THE MAJOR HISTOCOMPATIBILITY COMPLEX

-- The **success** of tissue and organ **transplants** depends on the donor's and recipient's **human leukocyte antigens (HLA)** encoded by the **HLA genes**.

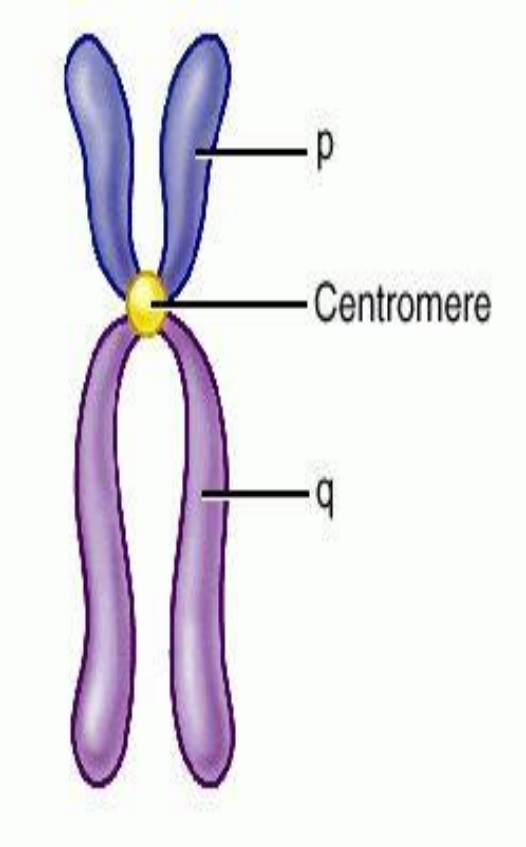
-- These genes **differ** among **members of the same species** and are called **alloantigens**.

-- If **HLA genes differ** between donor and recipient, an **immune response** occurs.

Alloantigen: An antigen that occurs in some (not all) individuals of the same species. Examples are the human blood group antigens.

-- The genes for HLA proteins are clustered in the **major histocompatibility complex (MHC)** located on the **short (p) arm of chromosome 6.**

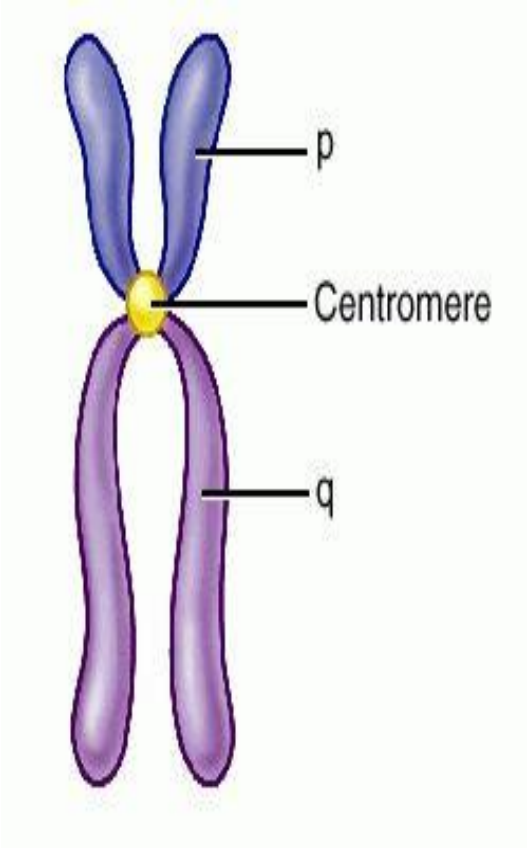
-- There are **23 pairs (46)** of chromosomes in humans.

