Major Histocompatibility Complex (MHC)

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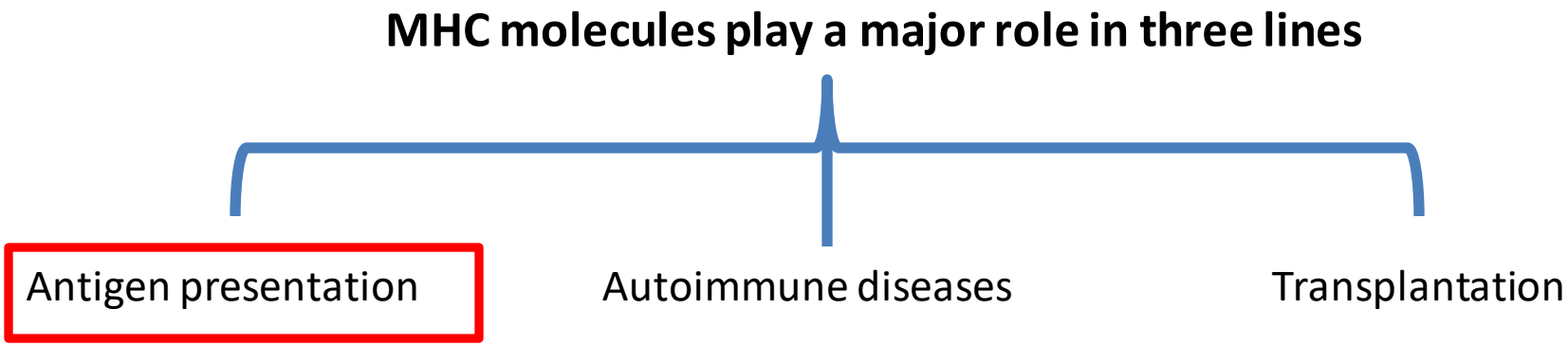
Introduction

Definition of the MHC

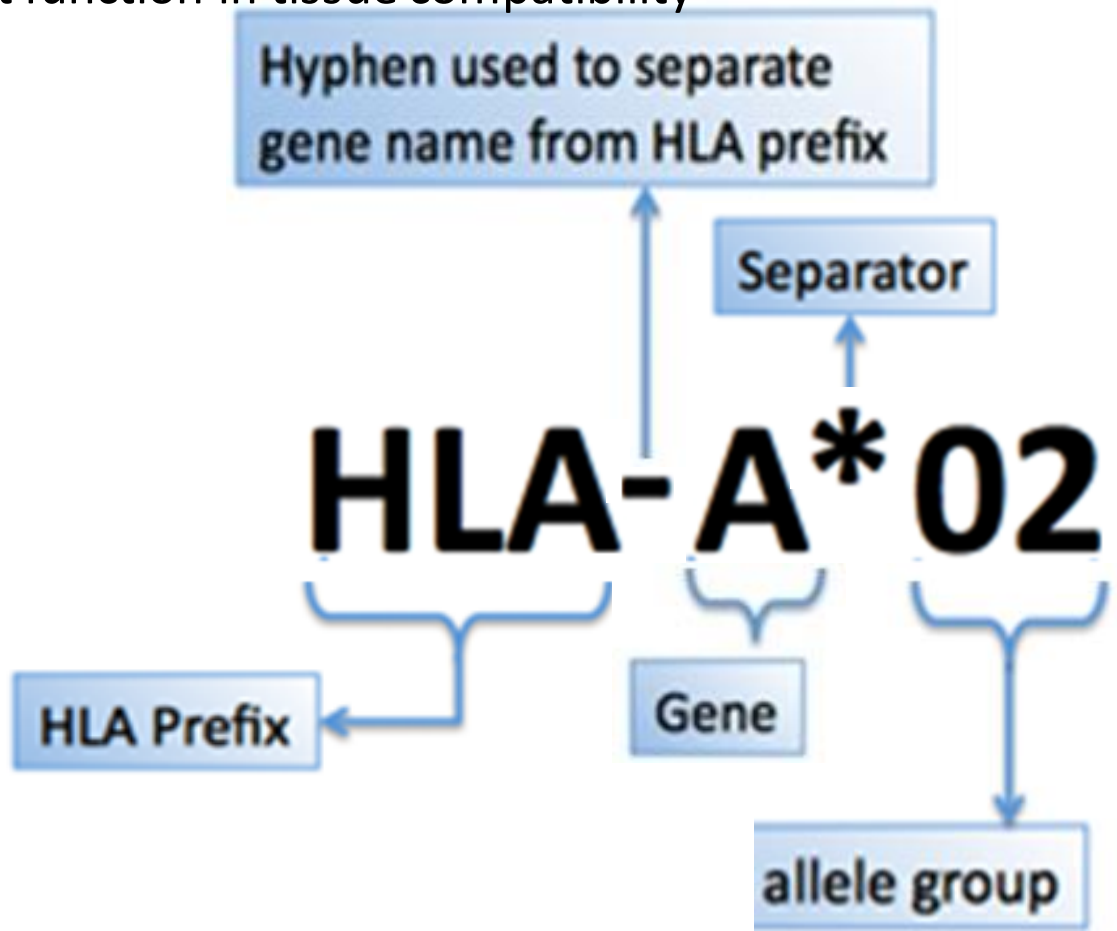
Is a set of cell surface proteins expressed on the surface of all nucleated cells and encoded by a large gene family which controls a major part of the immune system in all vertebrates



MHC molecules

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

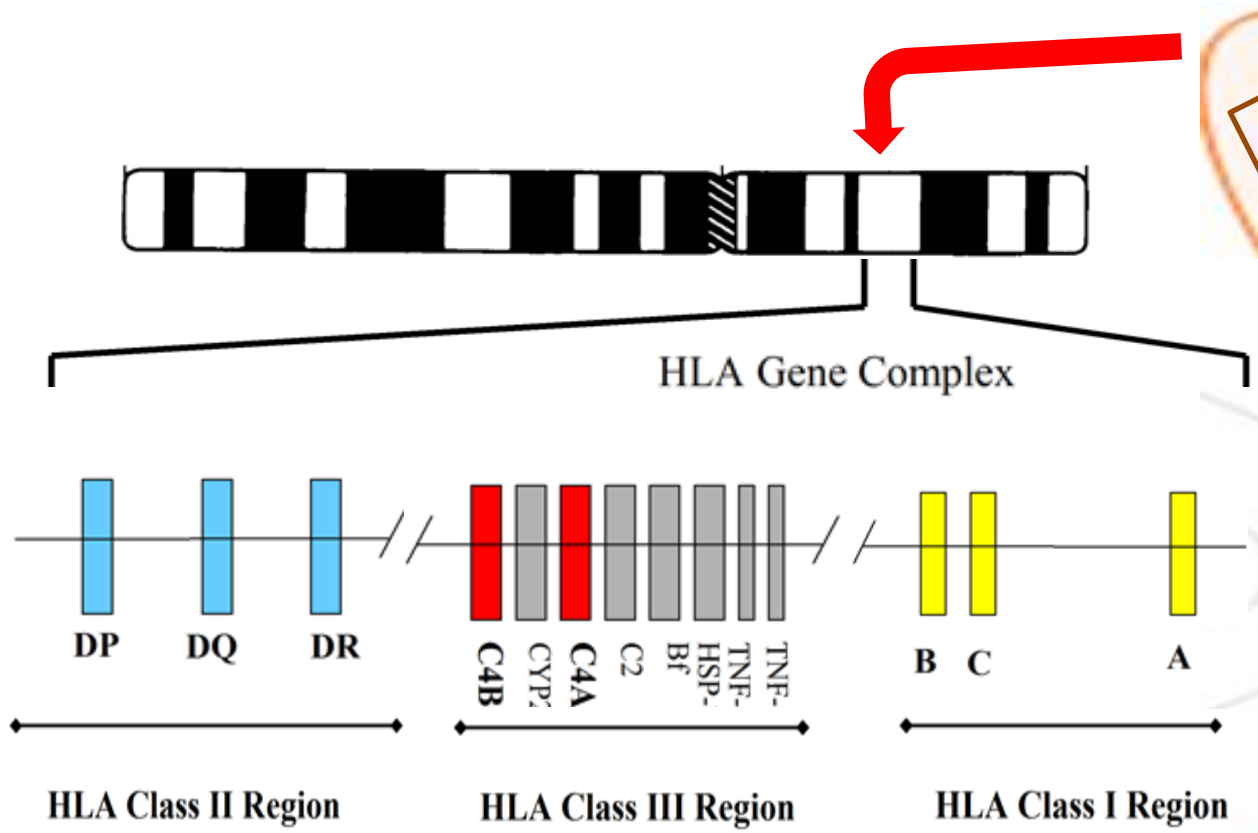
MHC genes in humans are found on the short arm of **chromosome 6** and are divided into three categories or classes.

