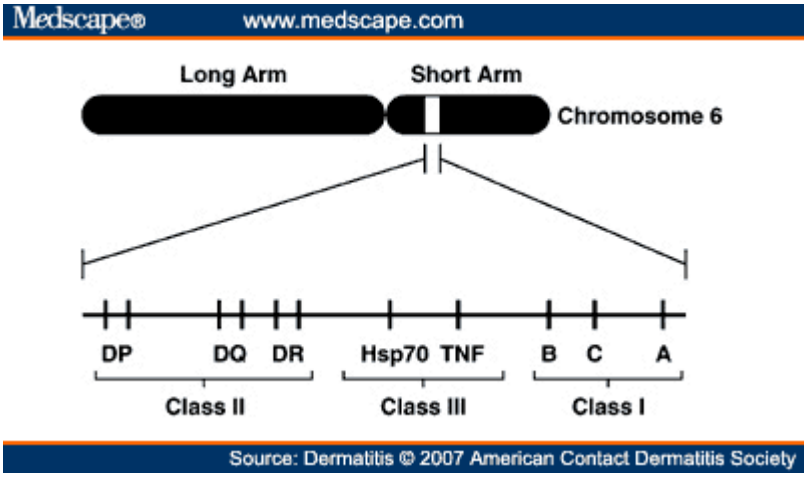
Major Histocompatibility Complex

They are a group of genes coding for proteins or tissue antigens. This complex is present in all mammals. In rats it is named as H2& located on chromosome no. 17.

In humans it is located on the *short arm* of chromosome **no.6**& is called HLA (Human Leukocyte Antigen).

Its discovery was in the mid of 1950s.



MHC gene products were identified as responsible for graft rejection. MHC gene products that control immune responses are called the immune response (Ir) genes. Immune response genes influence responses to infections.The essential role of the HLA antigens lies in the induction and regulation of the immune response and defense against microorganisms. The physiologic function of MHC molecules is the presentation of peptide antigen to T lymphocytes. These antigens and their genes can be divided into three major classes: class I, class II and class III.

Note:Locus:*Position of a gene on the chromosome.*

Allele: *One of several alternative forms of gene at a given locus.*

e.g. HLA A(locus), 124 (alleles)

HLA B(locus), 258 (alleles)

HLA C(locus), 74 (alleles)

MHC class I

Locus	#
Major Antigens	
HLA A	767
HLA B	1,178
HLA C	439
Minor Antigens	
HLA E	9
HLA F	21
HLA G	43