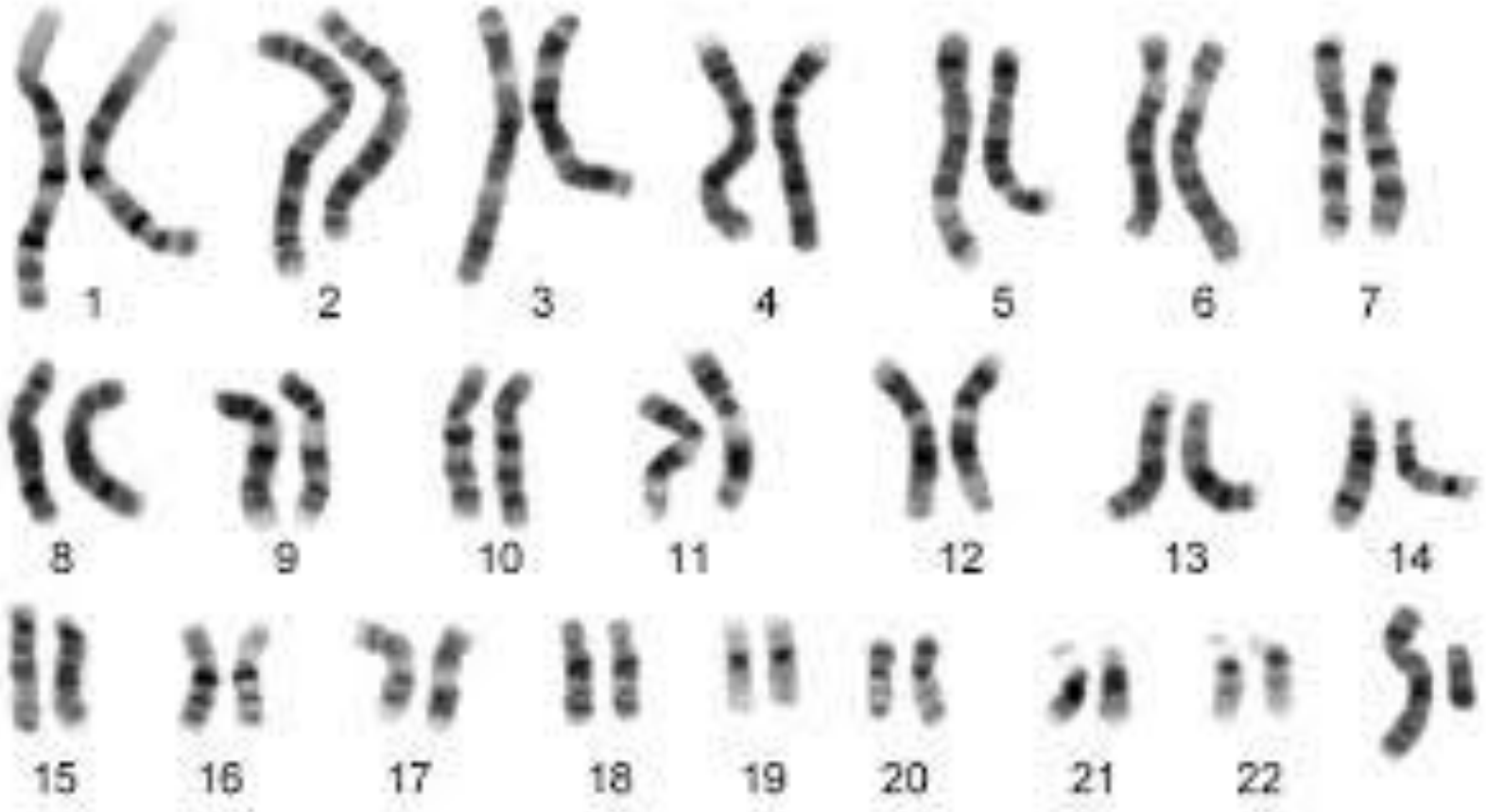


A **chromosome** is a threadlike structure of **nucleic acids** and **protein** found in the nucleus of most living cells, carrying genetic information in the form of genes.

All human **chromosomes** have 2 **arms-** the **p** (short)**arm** and the **q** (long) **arm.**

These arms are separated from each other only by a primary constriction, the **centromere**, the point at which the **chromosome** is attached to the spindle during cell division.