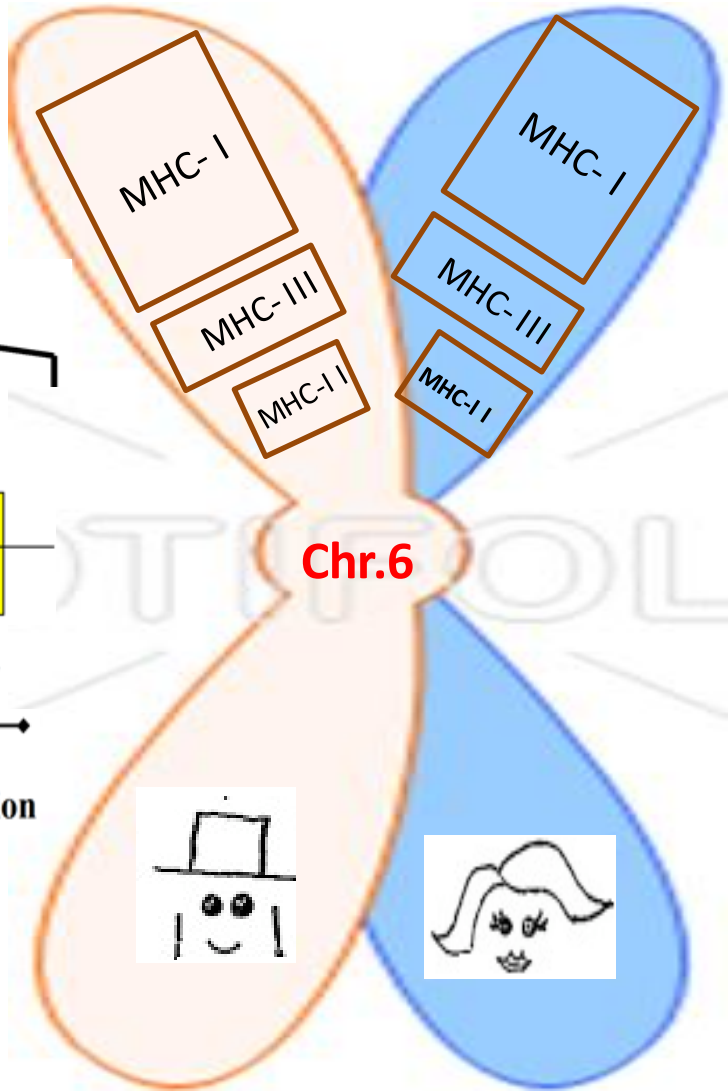
1. Class I molecules genes are coded for at three different locations or loci, termed A, B, and C. with Multiple alleles, expressed by all tissue cells
2. Class II genes are situated in the D region, and there are several different loci, known as DR, DQ, and DP. with Multiple alleles. Expressed mainly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

MHC genes (alleles)

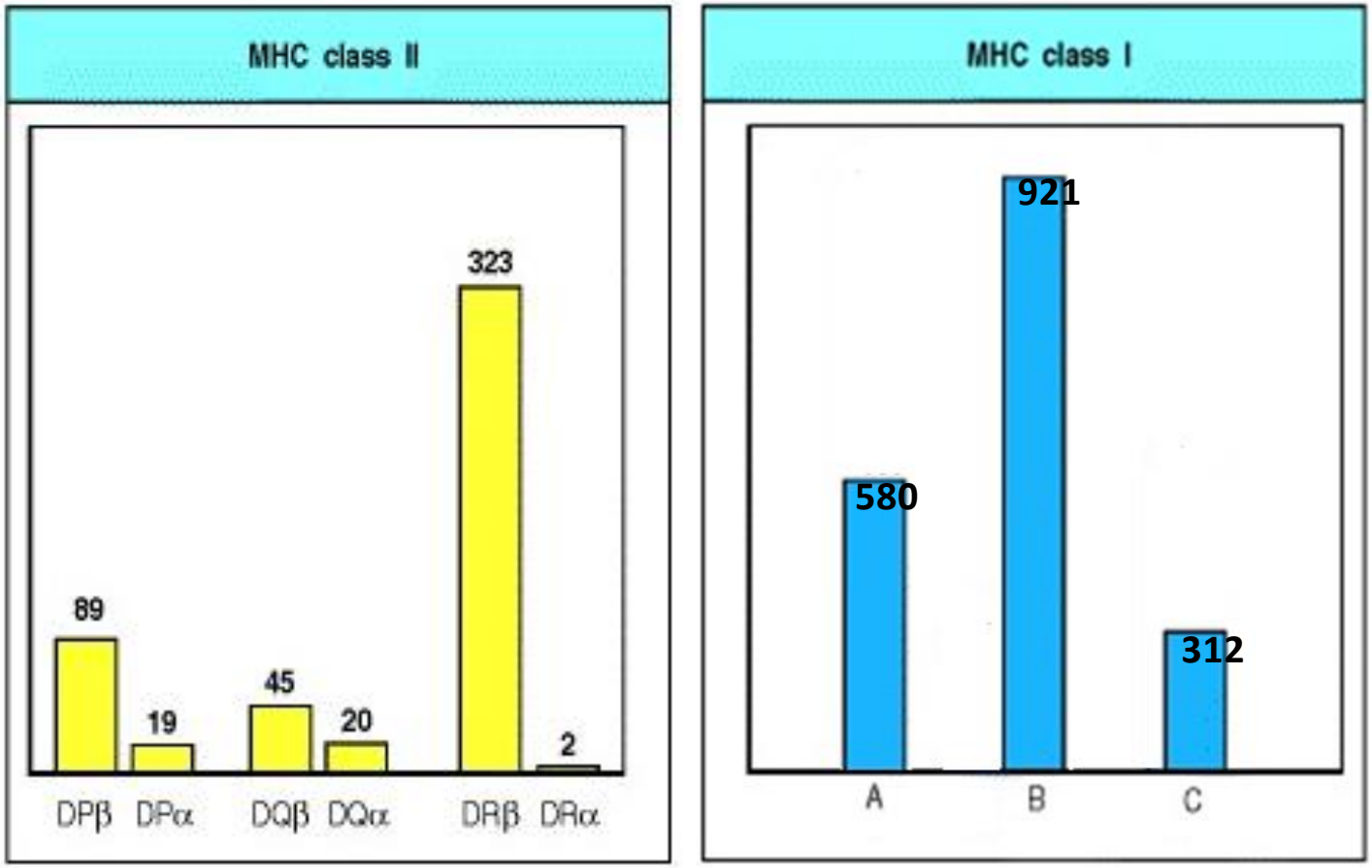
Inheritance of MHC genes

- ✓ Multiple allele are present at each of MHC gene





Human MHC Class 1 and 2 genes are highly polymorphic



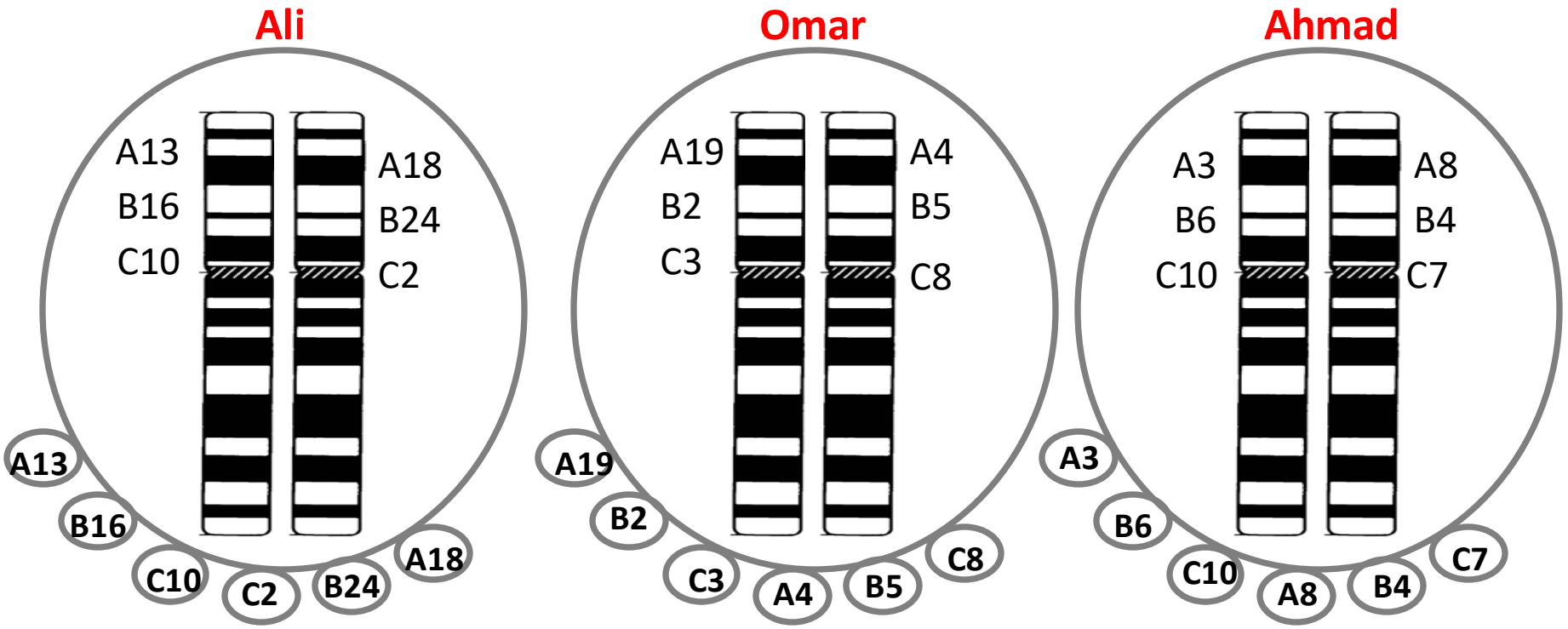
-MHC alleles are expressed in codominant fashion

