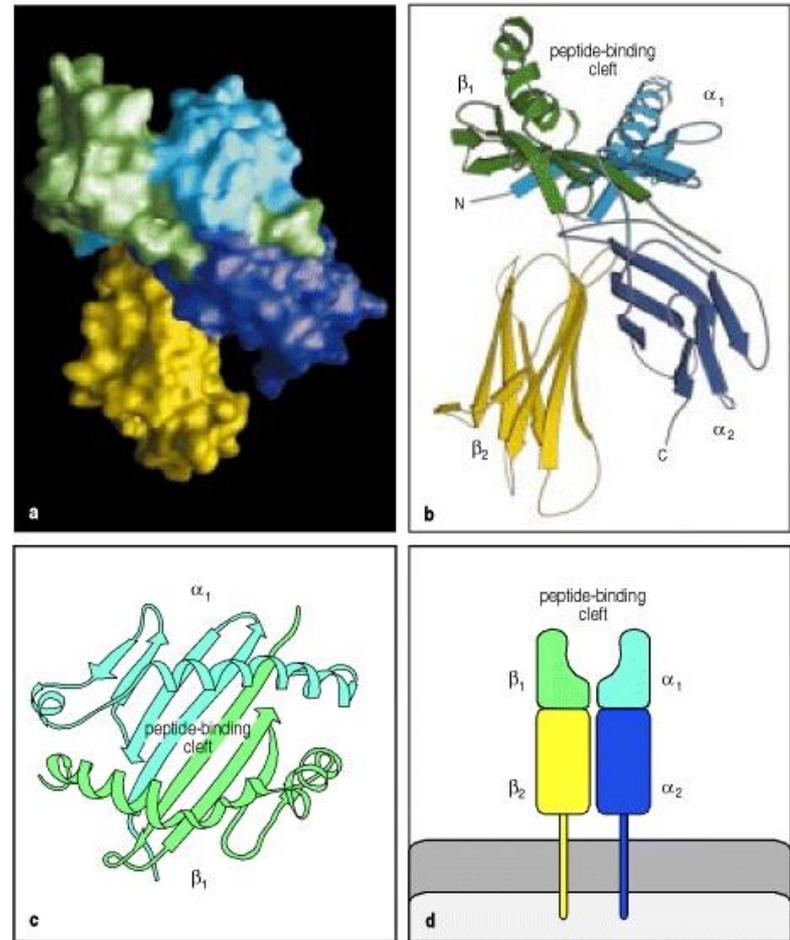
# MHC 1 protein structure

- four domains; Heavy chain ( $\alpha_1$ ,  $\alpha_2$ ,  $\alpha_3$ )  $\beta_2$  microglobulin, transmembrane and cytoplasmic tail
- Hypervariable parts are  $\alpha_1$ ,  $\alpha_2$ .
- $\alpha_3$  is the constant region bind CD8