Human Chromosomes

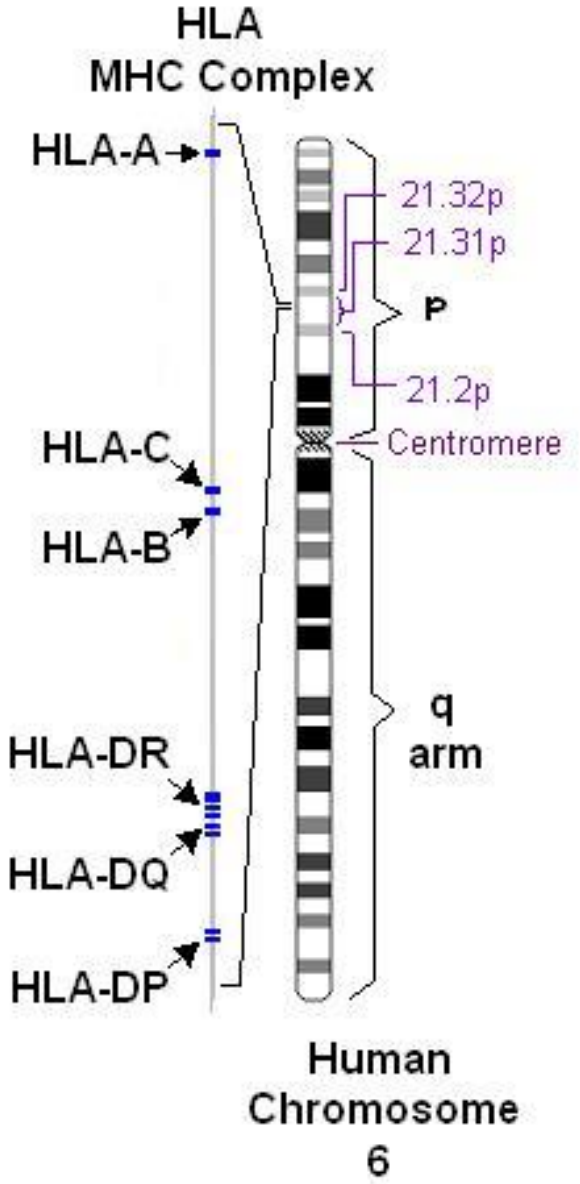
MHC Loci

In man and mouse, as in most species, **each class of MHC** is represented by **more than one locus (polygeny).**

In man this is called **HLA (Human Leucocyte Antigen) system**.

The **Class I loci** are **HLA-A, HLA-B,** and **HLA–C.**

Class II loci are **HLA-DR, HLA-DQ,** and **HLA-DP**.



-- The set of **linked MHC alleles** found on the **same chromosome** is called a **haplotype**.

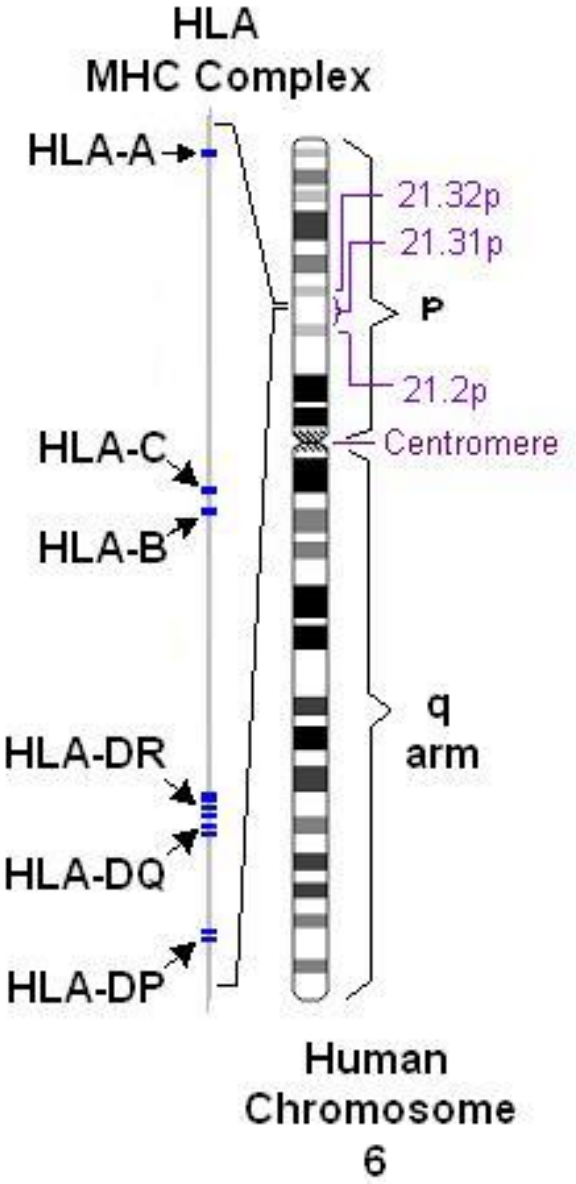
-- **Each** person has **two haplotypes** (**one paternal** and **one maternal** set).

-- All MHC loci are expressed **co-dominantly** (both the set of alleles inherited from one's father and the set inherited from one's mother are expressed on each cell).

-- In about 97% of cases the entire **linked MHC complex** is **inherited intact** from parent to offspring, i.e. without recombination.