- 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

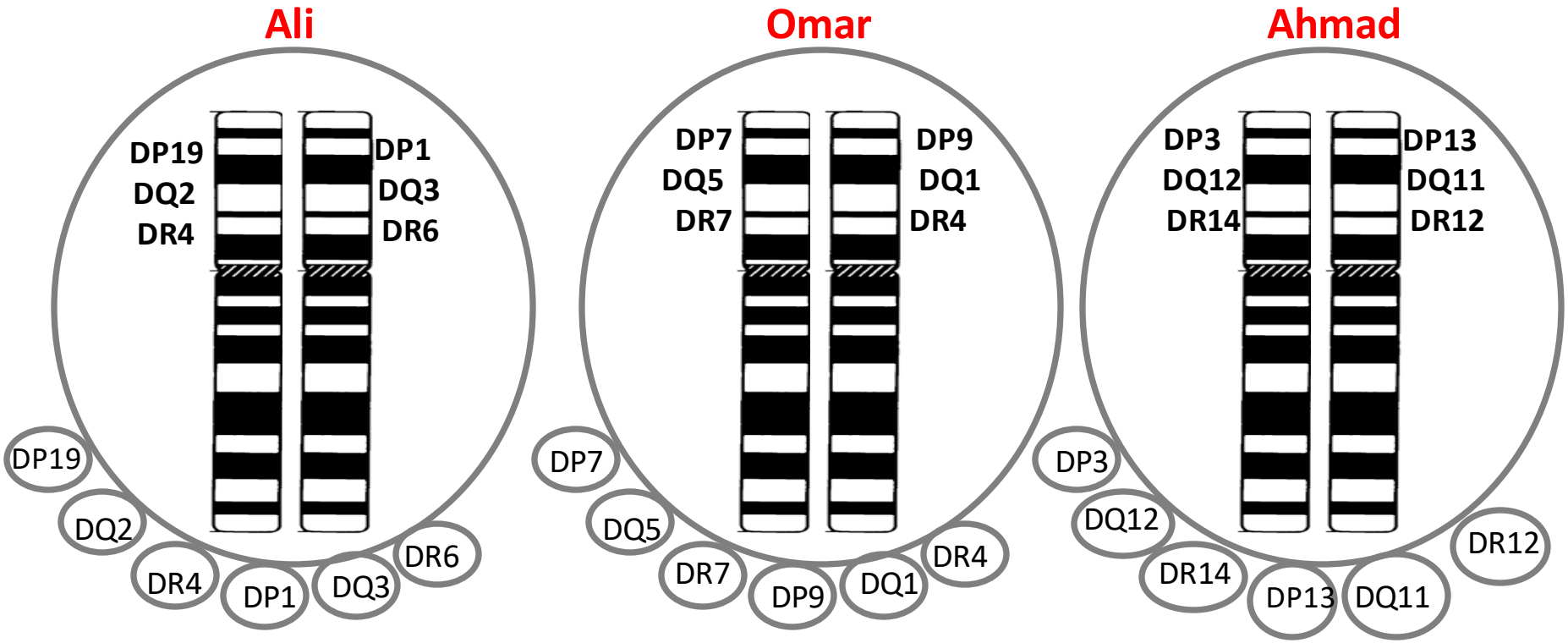
MHC-I

Inheritance of MHC-I



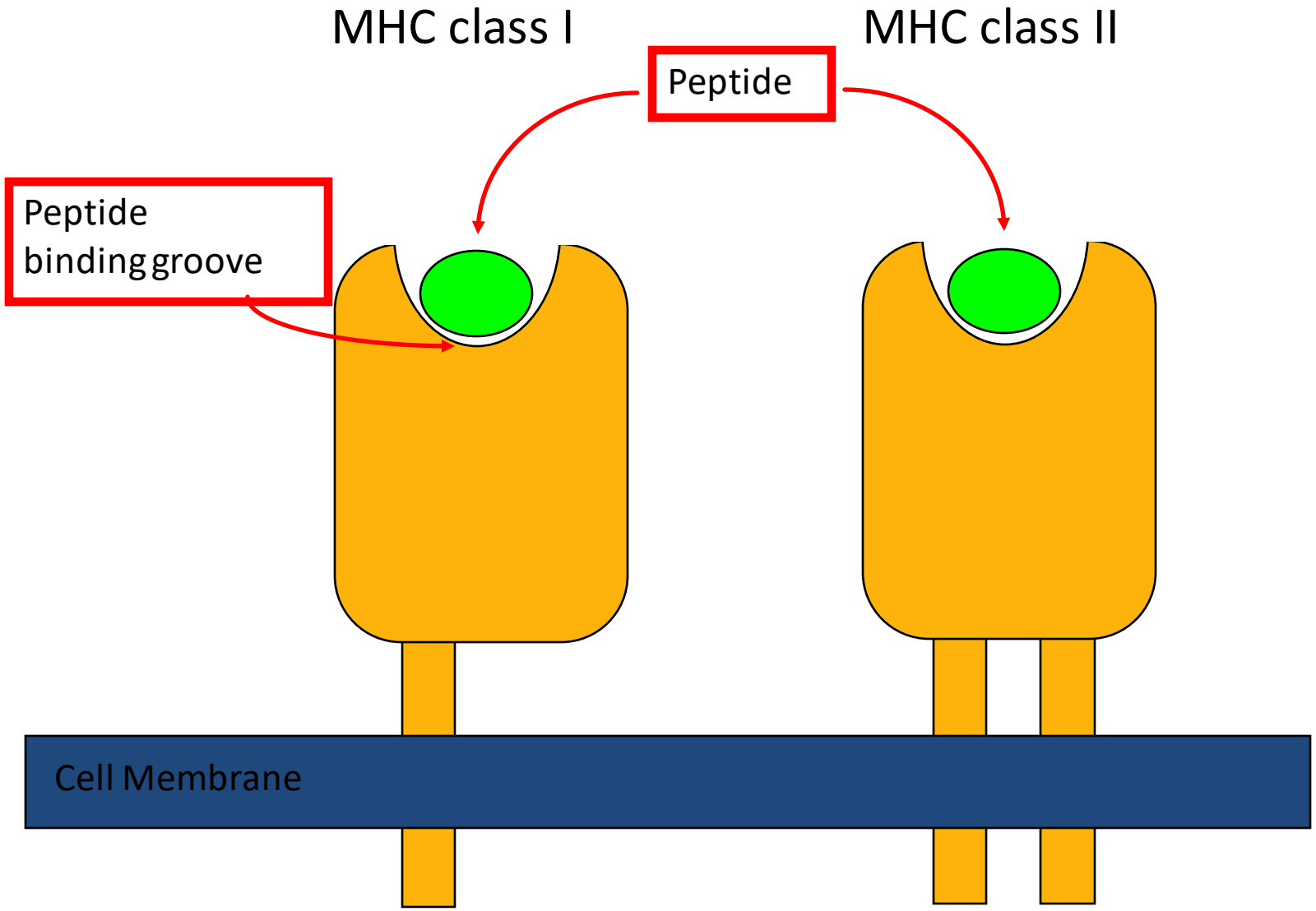
MHC-II

Inheritance of MHC-II



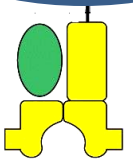
MHC-II

MHC-I vs. MHC- II

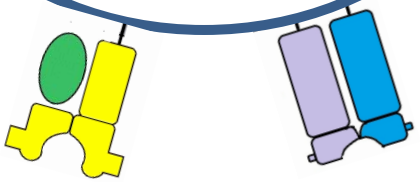


Expression of MHC molecules

All nucleated cells express MHC1

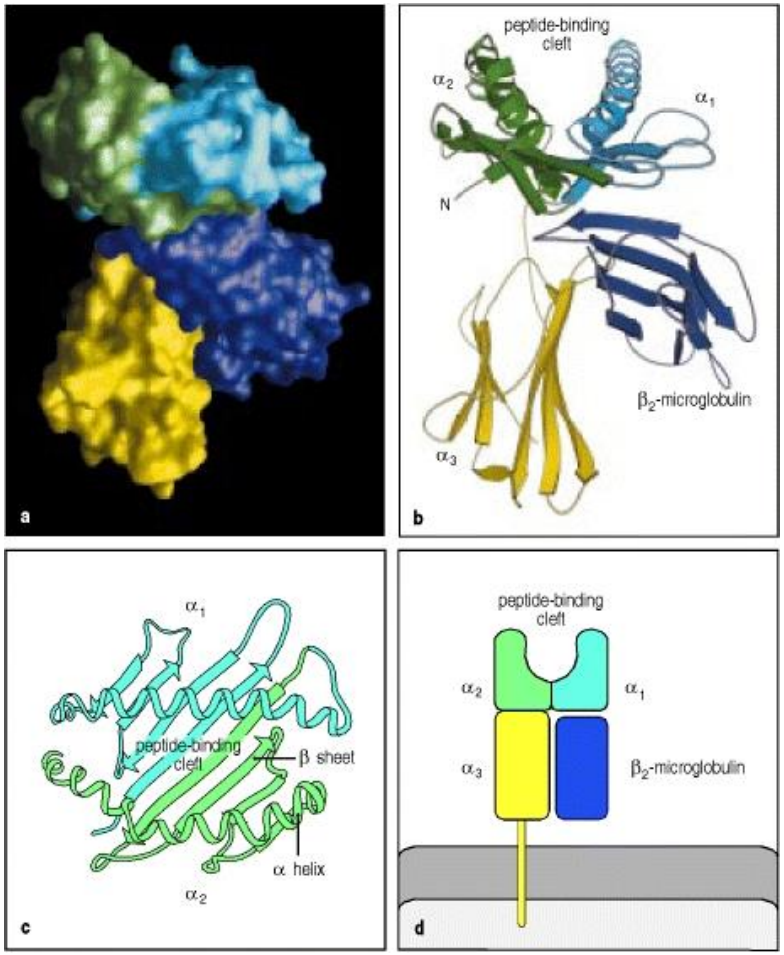


APC can express both MHC1 & MHC2



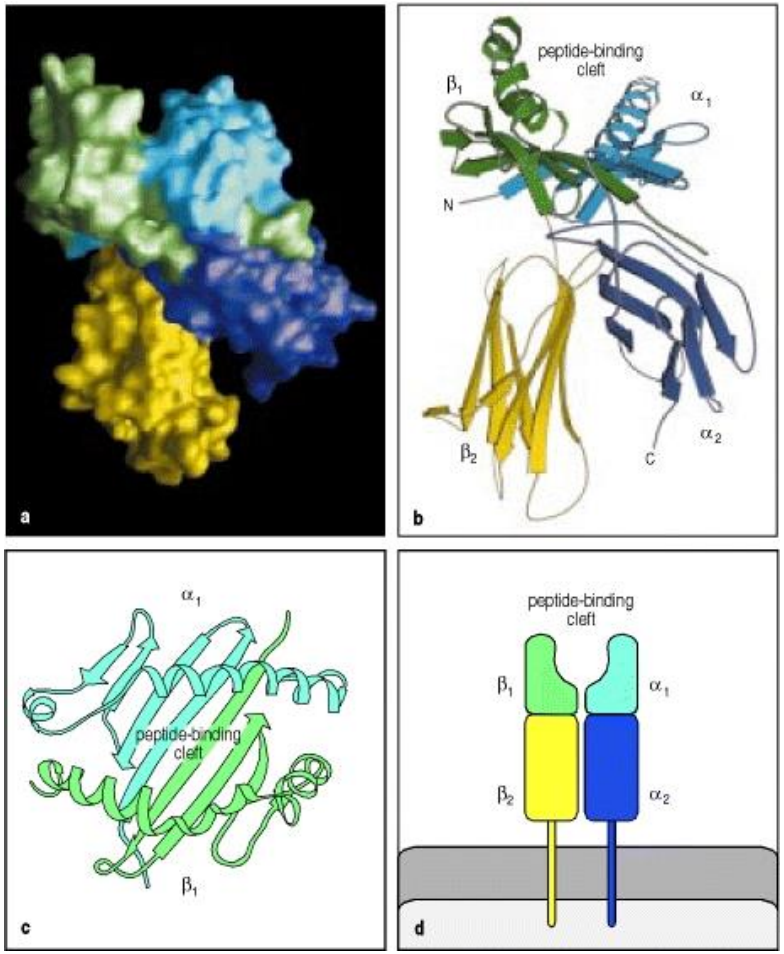
MHC 1 protein structure

- Four domains; Heavy chain (α1, α2, α3) ß2 microlobulin, transmembrane and cytoplasmic tail
- Hypervariable parts are α1, α2.
- α3 is the constant region bind CD8
- Transmembrane and cytoplasmic tail



MHC 2 protein structure

- Four domains; α1, α2, ß1, ß2