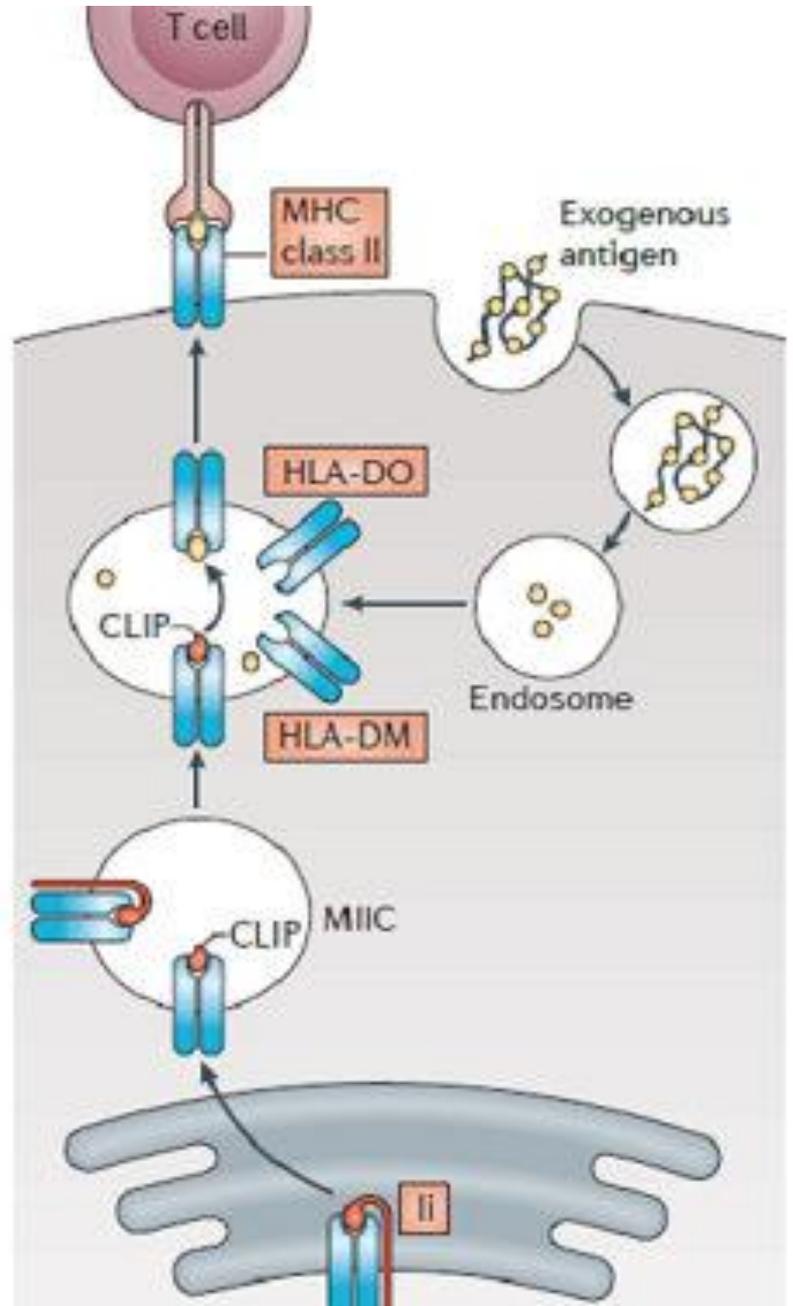
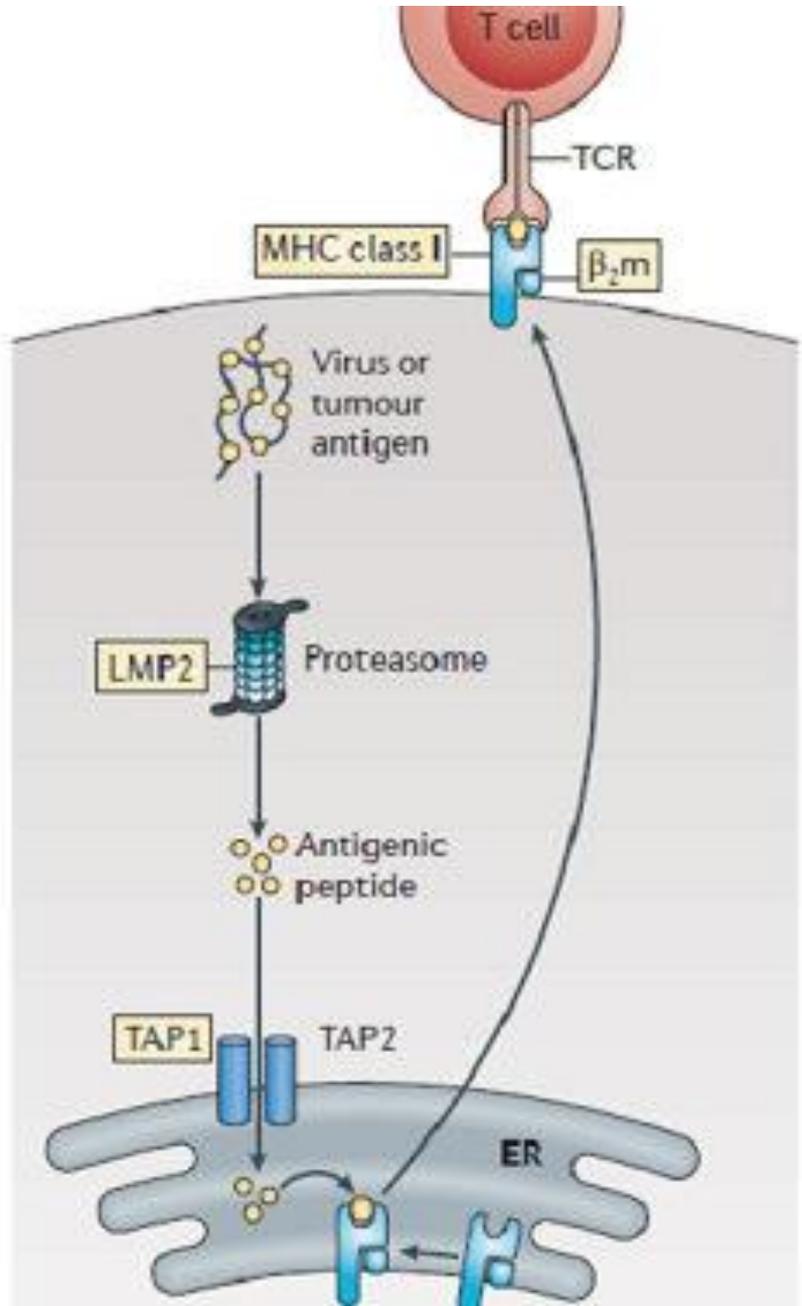
# MHC 2 protein structure

- 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 antigens
- 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 Ags to  $T_C$
  - Class II MHC genes
    - Glycoproteins expressed on APC such as  $M\Phi$ , B-cells, DCs
    - Major function to present processed Ags to  $T_H$
  - 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:**

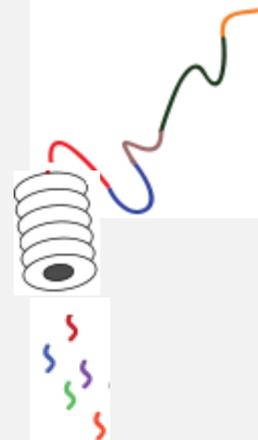
1. Intracellular bacteria
2. The mutated cellular proteins
3. The viral proteins (antigens)

**A small amount of these proteins are directed to the proteasome in which these proteins are degraded into short peptides (cytosolic degradation) 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)**