These **HLA** genes are very **diverse (polymorphic).**

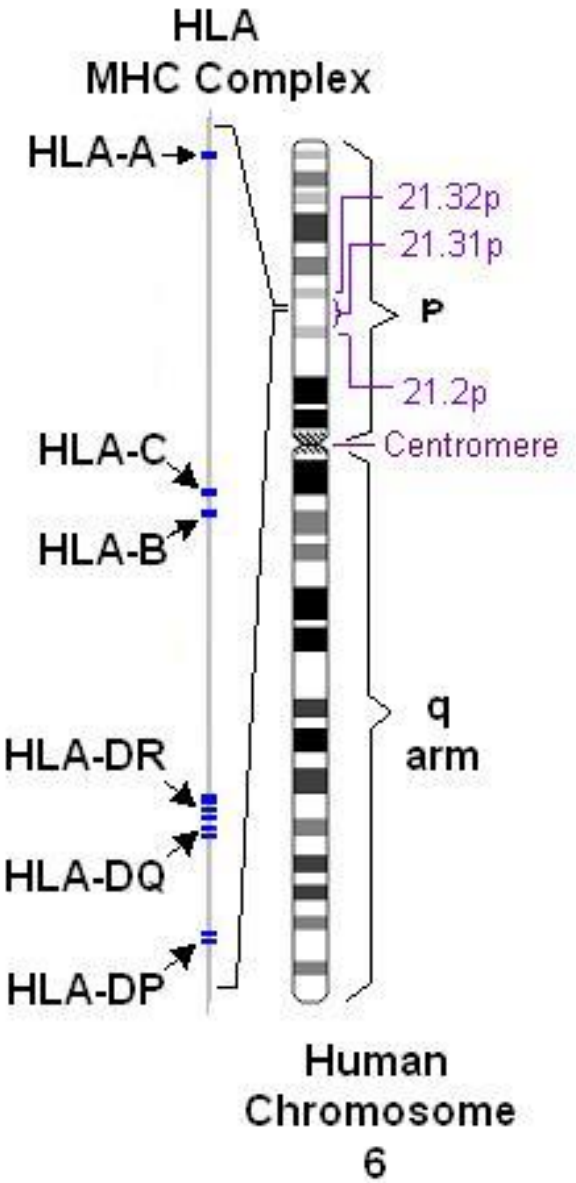
There are at least **47 HLA-A genes**, **88 HLA-B genes**, **29 HLA-C** and **300 HLA-D** genes.



Minor MHC loci

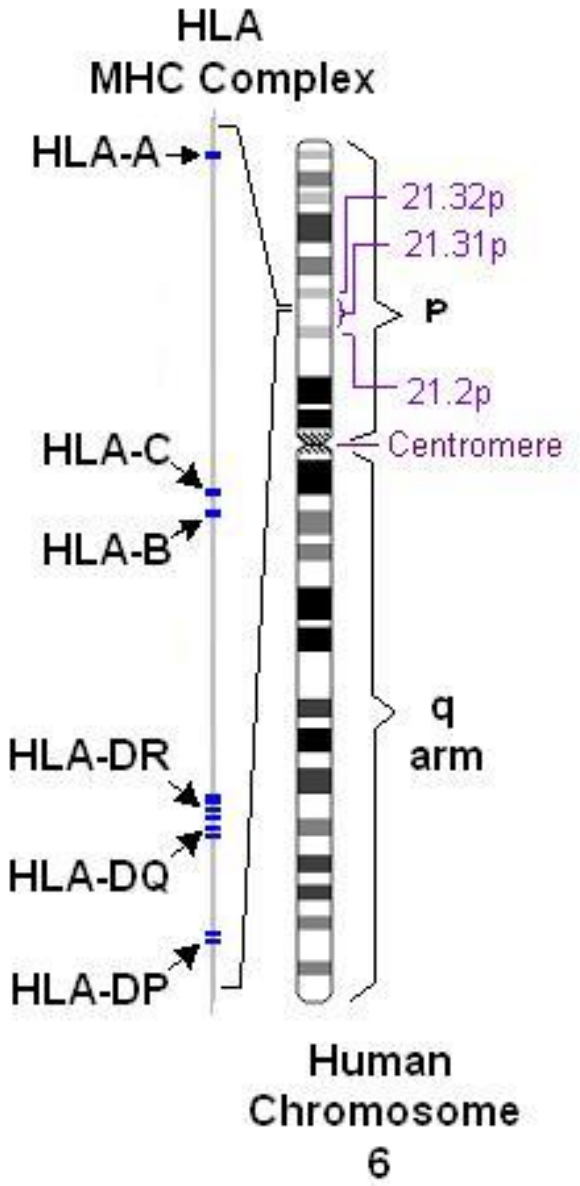
-- There also exist many **"minor“ histocompatibility loci** between the class I and class II gene loci **.**

-- Their products are **receptors** on the **cellular surface of donated organs** which also influence graft survival but which are **individually weak**.



-- The products can induce a **weak immune response** that can result in **slow rejection** of a graft.

-- The **products** of minor histocompatibility loci play an important role in **antigen recognition** by T cells.