- Hypervariable parts are α1, ß1.
- ß2 is the constant region bind CD4
- Transmembrane and cytoplasmic tail



Functions of MHC molecules

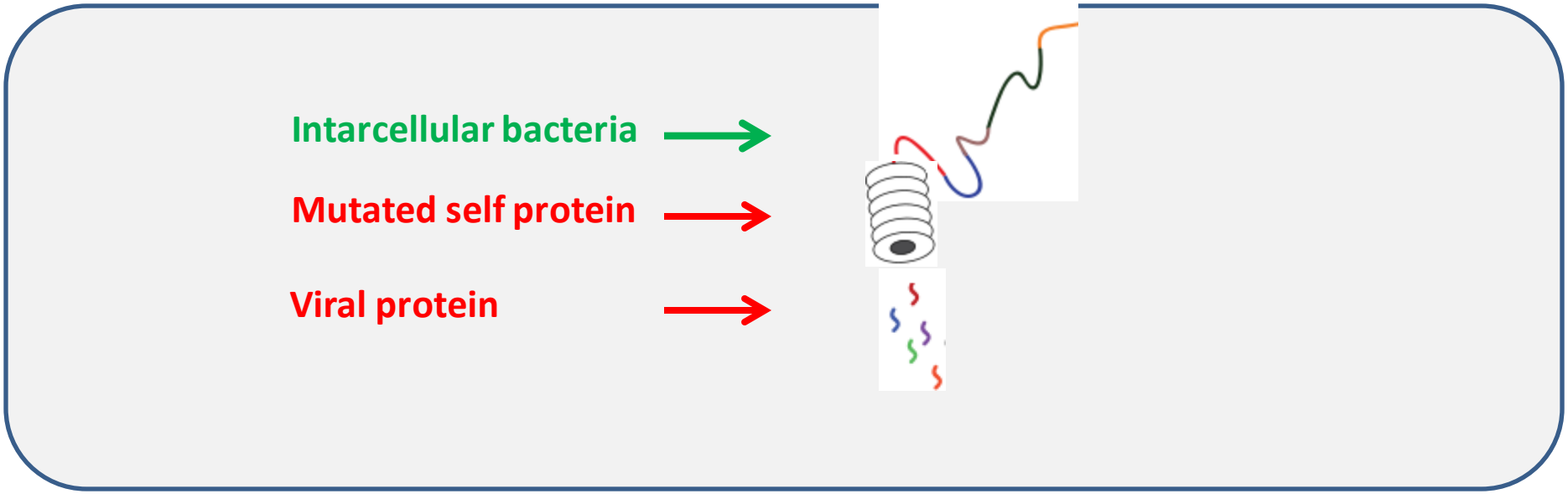
I. Their products play role in discriminating self/non-self
II. Participate in both humoral and cell-mediated immunity
III. MHC Act As Antigen Presenting Structures
IV. Genes Of MHC Organized In 3 Classes
    - Class I MHC genes
        - Glycoproteins expressed on all nucleated cells
        - Major function to present processed Ags to T_C
    - Class II MHC genes
        - Glycoproteins expressed on APC such as MΦ, 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

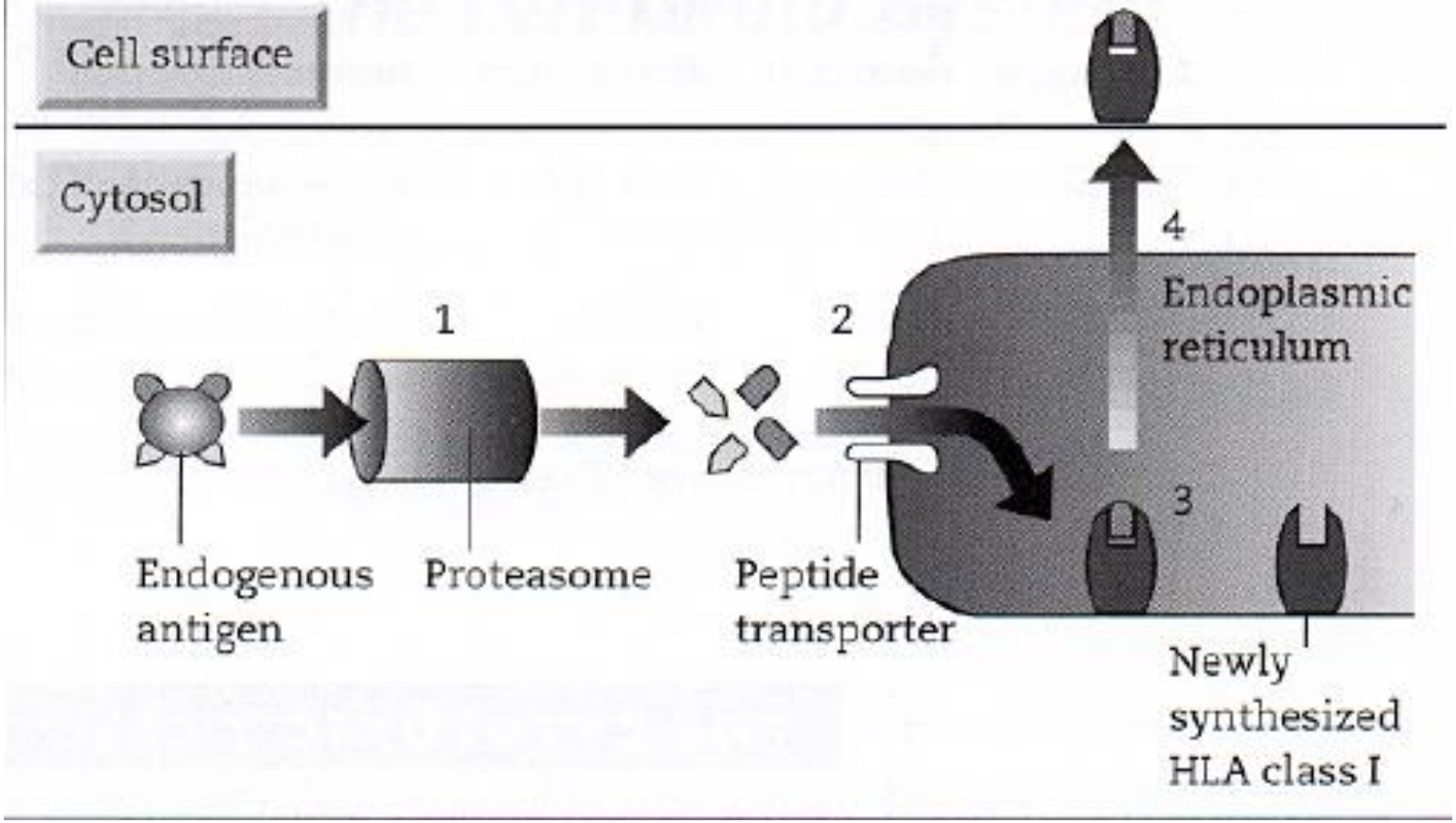
Express all Types of endogenous proteins synthesized, live and multiply in the human cells cytoplasm including:

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

A small amount of these proteins are directed to the proteosome 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)

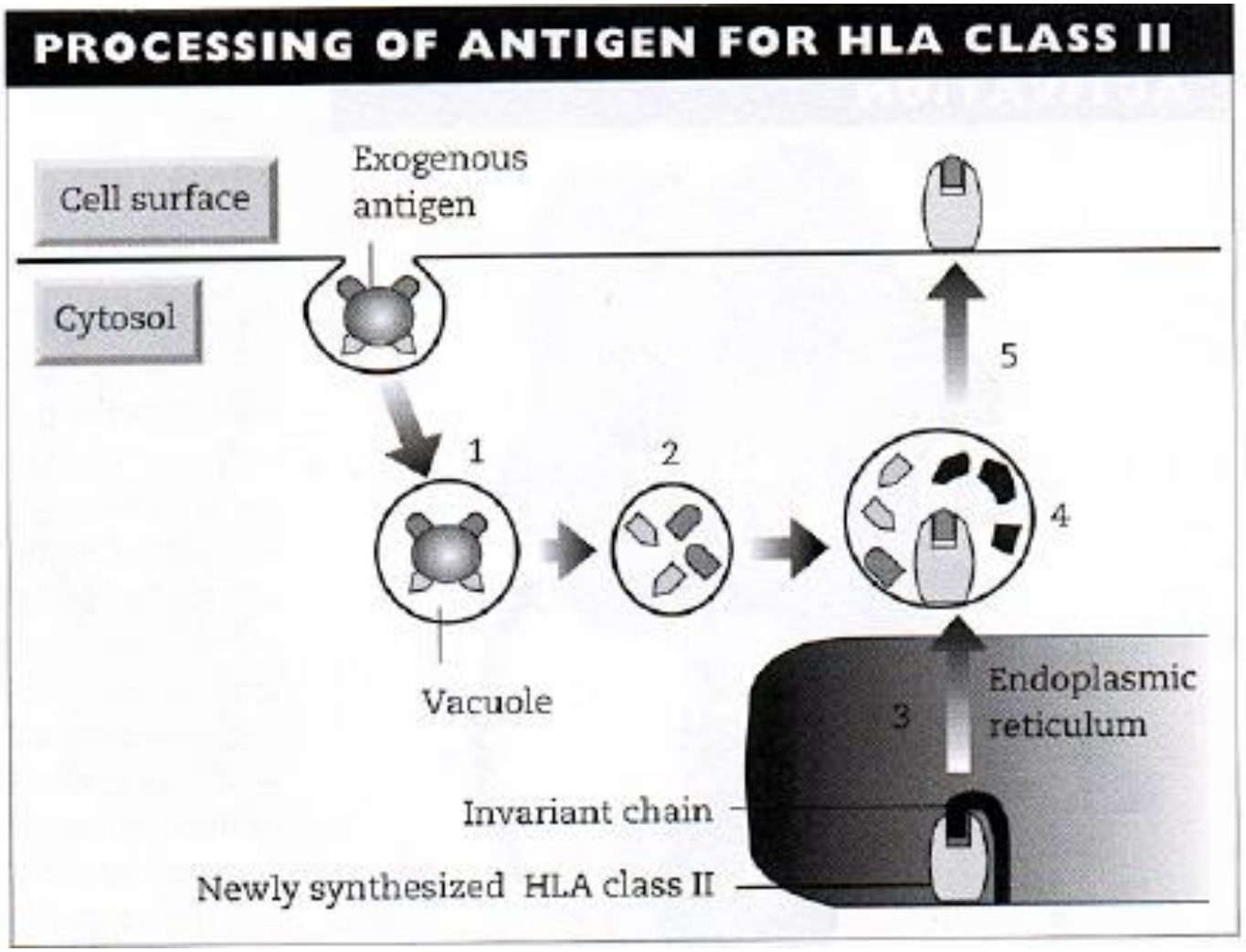


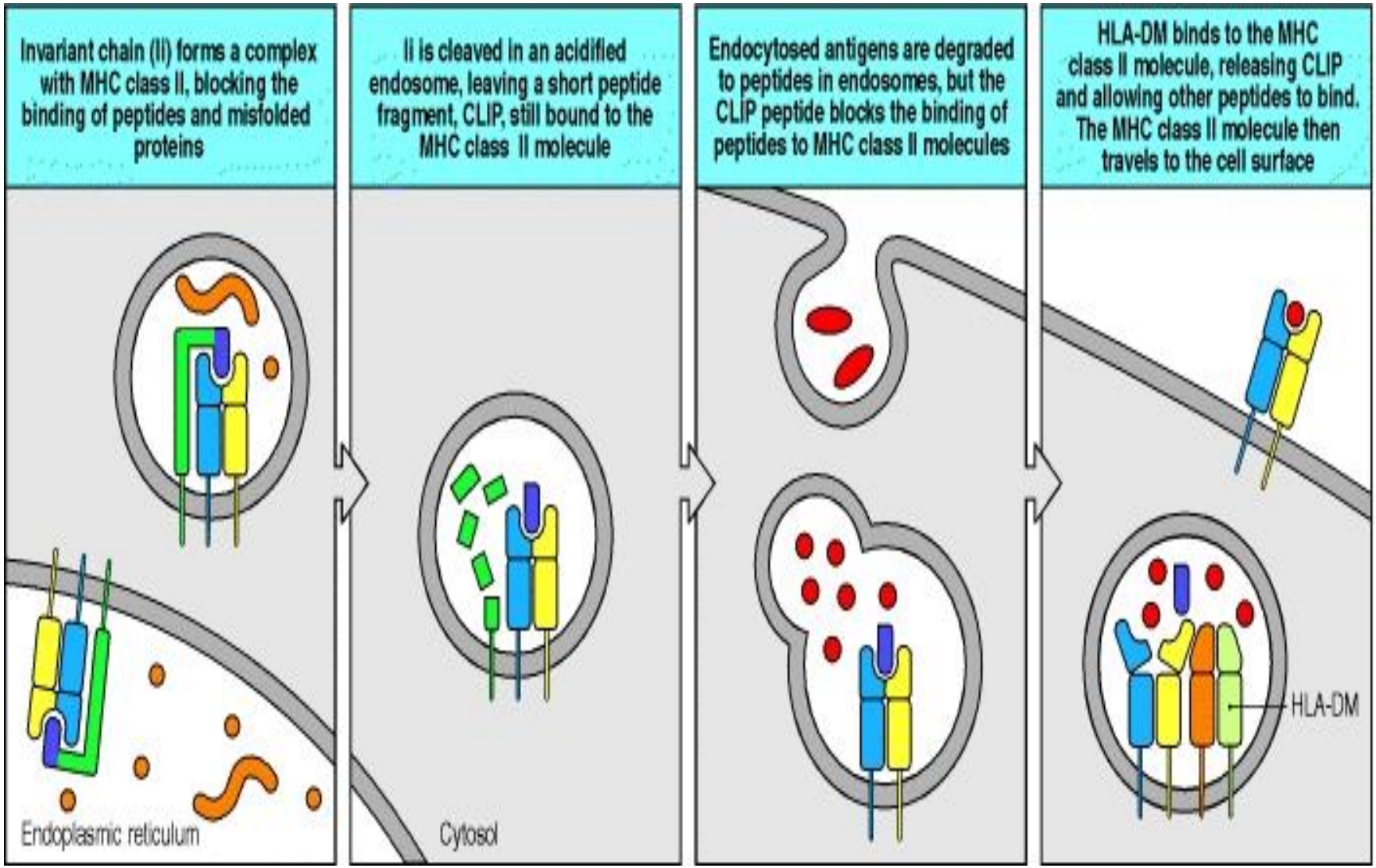
PROCESSING OF ANTIGEN FOR HLA CLASS I



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 in endoplasmic reticulum moved the 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.