Intracellular bacteria →

Mutated self protein →

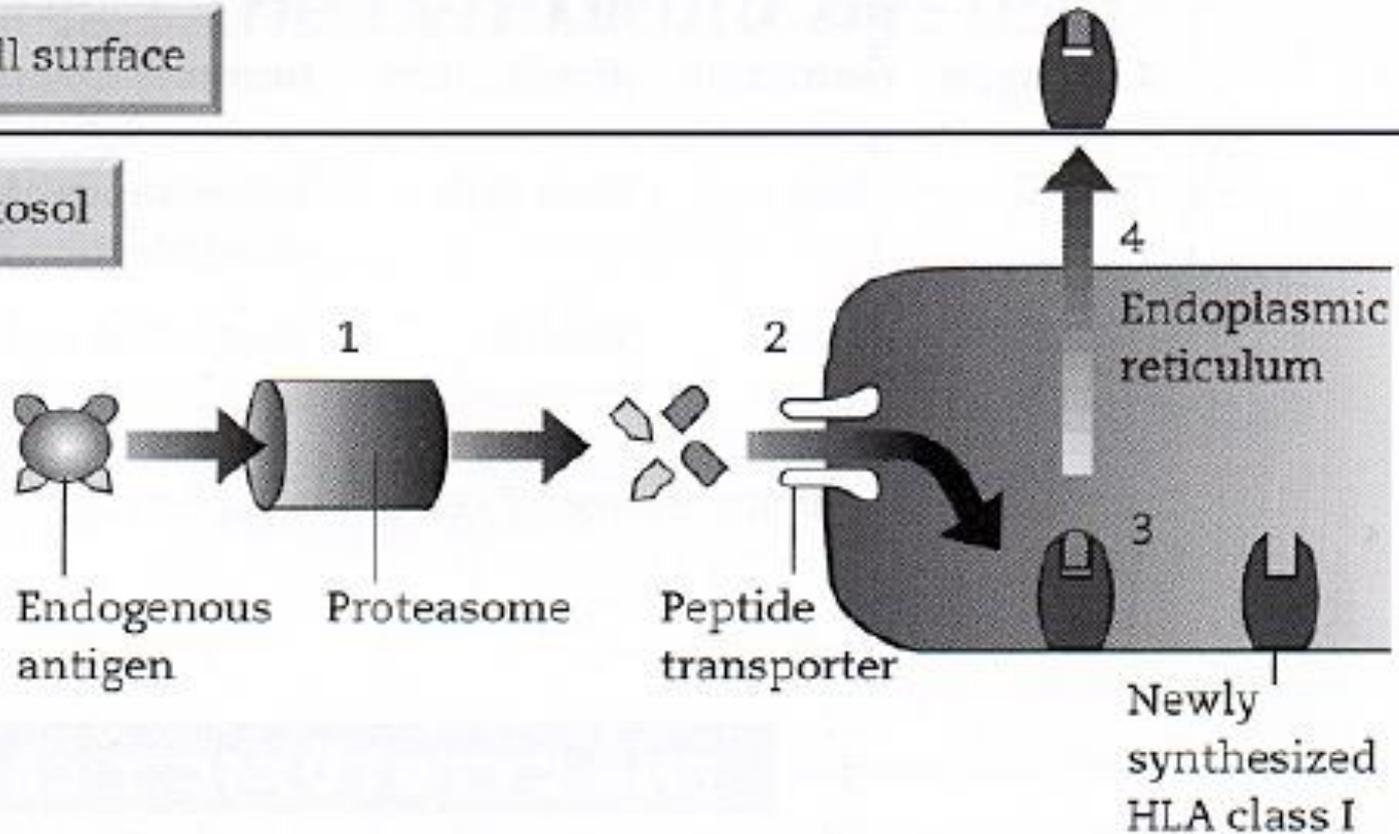
Viral protein →



# PROCESSING OF ANTIGEN FOR HLA CLASS I

Cell surface

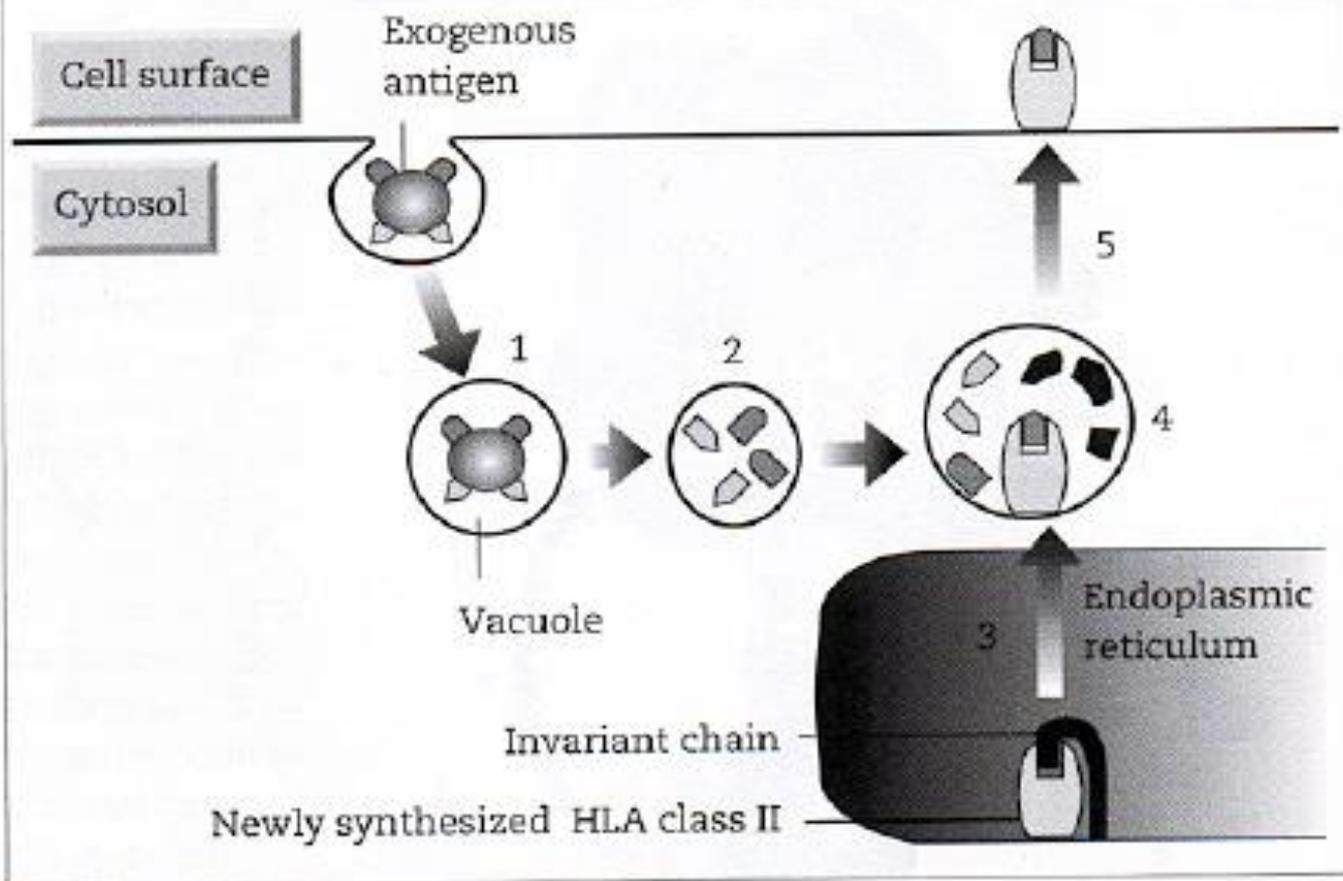
Cytosol



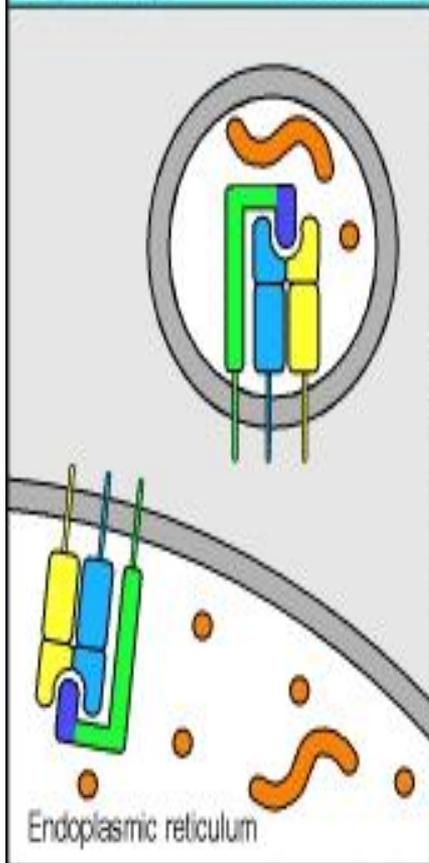
# MHC2

- Peptides that bind to MHC class 2 molecules are exogenous peptides that internalized to endosome (vesicle) and lysed there by enzymes (endocytic degradation)