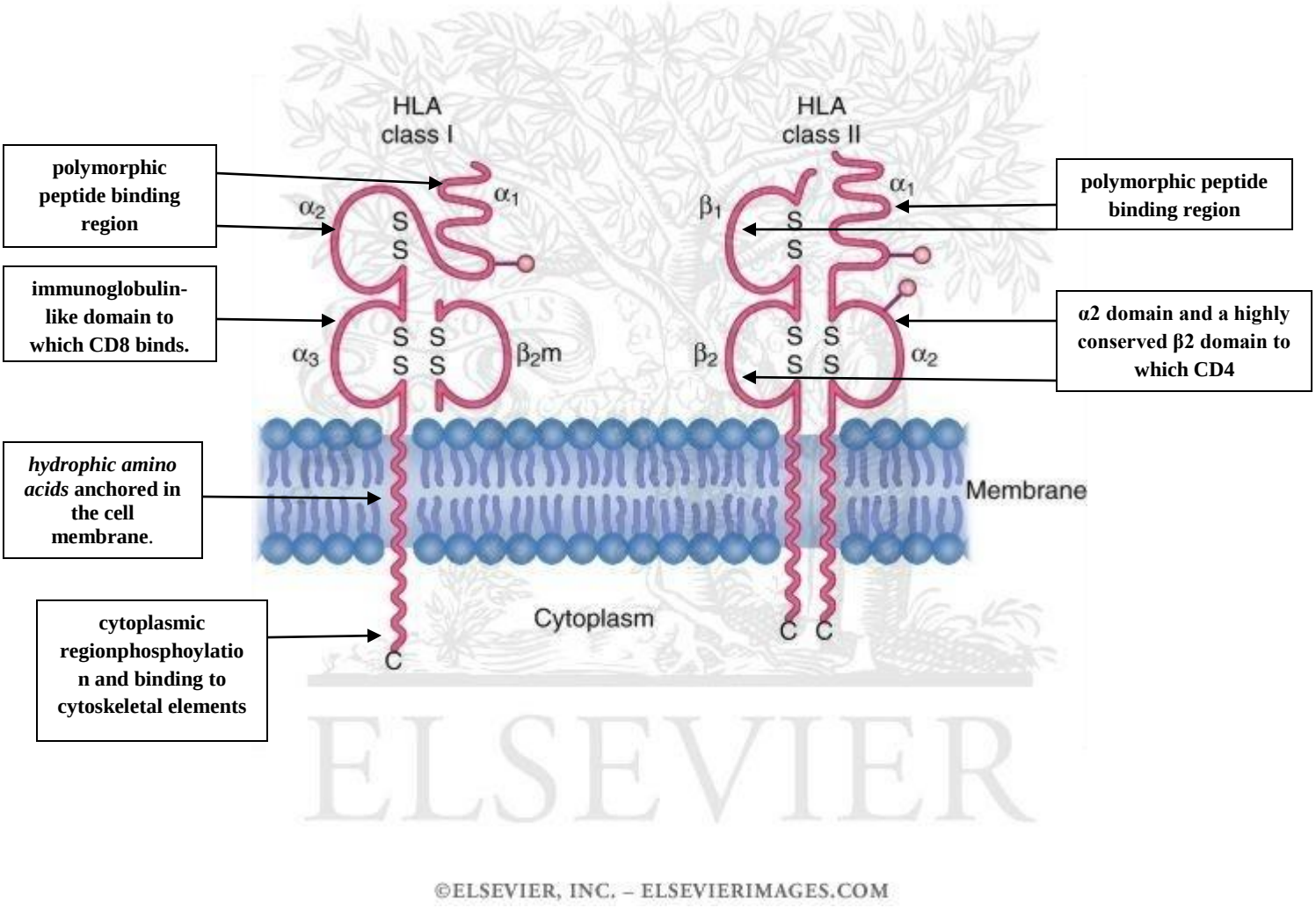
MHC class II

HLA locus	-A1 #[8]	-B1 #[8]	-B3 to -B5[1] #[8]	Potential Combinations
DM-	4	7		28
DO-	12	9		72
DP-	27	133		3,591
DQ-	34	96		3,264
DR-	3	618	82	2,121

[1]DRB3, DRB4, DRB5 have variable presence in humans

NOMENCLATURE:

HLA specificities are identified by a letter for locus and a number (A1, B5, etc.), and the haplotypes are identified by individual specificities (e.g., A1, B7, **Cw4**, DP5, DQ10, DR8). Specificities which are defined by genomic analysis (PCR), are named with a letter for the locus and a four digit number (e.g. A0101, B0701, C0401, etc.)



Structure of Class I MHC Molecules

Class I MHC molecules are composed of **two polypeptide chains**, a **long α chain and a short β chain called β2-microglobulin**. The chain has four regions. **First:** a cytoplasmic region, containing sites for *phosphoylation and binding to cytoskeletal elements*. **Second,** a transmembrane region containing *hydrophic amino acids* by which the molecule is **anchored** in the cell membrane. **Third**, a highly conserved α3 immunoglobulin-like domain to which CD8 binds. **Fourth**, a highly polymorphic peptide binding region formed from the α1 and α2 domains. The β2- microglobulin associates with the alpha chain and helps maintain the **proper conformation of the molecule.**

Within the MHC there are 6 genes that encode class I molecules HLA-A, HLA –B, HLA-C, HLA-E, HLA-F and HLA-G. Among these HLA-A, HLA –B, and HLA-C are the most important and are most polymorphic.