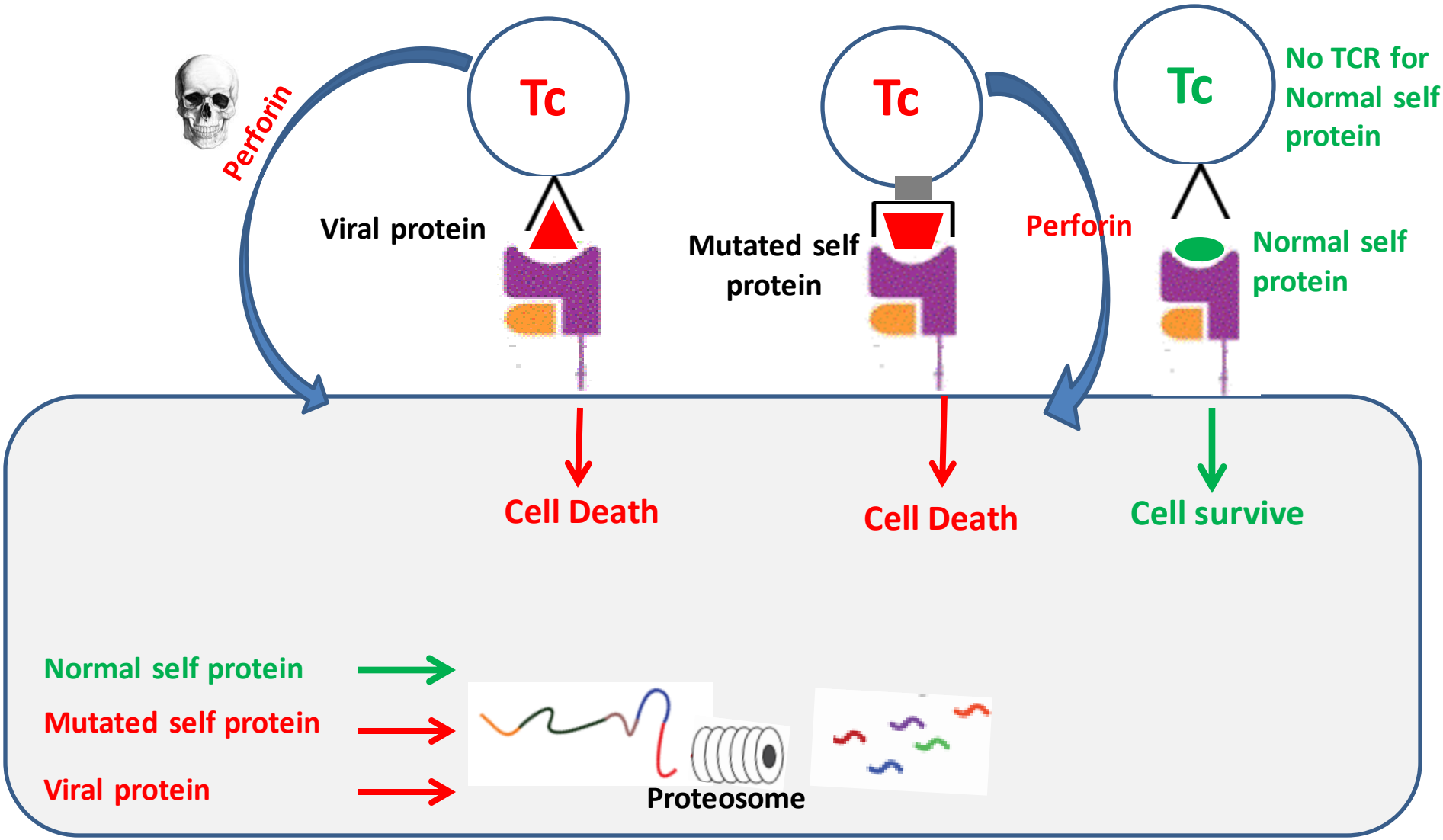

PROCESSING OF ANTIGEN FOR HLA CLASS II
Cell surface
Cytosol
Exogenous antigen
1
2
3
4
5
Vacuole
Endoplasmic reticulum
Invariant chain
Newly synthesized HLA class II

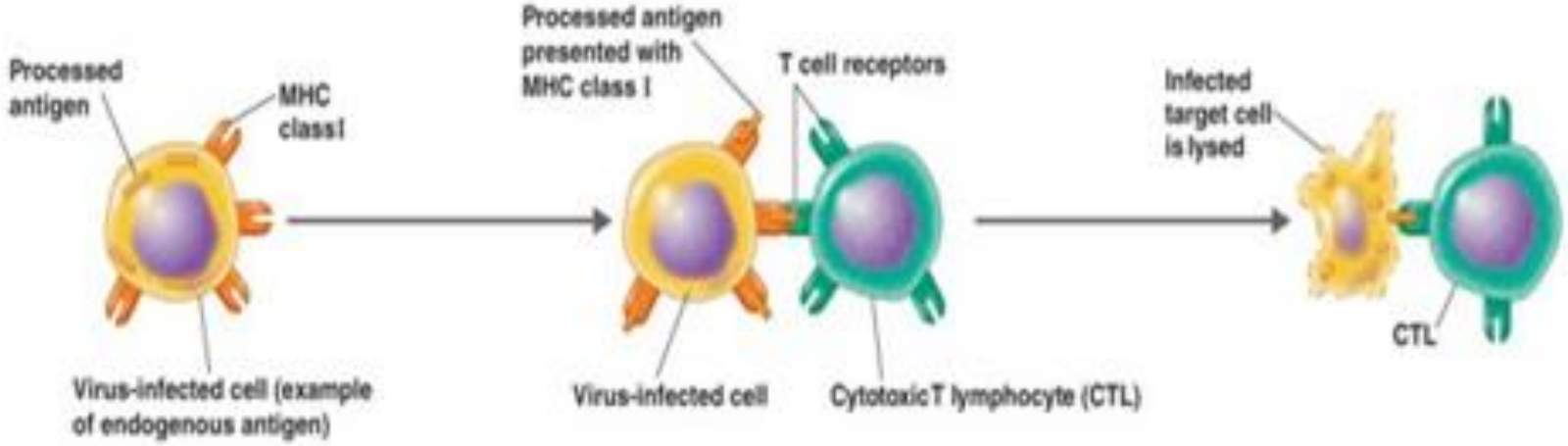

Invariant chain (Ii) forms a complex with MHC class II, blocking the binding of peptides and misfolded proteins
Ii is cleaved in an acidified endosome, leaving a short peptide fragment, CLIP, still bound to the MHC class II molecule
Endocytosed antigens are degraded to peptides in endosomes, but the 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
Endoplasmic reticulum
Cytosol
HLA-DM

Functions of MHC-I molecules

MHC-I molecules

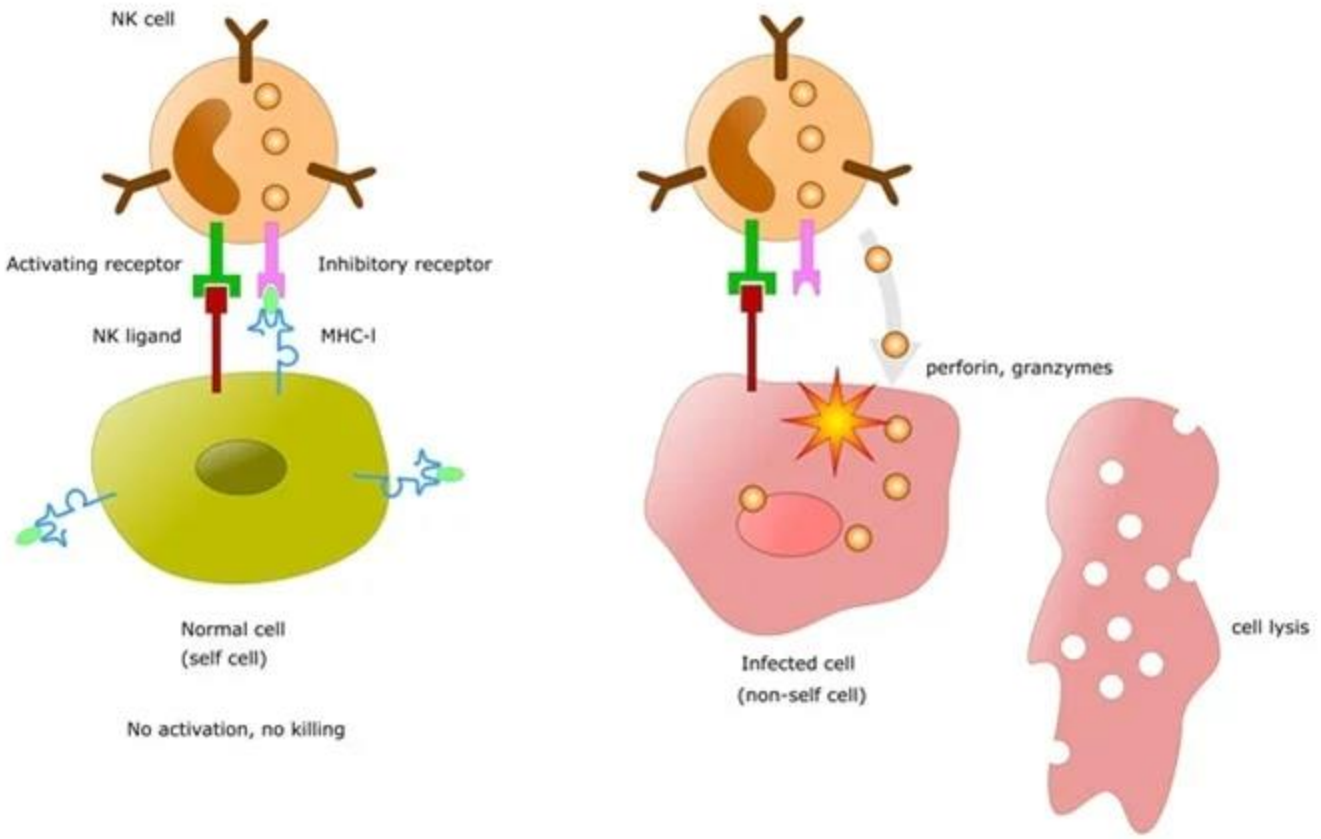
1. Antigen presentation to CTL to check the normal expression of cellular proteins
2. NK to check the normal expression of cellular proteins by their KIR





1. A normal cell will not trigger a response by a cytotoxic T lymphocyte (CTL), but a virus-infected cell (shown here) or a cancer cell produces abnormal endogenous antigens.
2. The abnormal antigen is presented on the cell surface in association with MHC class I molecules. $CD8^+$ T cells with receptors for the antigen are transformed into CTLs.
3. The CTL induces destruction of the virus-infected cell by apoptosis.