- 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 the antigen 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.

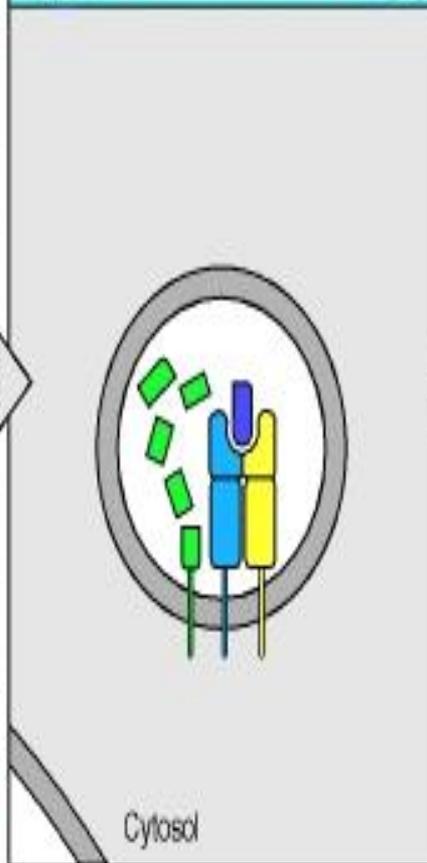
# PROCESSING OF ANTIGEN FOR HLA CLASS II



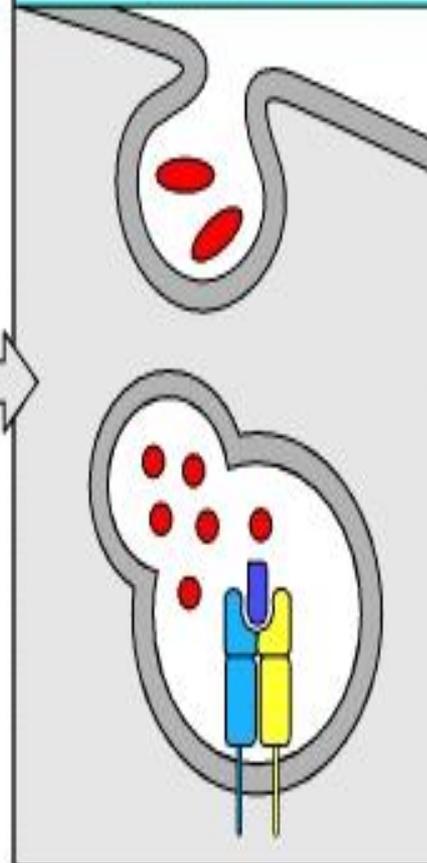
Invariant chain (Ii) forms a complex with MHC class II, blocking the binding of peptides and misfolded proteins



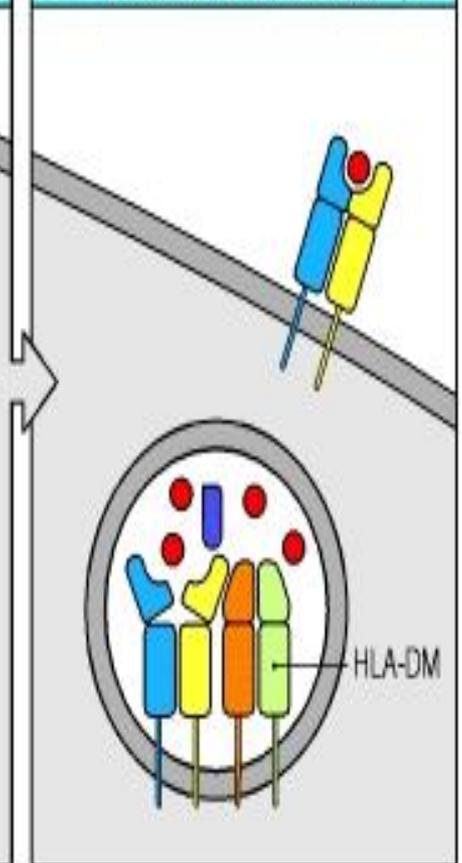
Ii is cleaved in an acidified endosome, leaving a short peptide fragment, CLIP, still bound to the MHC class II molecule