Structure of Class II MHC Molecules

Class II MHC molecules are composed of two polypeptide chains an alpha and a β chain of approximately equal length. Both chains have four regions: **first**, a cytoplasmic region containing sites for phosphoylation and binding to cytoskeletal elements; **second**, a transmembrane region containing hydrophic amino acids by which the molecule is anchored in the cell membrane, **third**, a highly conserved **α2 domain and a highly conserved β2 domain to which CD4** binds and **fourth**, a highly polymorphic peptide binding region formed from the α1 and β1 domains.

Within the MHC there are 5 loci that encode class II molecules, each of which contains a gene for **an alpha chain and at least one gene for a β chain**. The loci are designated as HLA-DP, HLA –DQ, HLA-DR, HLA-DM, and HLA-DO. Among these, HLA-DP, HLA –DQ and HLA-DR are the most important and are most polymorphic.

HLA- E: *it produces **an inhibitory effect on the cytotoxic activity of the NK cell** to prevent cell lysis.*

HLA-F: *binds a **restricted subset of peptides derived from the leader peptides of**other class I molecules.*

HLA-G: *It may play a role in Immune tolerance in pregnancy, being expressed in the placenta, while the classical MHC class I genes HLA-A and HLA-B are not.*

HLA-DM: *is an intracellular protein involved in peptide presentation by MHC class II.*

HLA-DO: *assists in the down-regulation of HLA-DM*

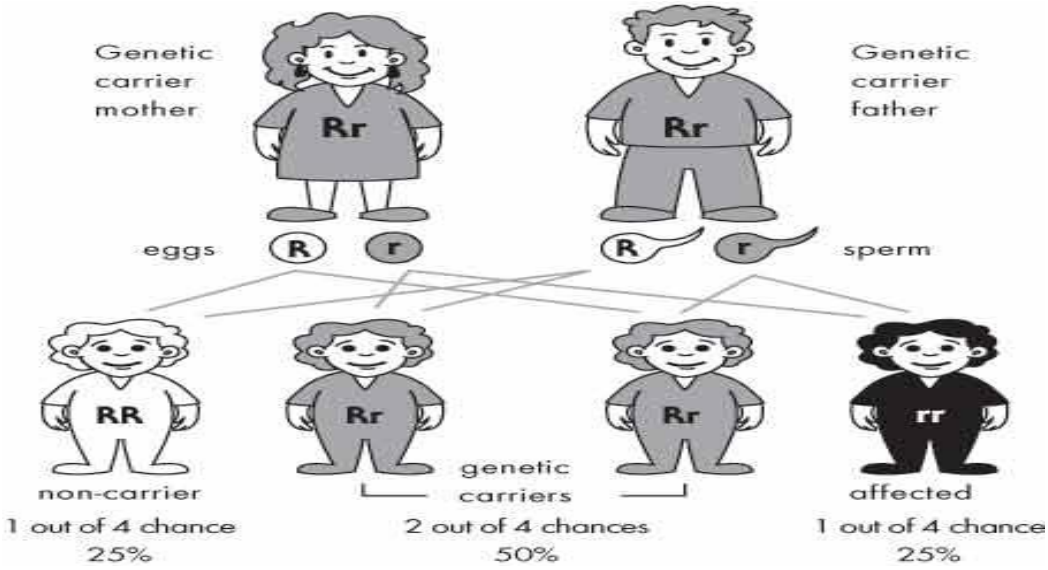
MHC Class III

Genes encode several components of the complement system (C2, C4) , a collection of soluble proteins found in the blood that targets foreign cells and breaks open their membranes. Adjacent to the class III region is a group of genes that control inflammation. Further genes with various immune and non-immune functions are dotted throughout the complex.(Heat shock protein, C2, C4, Tumor Necrotizing Factor and Leukotrienes.