NK


NK cell
Activating receptor
Inhibitory receptor
NK ligand
MHC-I
Normal cell
(self cell)
No activation, no killing
perforin, granzymes
Infected cell
(non-self cell)
cell lysis

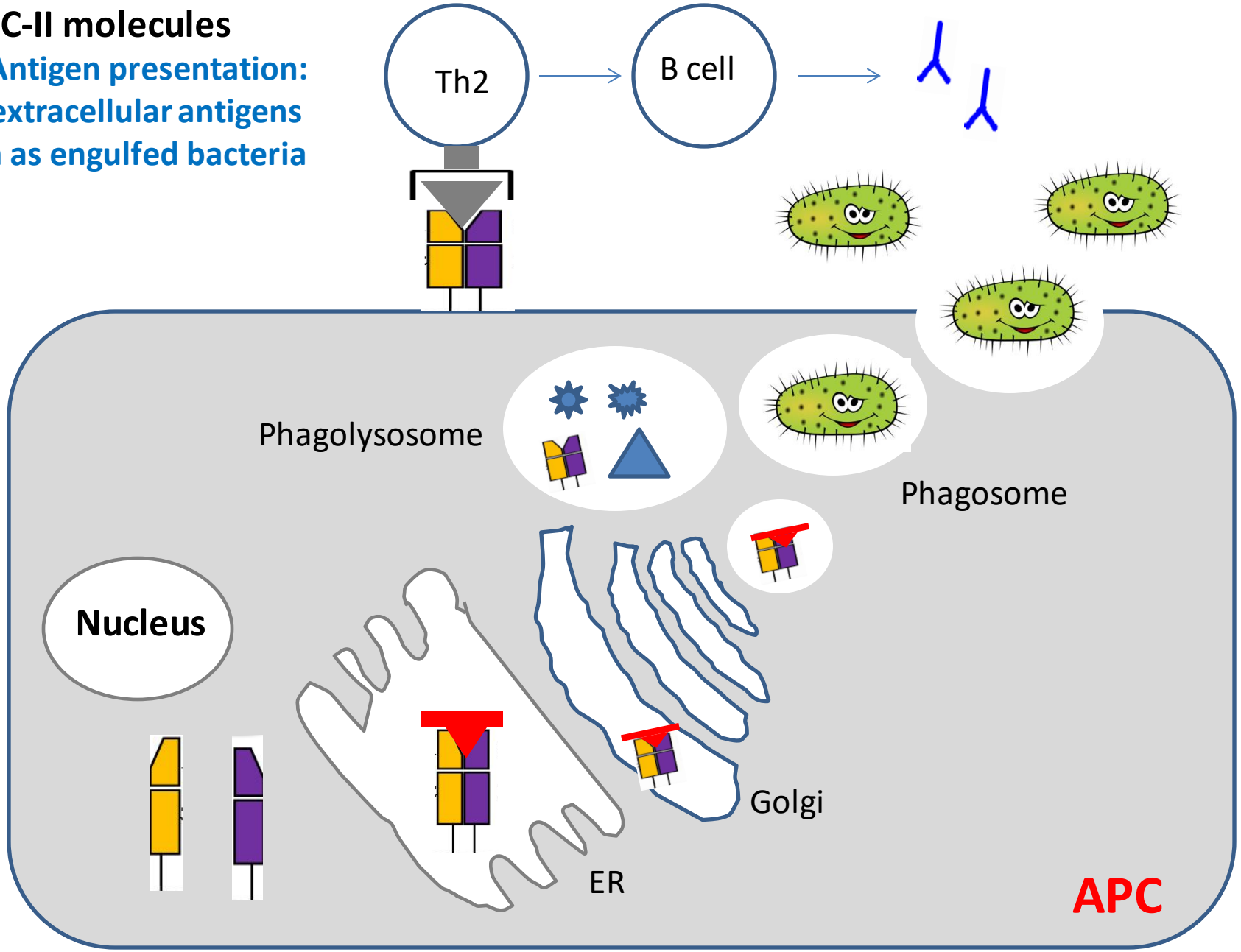
Functions of MHC-II molecules

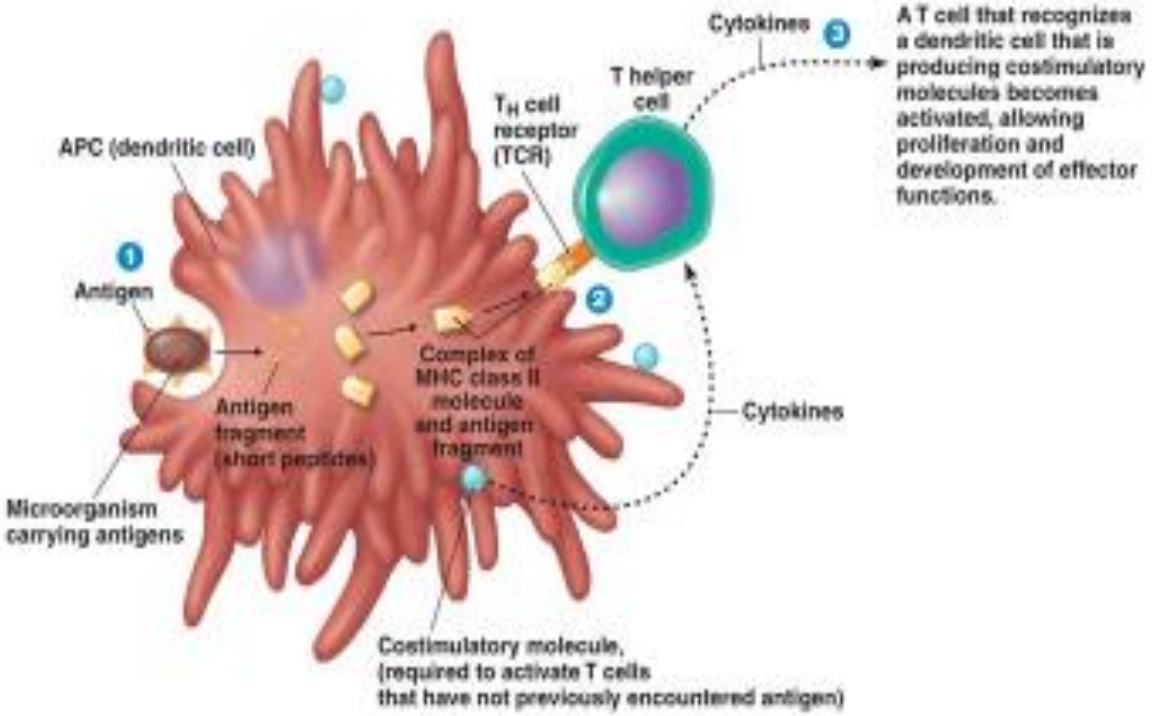
MHC-II molecules

1. Antigen presentation:

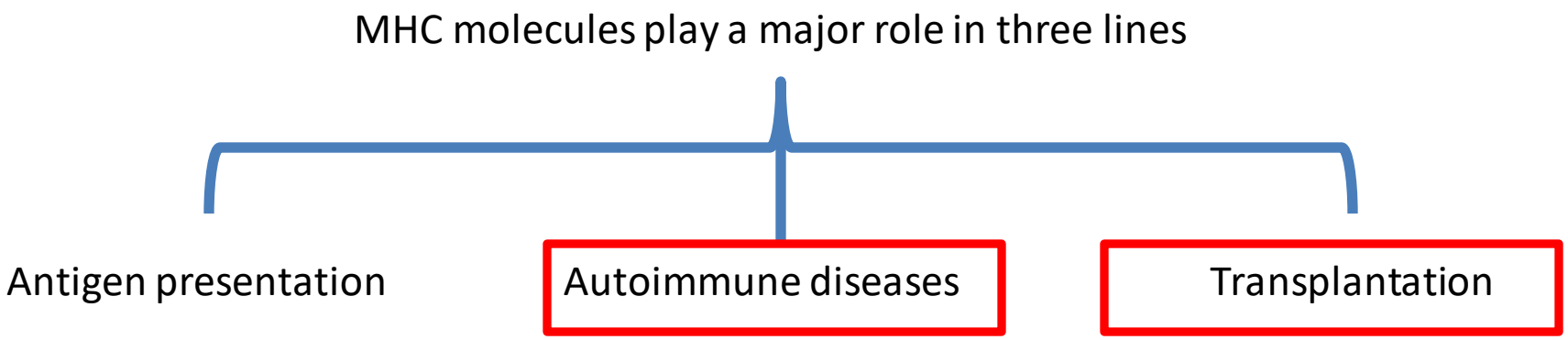
For extracellular antigens

Such as engulfed bacteria



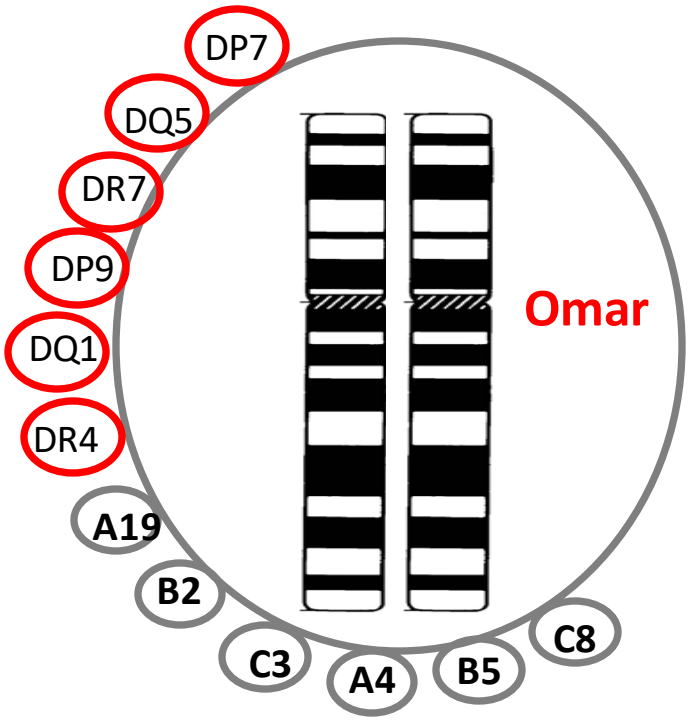

Cytokines
3
A T cell that recognizes a dendritic cell that is producing costimulatory molecules becomes activated, allowing proliferation and development of effector functions.
T helper cell
T_H cell receptor (TCR)
APC (dendritic cell)
1
Antigen
2
Complex of MHC class II molecule and antigen fragment
Antigen fragment (short peptides)
Cytokines
Microorganism carrying antigens
Costimulatory molecule, (required to activate T cells that have not previously encountered antigen)