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



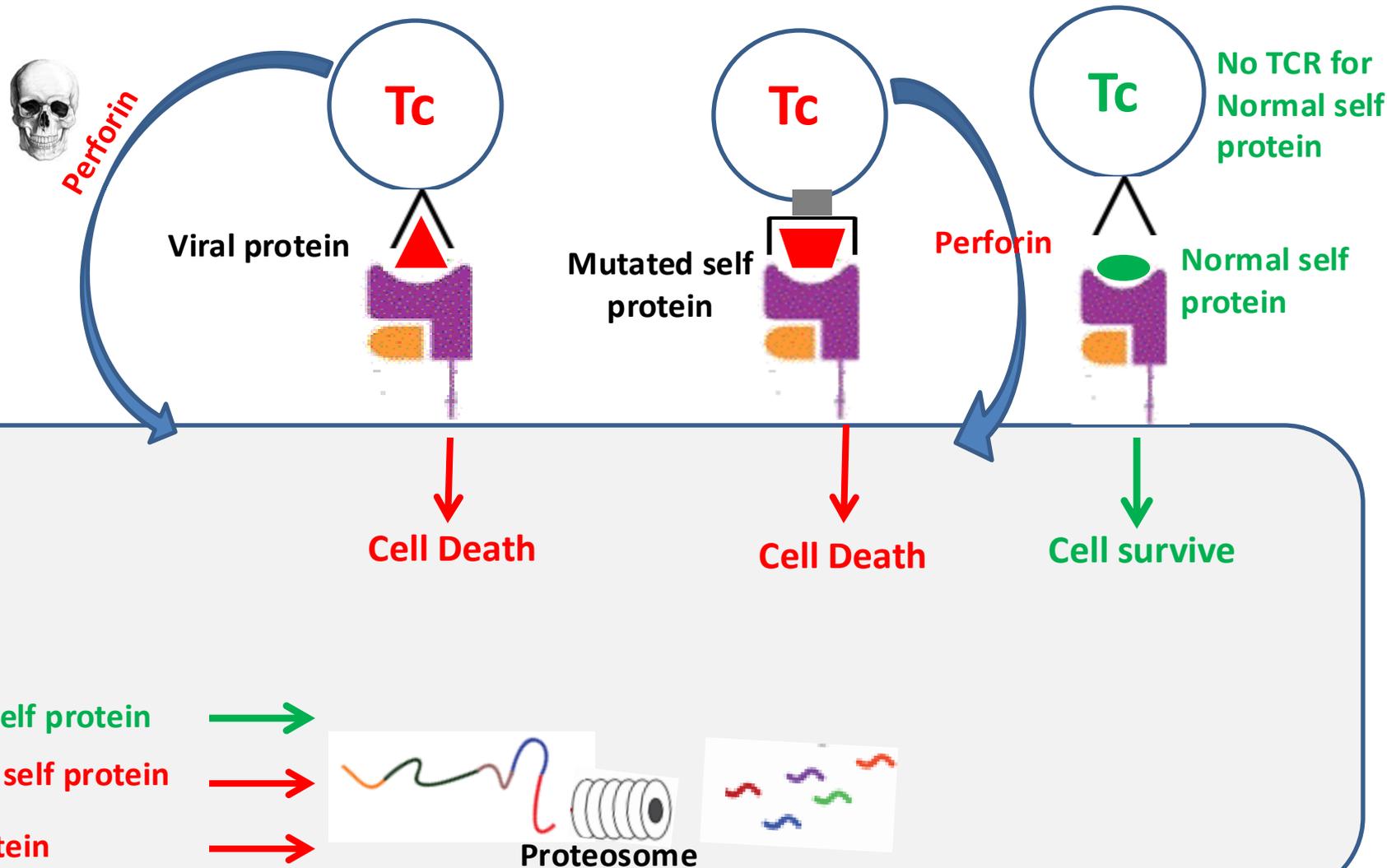
HLA-DM binds to the MHC class II molecule, releasing CLIP and allowing other peptides to bind. The MHC class II molecule then travels to the cell surface



# Functions of MHC-I molecules

## MHC-I molecules

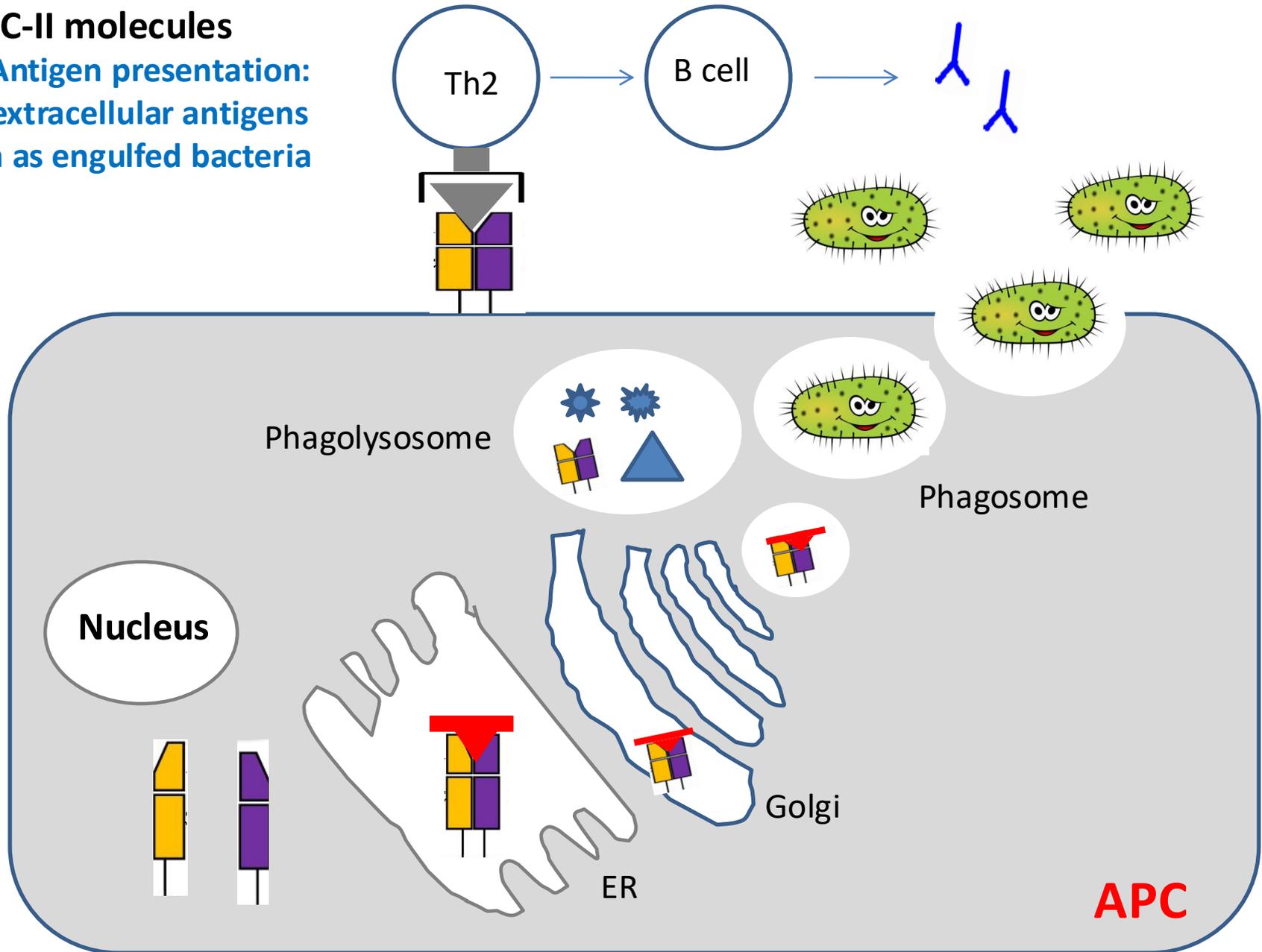
### 1. Antigen presentation to CTL to check the normal expression of cellular proteins