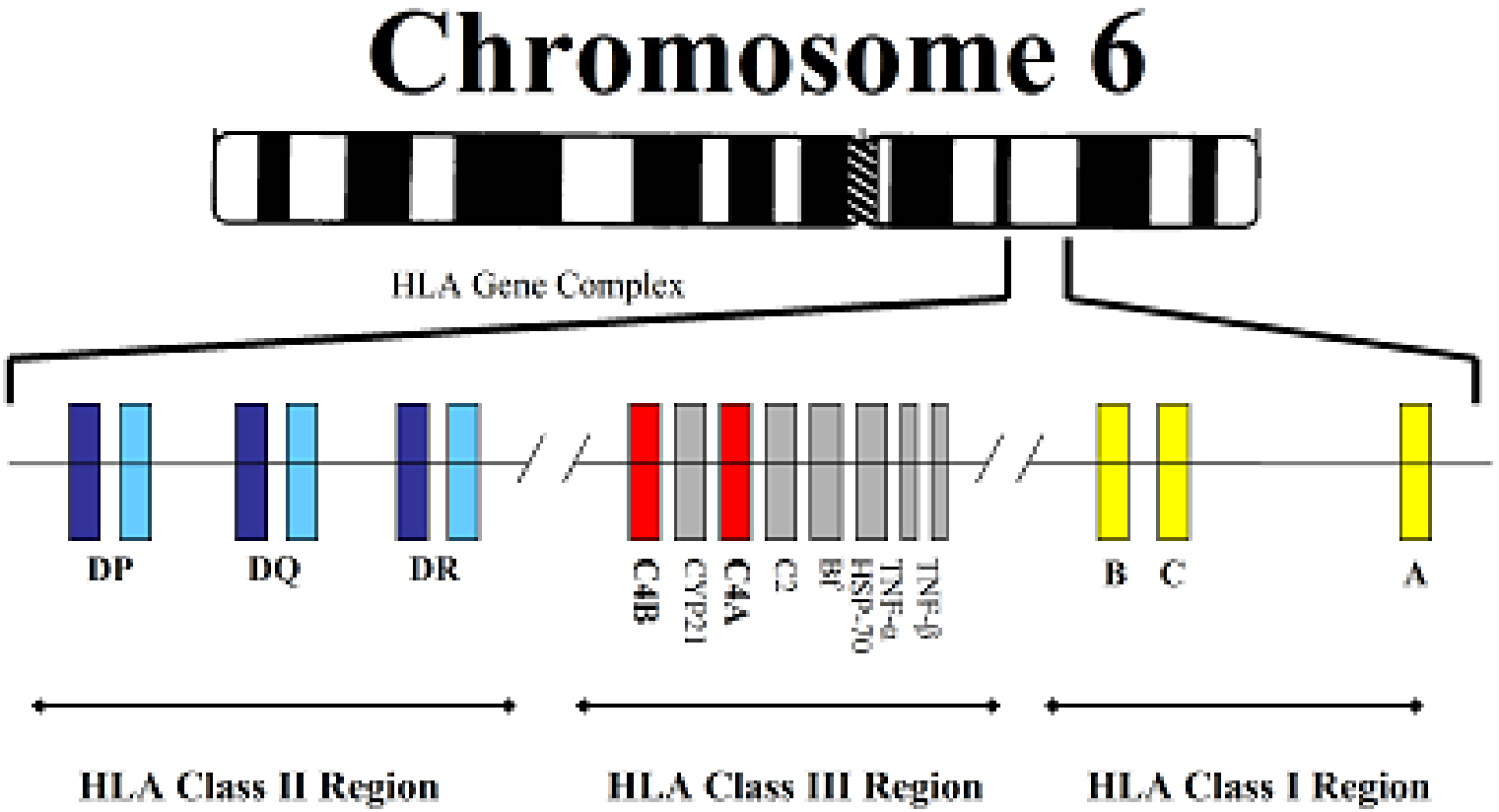
HLA class III

-- Between the class I and class II gene loci is also a **third** locus sometimes called **HLA class III**.

-- This locus contains several **immunologically important** genes.

-- These include genes encoding for **two** *cytokines* **tumor necrosis factor** and **lymphotoxin**, and **two** *complement* components **C2** and **C4**.

-- It **does not** have any genes for **histocompatibility antigens.**


Chromosome 6
HLA Gene Complex
DP
DQ
DR
C4B
CYP21
C4A
C2
BF
HSP-70
TNF-a
TNF-b
B
C
A
HLA Class II Region
HLA Class III Region
HLA Class I Region

Comparison of Class I and Class II MHC Proteins

Feature	Class I MHC	Class II MHC
Present antigen to CD4+ T cells	No	Yes
Present antigen to CD8+ T cells	Yes	No
Found on surface of all nucleated cells	Yes	No
Found on surface of professional APCs	Yes	Yes
Encoded by genes in the HLA locus	Yes	Yes
Expression of genes is codominant	Yes	Yes
Multiple alleles at each gene locus	Yes	Yes