INHERITANCE:

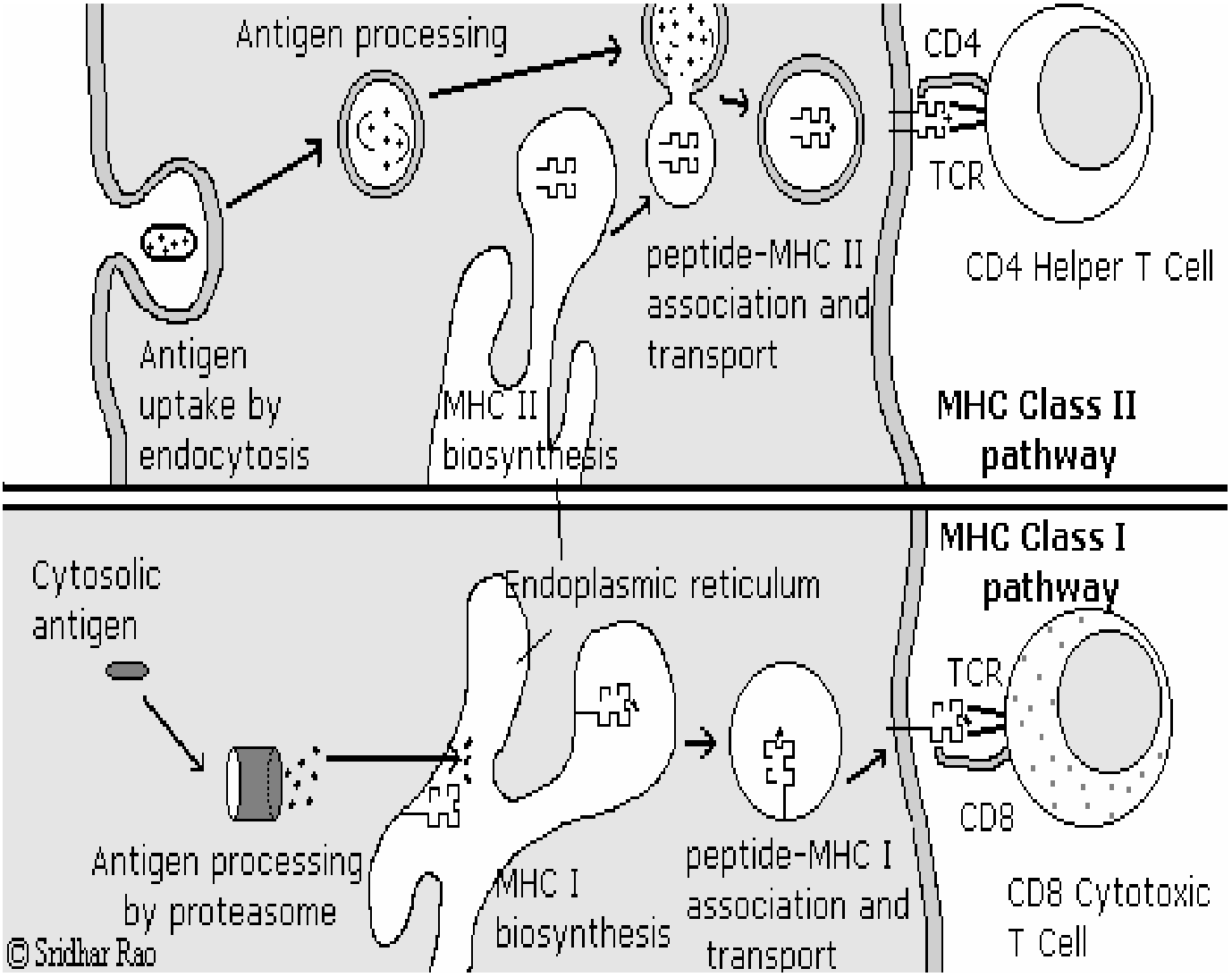
Histocompatibility genes are inherited as a group (haplotype), one from each parent. Thus, MHC genes are co-dominantly expressed in each individual. A heterozygous human inherits one paternal and one maternal haplotype, each containing **three Class-I** (B, C and A) and **three Class II** (DP, DQ and DR) loci. Each individual inherits a **maximum of two alleles for each locus**. The maximum number of class I MHC gene products expressed in an individual is **six**; *that for class II MHC products can exceed six but is also limited*. Thus, as each chromosome is found twice (diploid) in each individual, a normal tissue type of an individual will involve **12 HLA antigens**. Haplotypes, normally, are inherited intact and hence antigens encoded by different loci are inherited together.