# Functions of MHC-II molecules

## MHC-II molecules

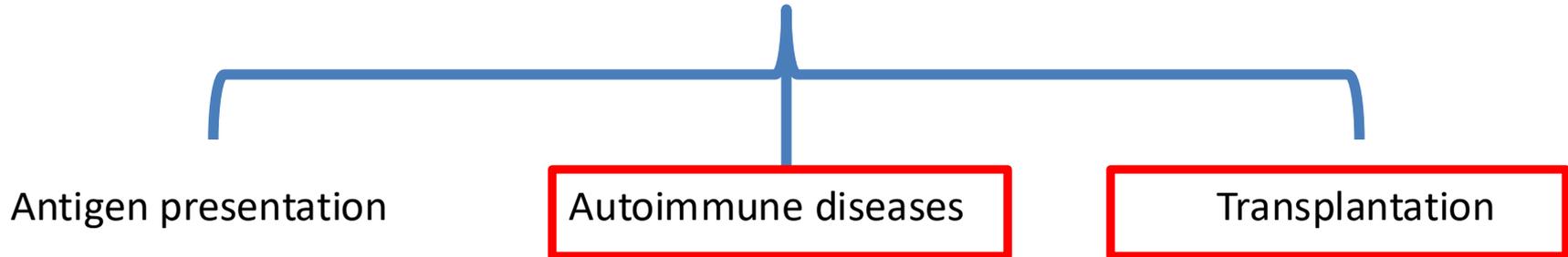
1. Antigen presentation:  
For extracellular antigens  
Such as engulfed bacteria



# Biological Importance of MHC

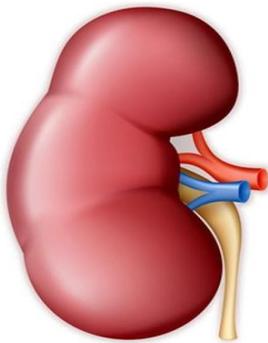
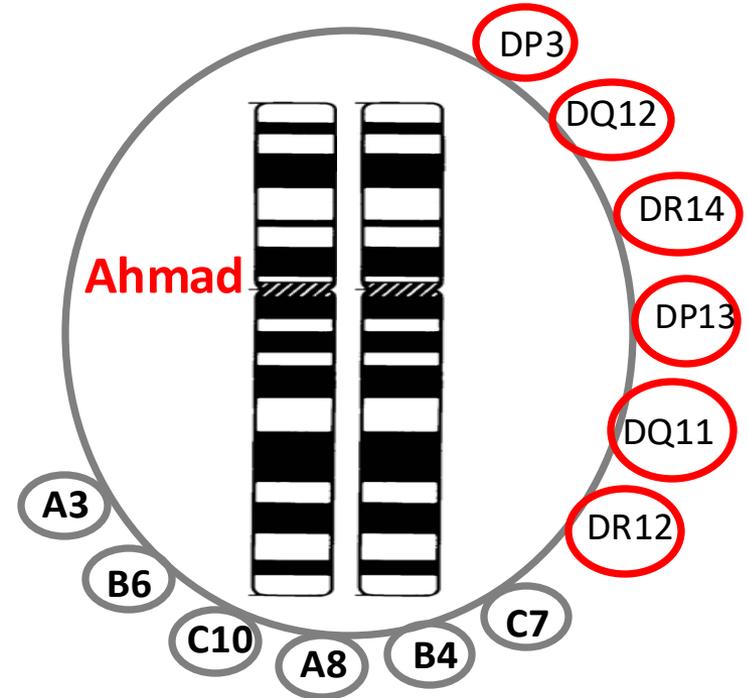
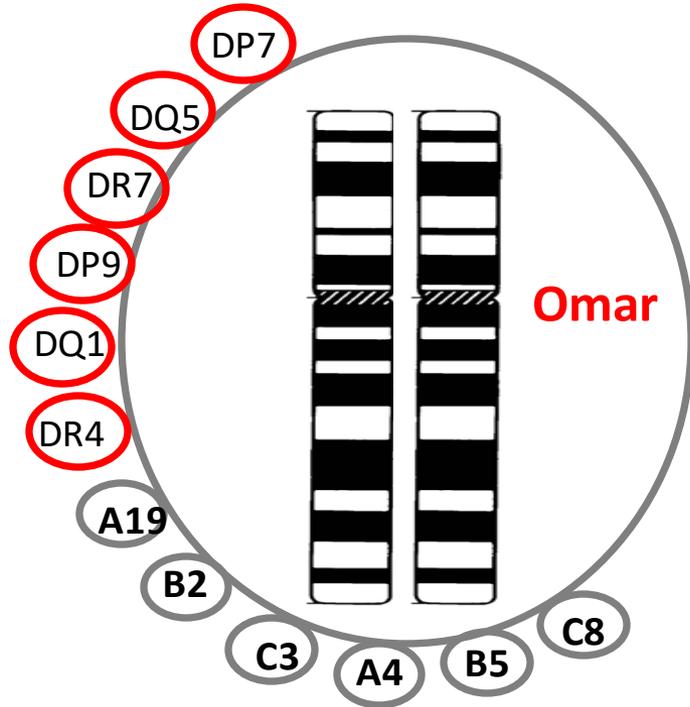
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MHC molecules play a major role in three lines