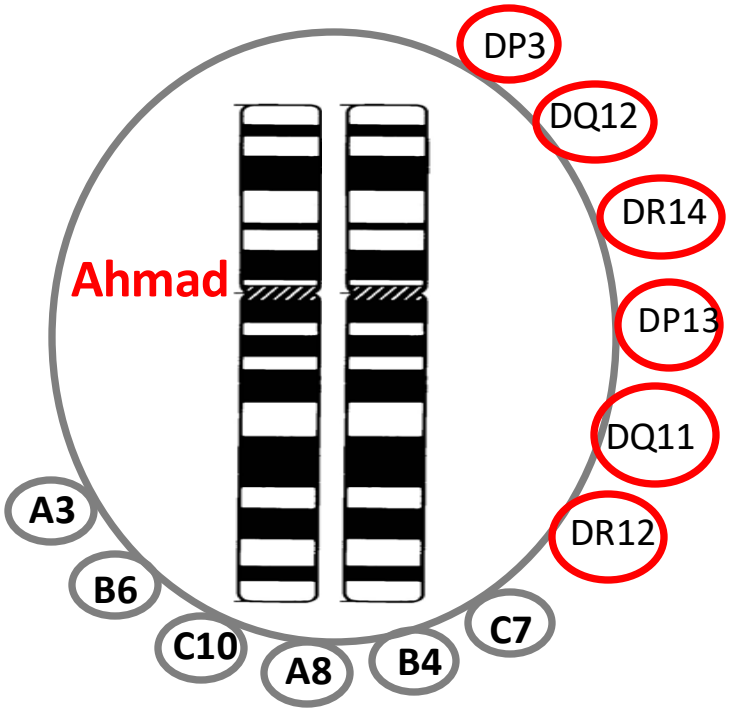
Biological Importance of MHC

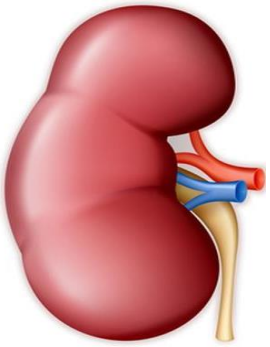


Functions of MHC molecules

2- Transplantation







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

Rejected

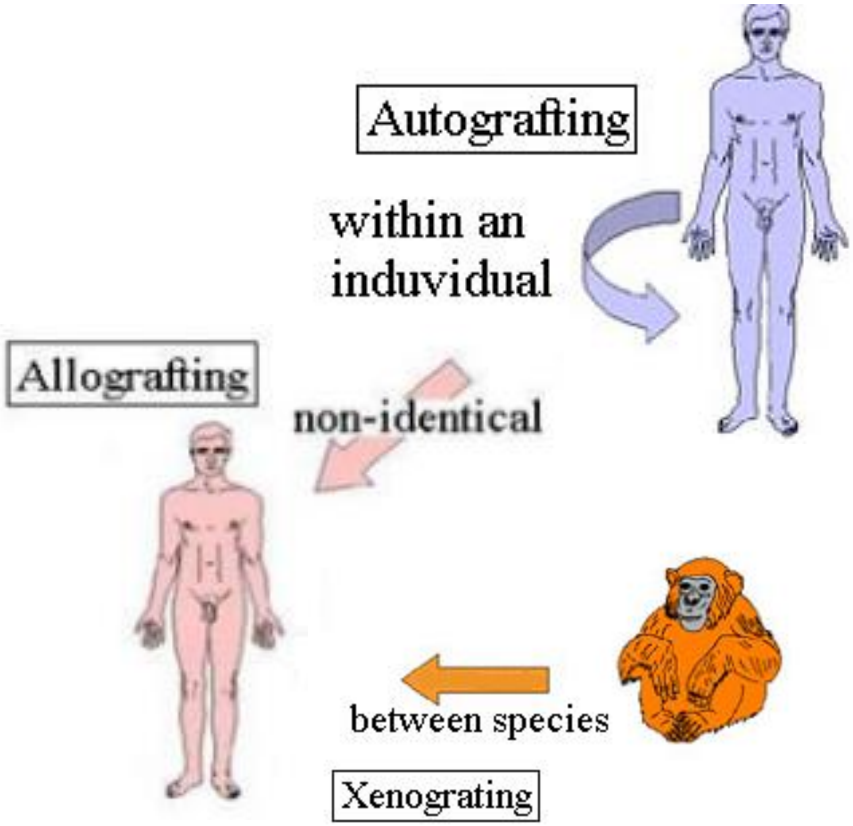
Functions of MHC molecules

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 MHC antigens and RBC antigens of the recipient, to minimize antigen disparities
  - requires donor and recipient cells to be identified for MHC and ABO-RH antigens
- Cross-matching: testing the SERUM of the recipient for antibodies against the donor antigens, if present no donation

❖Tissue typing or HLA typing

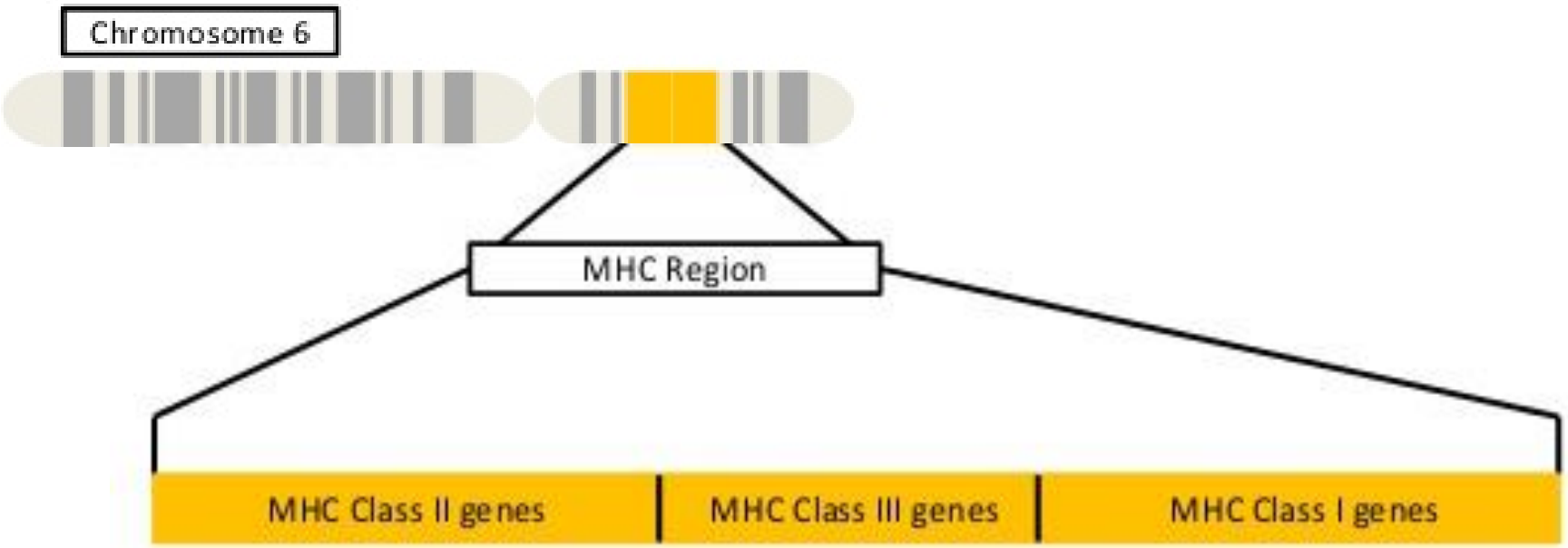
A. Mixed lymphocyte reaction (MLR) mixed leukocytes from donor and recipient in culture; can be used to assess the degree of major histocompatibility complex (MHC) class I and class II compatibility. In mismatch; DNA synthesis and cellular proliferation

B. Molecular HLA typing. (genotyping of the transplanted epitope)

C. In the lymphocytotoxicity assay, recipient sera are tested for reactivity with donor lymphocytes. A positive crossmatch is a contraindication to transplantation

D. Panel-reactive antibody (PRA) lab specialist will test a patient's blood (serum) against lymphocytes (white blood cells) obtained from a panel of about 100 blood donors. test that quantifies the risk of transplant rejection. A high PRA usually means that the individual is sensitized and high percentage of rejection may occure

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

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

Than You