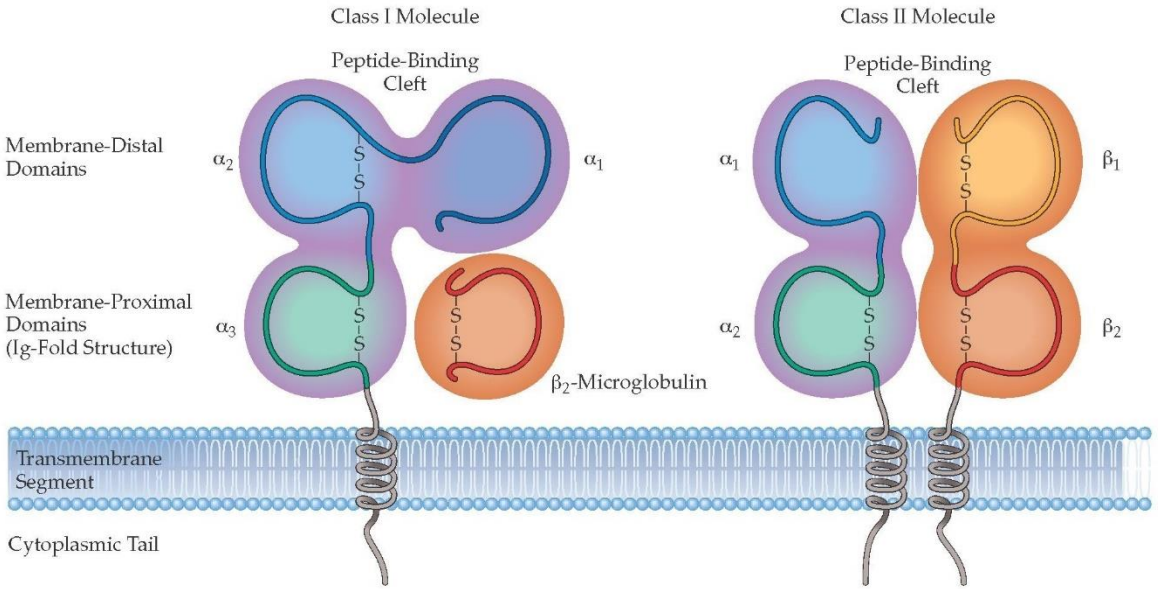
Structure of MHC proteins

-- The **MHC genes** and their **products** are grouped into **2 classes Class I** and **II** on the basis of their **chemical structure** and **biological properties**.

-- The **Class I** and **II molecules** have a **similar secondary and tertiary structure** with **subtle functional differences**.

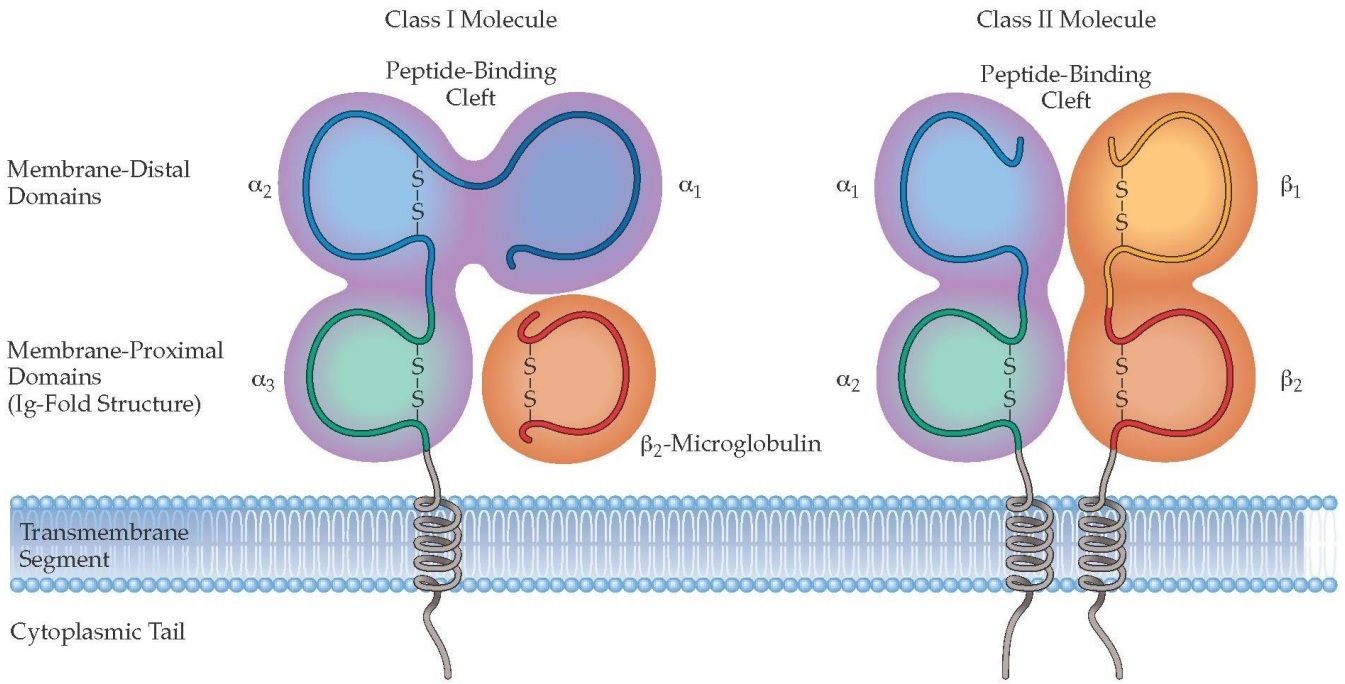
Class I: 43 kDa **α chain** (heavy) associated **noncovalently** with 12 kDa **β2-microglobulin** molecule (light chain).