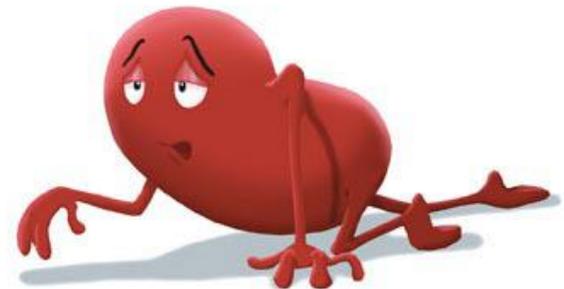


# Functions of MHC molecules

## 2- Transplantation



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



Rejected

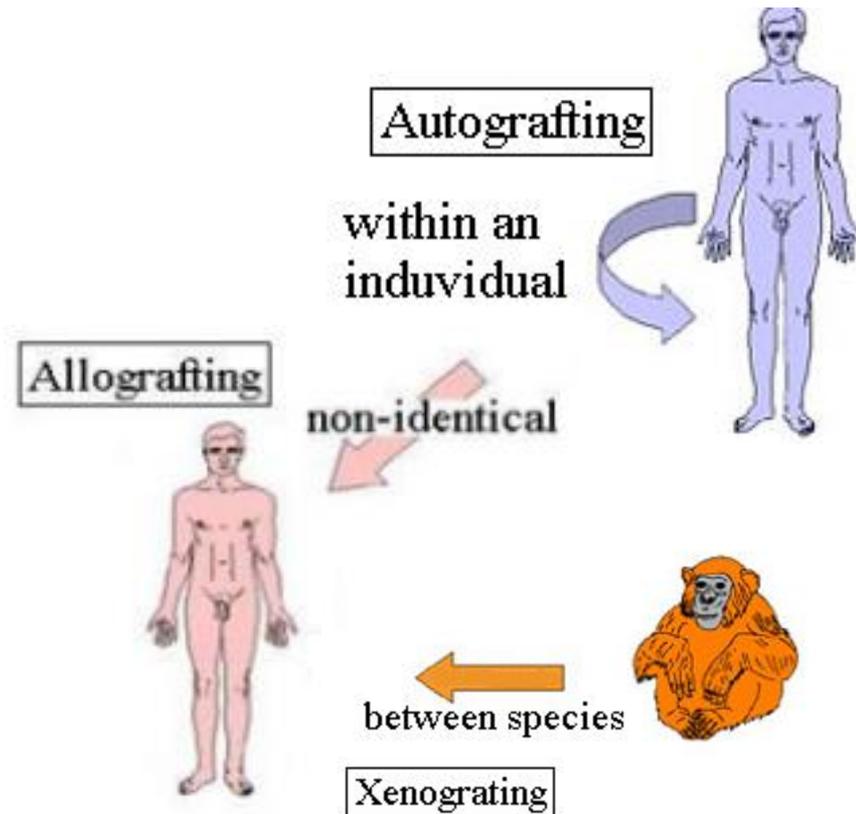
# Functions of MHC molecules

## 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)



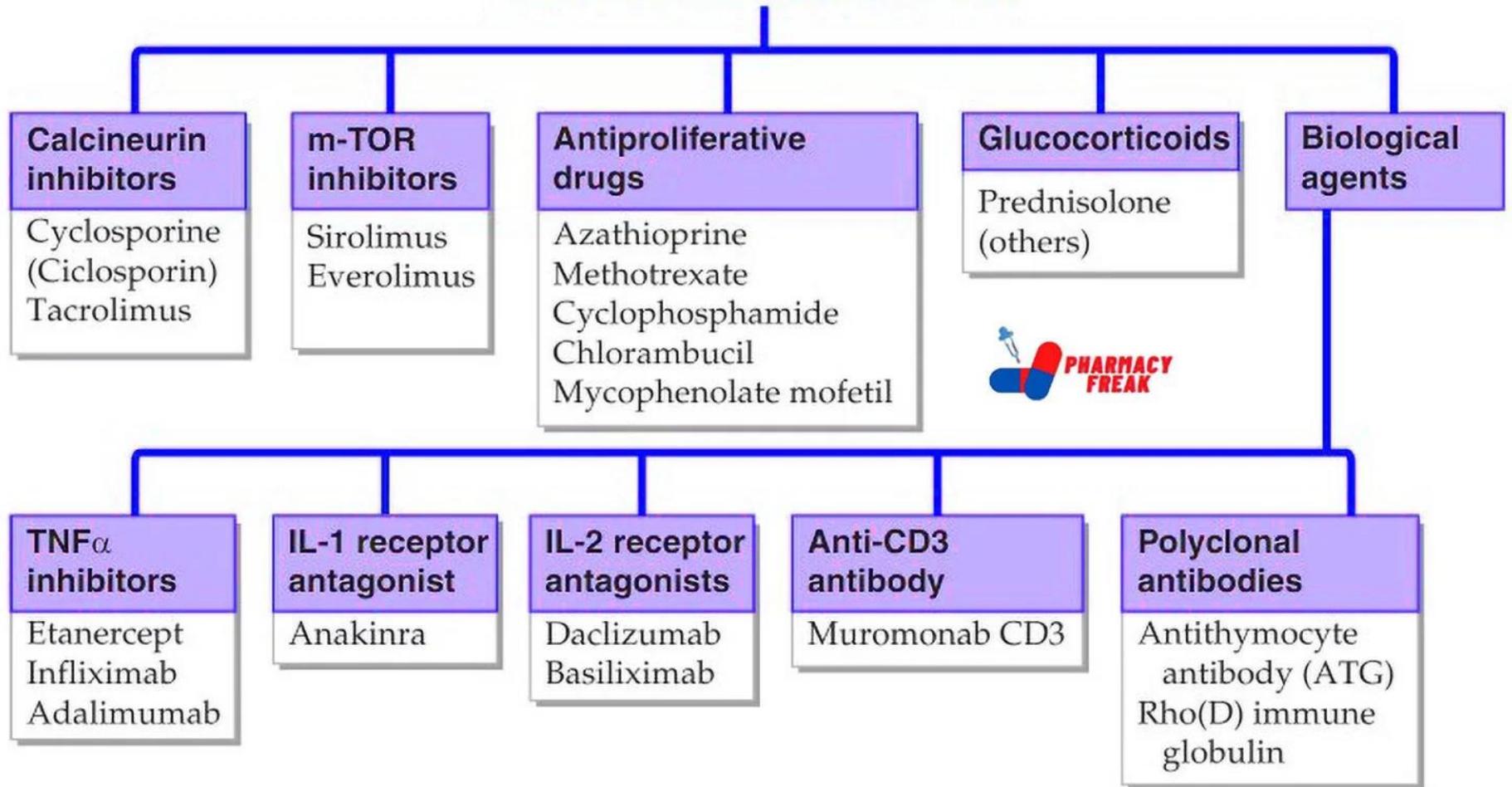
# Matching and cross-matching

- 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

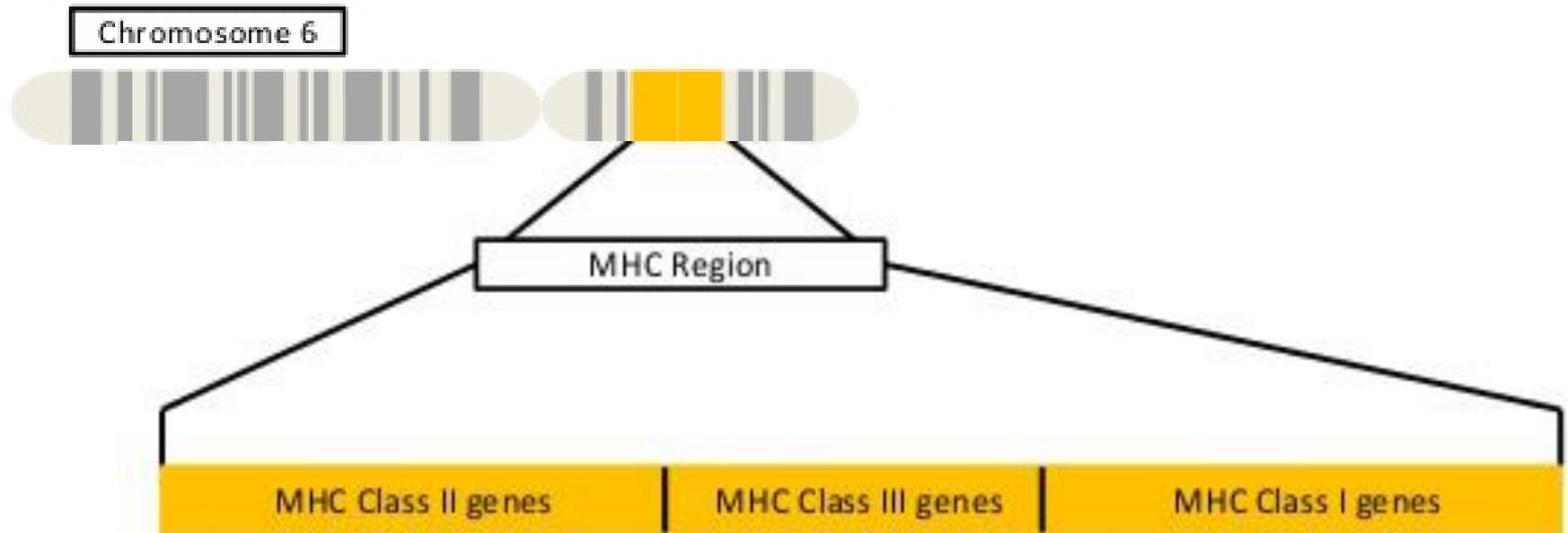
Transplant Rejection				
	Type	Onset	Mechanism & Vessel Histology	Type of Hypersensitivity
"Host vs. Graft"	Hyperacute	Immediate	Preformed antibodies directed against the donor tissue. Caused by accidental ABO <b>blood type incompatibility</b> which is very rare. Presents while still in surgery with <b>thrombosis and occlusion</b> of graft vessels	II
	Acute	Weeks to months	T-Cell mediated immune response directed against the foreign MHC. Inflammation and <b>leukocyte infiltration of graft vessels</b> results. Most common type.	IV