Note : 3(Class-I) X 2 (alleles) X 2 (chromosome) = 12
3(Class-II) X 2 (alleles) X 2 (chromosome) ≈12



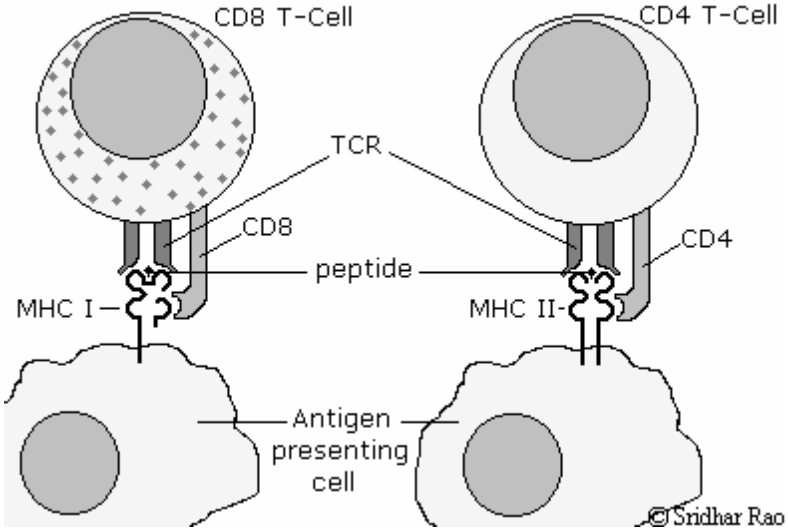
EXPRESSION:

Class I antigens are expressed on all nucleated cells (**except those of the central nervous system and platelets**). The class II antigens are expressed on **antigen presenting cells such as B lymphocytes, dendritic cells, macrophages, monocytes, Langerhans cells, endothelial cells and thymic epithelial cells**. **Cytokines, especially interferon gamma (IFN-γ), increase the level of expression of class I and class II MHC molecules.**



CD 4 Helper T lymphocytes can recognize peptide antigen only when presented along MHC II molecules.

CD8 Cytotoxic T lymphocytes can recognize peptide antigen only when presented along MHC I molecules.



SIGNIFICANCE OF HLA TYPING:

Applications of Histocompatibility Testing

Anthropology: The fact that HLA types vary very widely among different ethnic populations has allowed anthropologists to establish or confirm relationship among populations and migration pattern. HLA-A34, which is present in 78% of Australian Aborigines, has a frequency of less than1% in both Australian Caucasoids and Chinese.

Paternity Testing: If a man and child share a HLA haplotype, then the possibility is there that the man may be the father but not proven. However, if they don't match or share a haplotype then it is agreed that he is not the father.

Transplantation: Because HLA plays such a dominant role in transplant immunity, pre-transplant histocompatibility testing is very important for organ transplantation. Results with closely related living donors matched with the recipient for one more both haplotypes are superior than those obtained with unrelated cadaveric donors.

Transfusion

Forensic science

Disease Correlation

A number of diseases have been found to occur at a higher frequency in individuals with certain MHC haplotypes. Most prominent among these are ankylosing spondylitis (B27), celiacdisease (DR3), Reiter's syndrome (B27).

I. Disease associations with Class I HLA Ankylosing spondylitis (B27), Reiter's disease (B27), Acute anterior Uvietis (B27), Psoriasis vulgaris (Cw6)

II. Disease associations with Class II HLA

Hashimoto's disease (DR5), Primary myxedema (DR3), Graves thyrotoxicosis (DR3), Insulin-dependent diabetes(DQ2/8), Addison's disease (adrenal) (DR3), Goodpasture's syndrome (DR2),Rheumatoid arthritis (DR4), Juvenilerheumatoid arthritis (DR8), Sjogren's syndrome (DR3), Chronic active hepatitis(DR3), Multiple sclerosis (DR2,DR6), Celiac disease (DR3), Dermatitis herpetiformis (DR3).

In cancer

Some HLA-mediated diseases are directly involved in the promotion of cancer. Gluten-sensitive enteropathy is associated with increased prevalence of

enteropathy-associated T-cell lymphoma, and DR3-DQ2 homozygotes are within the highest risk group, with close to 80% of gluten-sensitive enteropathy-associated T-cell lymphoma cases.