α chain has **3 domain** and **β2-microglobulin** forms the **4th domain .**

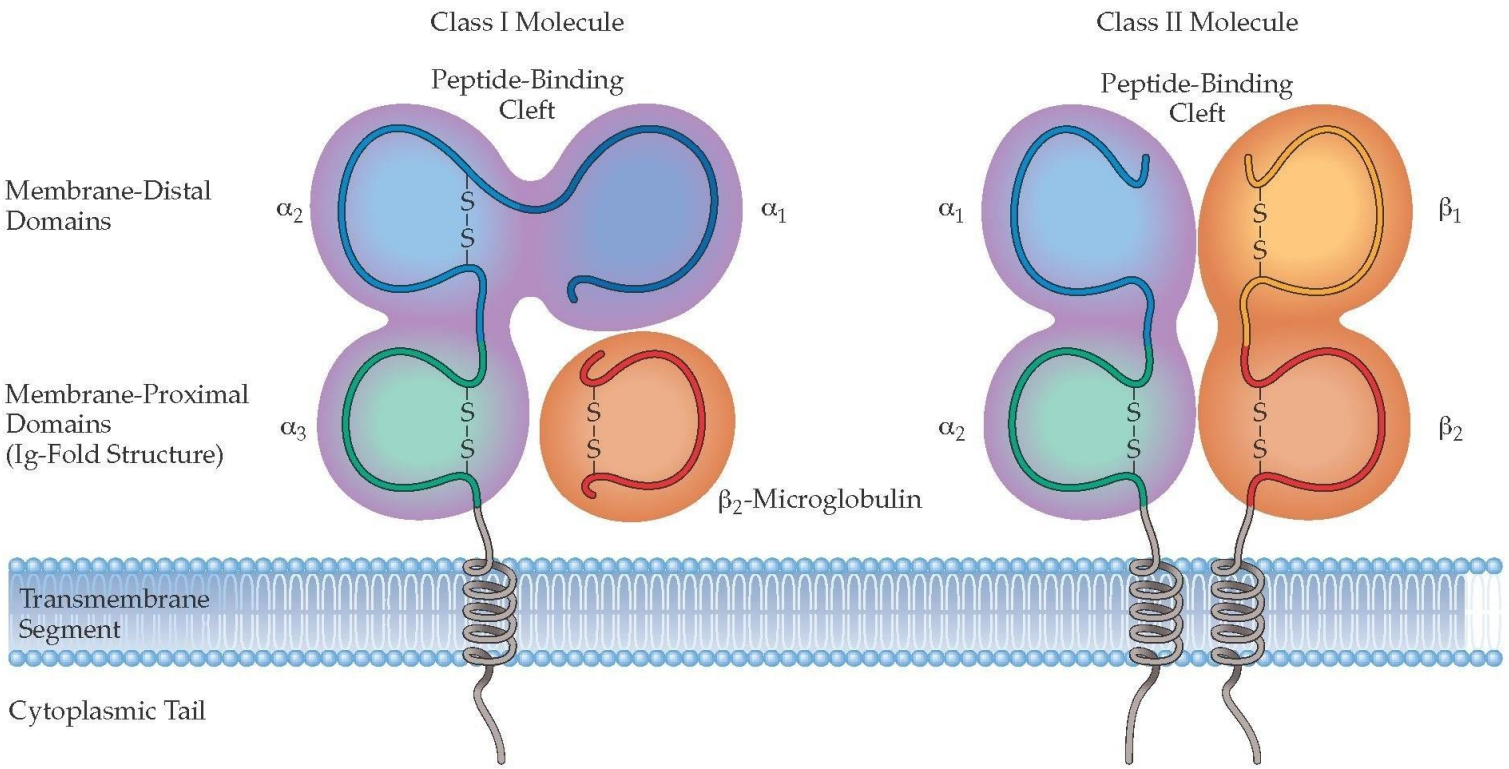


Class II: 33 kDa **α chain** associated noncovalently with a 30 kDa **β chain.**

α chain and **β chain** have **two domains each.**



Additionally **both** have **transmembrane segments (one** in **Class I** and **two** in **Class II)** and a **cytoplasmic tail.**



Allelic Polymorphism

-- The **MHC** is **highly polymorphic**. There are a large number of **alleles** at each genetic locus.