	Chronic	Months to years	T-Cell mediated process resulting from the foreign MHC "looking like" a self MHC carrying an antigen. Results in <b>intimal thickening and fibrosis of graft vessels</b> as well as graft atrophy	III & IV
Graft vs. Host		Varies	Donor T-Cells in the graft proliferate and attack the recipient's tissue. Most commonly seen in <b>bone marrow transplants</b> . Presents with <b>diarrhea, rash and jaundice</b> .	IV

\* The most important thing to remember is the timeframe for the onset of symptoms as you can often determine what type of rejection it is based on time alone

# IMMUNOSUPPRESSANT DRUGS



# MHC and associated diseases



- Multiple Sclerosis
- Psoriasis
- Systemic Lupus
- Asthma
- Childhood Acute Lymphoblastic Leukemia (ALL)
- HIV-related disease
- Thyroid Carcinoma
- Nephropathy
- Kawasaki disease
- Celiac Disease

- Leprosy
- Multiple Sclerosis
- Lymphoid Leukemia
- Rh(D) isoimmunization
- Psoriasis
- Ankylosing spondylitis
- Hemophilia with synovitis
- Malaria
- Susceptibility or Resistance to HIV-1
- Type1 autoimmune hepatitis
- ANCA-positive autoimmune disease

# 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