-- This polymorphism is important in recognition of **self and non-self.**

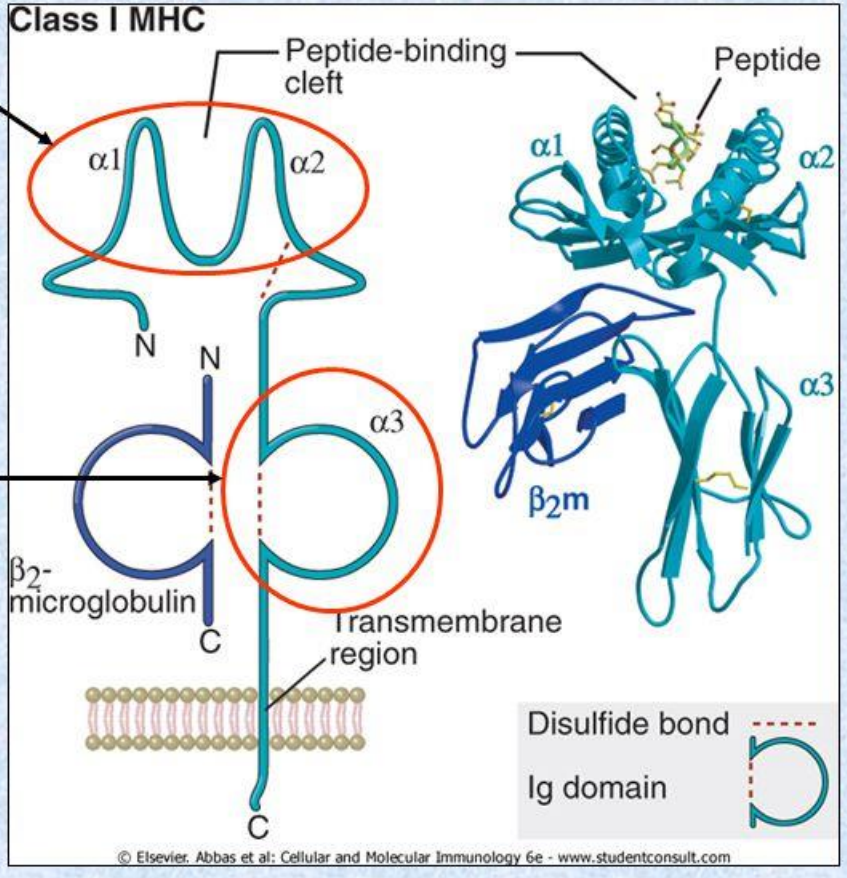
-- **Better similarity** will **improve chances** of **acceptance** of foreign grafts.

Heavy chain of **Class I** molecules also has a **constant region** where the **CD8 protein** of the **cytotoxic** T cells binds.

Structure of Class-I MHC molecule

α1α2 domains are polymorphic and form the peptide-binding cleft.

α3 domain is conserved among all MHC class-I, and folds into an Ig domain for CD8 binding.



Class II MHC glycoproteins are found on the surface of antigen-presenting cells **(APCs)** such as:

-- **Macrophages**

-- **B cells**

-- **Dendritic cells** of spleen

-- **Langerhan's cells (**dendritic cells of skin)

Biological role of the MHC

-- The **products of the MHC** play a **fundamental** role in **regulating** immune responses.

-- T cells must recognize antigen as a **complex** with MHC molecules. Antigen alone has **no recognition** for T cells.

This requires antigen to be processed by **unfolding** and **proteolytic digestion** before it complexes with the MHC molecule.

-- Once formed, the complex of antigenic peptide and MHC are generally **very stable** (half life ~ 24hrs).

-- Thus the **biological role** of MHC proteins is to **bind** small peptides and to **"present"** these at the cell surface for the **inspection** of T cell antigen receptors.

-- In a **normal** animal or cell the **majority** of MHC molecules will be **complexed with self peptides**.

-- **“Empty" MHC molecules** are less stable especially in the case of class I products.

-- Requirement to recognize antigen in association with a “self” MHC protein is called **MHC restriction**.

-- T cells recognize antigens **only** when they are presented on **cell surface** by **class I** (for T killer cells) **or II** (for T helper cells) **MHC** molecules

-- B cells have the ability to recognize **soluble antigens** in plasma with their **surface monomer IgM** acting as the **antigen receptor without the help of MHC molecules**.

MHC genes and proteins are important in **two** medical contexts:

-- Many **autoimmune diseases** occur in people who carry **certain** MHC genes.

-- Success of organ transplants is **greatly influenced** by **compatibility** of the MHC genes of the donor and recipient.


COLLECT MOMENTS
NOT THINGS


Dr. Barry J. Marshall was convinced that H. pylori bacteria causes stomach ulcers, but no one believed him. Since it was illegal to test his theory on humans, he drank the bacteria himself, developed ulcers within days, treated them with antibiotics, and went on to win a Nobel Prize.


Thank You!