MHC (HLA):  
**Definition:** It is a group of tissue antigens, controlled by chromosomal region, bearing a no. of genetic loci, each with multi alleles, that have relevance to transplantation rejection reaction & other immunological phenomena.  
**Locus:** position of gene on chromosome.  
**Allele:** one of the several alternative forms of gene at a given locus.  
This system was discovered in mid 1950s, as histocompatibility transplantation antigens. (Histocompatibility refers to the ability to accept tissue growth from unrelated donor). In human, the genes coding for this system (HLA) are locating on short arms of chromosome No.6
Human HLA gene complex encode 3 classes of antigens:

1- **Class I genes** include 3 main loci:
   
<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
</table>
   
   This group of genes encode **class I HLA antigens**

2- **Class II genes** include 3 main loci:

<table>
<thead>
<tr>
<th>DP</th>
<th>DQ</th>
<th>DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>58</td>
<td>265</td>
</tr>
</tbody>
</table>

   This group of genes encodes **class II HLA antigens**

   *MHC system is highly polymorphic with multiple different alleles within each locus.*

3- **Class III genes** named as complement region located between class I & class II regions.

   Class III genes generally encode various secreted proteins that have immune functions, including components of the complement system (C2,C4,BF) & molecules involved in inflammation (tumor necrosis factor...
- TNF, & heat-shock proteins).

**Nomenclature of HLA system:**
Locus + no. of allele
e.g. HLA-A1
HLA-DR4
HLA-CW2 (W=workshop)

**Inheritance of HLA-antigens:**
It follows Mendelian Rule of heredity.
Within a family, each child inherits -half of HLA- complex (1 haplotype) from his mother & another half from his father.
In other words, for each HLA locus he inherits one allele from his mother & one allele from his father, & as MHC system is highly polymorphic, therefore, by coding these alternative forms together, we'll end with huge possibilities reach to thousands of millions. So it is difficult to find two identical individuals except in identical twins.
Furthermore, HLA genes are co-dominant, both alleles at a given HLA locus are expressed & two complete sets of HLA Ags can be detected on cells, that's why organ transplantation faces rejection reactions.

i.e.
Because of extensive polymorphism of MHC molecules, an individual is likely to inherit different alleles from the mother & father, & as these alleles are co-dominant, this result in production & expression of both maternal & paternal MHC molecule on the surface of one cell.
The inheritance of HLA haplotypes from heterozygous human parents is illustrated in figure below. When the mother & father have different haplotypes, there is one-in-four chance that siblings will inherits the same paternal & maternal haplotypes & therefore be histocompatible
with each other, none of the offspring is histocompatible with the parents.

- 25% chance that 2 siblings will share both haplotypes (e.g. ac & ac) » Identical
- 50% → share one haplotype (e.g. ac & ad) » semi-identical
- 25% → share no haplotype (e.g. ac & bd) » non-identical

**Medical importance of HLA - typing:**
1- Paternity testing
2- Disease association: A number of different diseases have been associated with particular MHC alleles.
   - HLA - B27 → ankylosing spondylitis
   - HLA - B8 → myasthenia gravis
   - HLA-DR3 → I.D.D.M
   - HLA - DR4 → rheumatoid arthritis
   - HLA - CW6 → psoriasis
3- HLA typing is used primarily for determination of HLA compatibility between donor & recipient prior to transplantation.
4- Anthropology to study races & nations.
MHC molecule (HLA antigens)

![Schematic of MHC structure](image)

**Class I antigens**

Are named as **classical histocompatibility** Ags or **transplantation Ags** because these are the principle Ags recognized by the host immune cells during graft rejection.

These antigens are expressed on cell membrane of all nucleated cells including leukocytes except the sperms & RBCs.

- Class I MHC mol. are specialized in binding to endogenous antigens.
- The major function of class I MHC molecules is presentation of peptide antigen to Tc cells.

- Class I Ags are glycoprotein in nature. They consist of **heavy chain** with molecular wt. of 44,000 Dalton, non-covalently associated with **β-2 microglobulin light chain** with molecular wt. 12,000 Dlaton, (β2-encoded by gene No.15).
Class I heavy chain consists of:
- three extra cellular domains, designated – α1, α2 & α3.
- a trasmembranous region
- a cytoplasmic tail

Heavy chain α1 & α2 domains form the antigen binding groove of class I MHC mol.
*(β2-microglobulin is required for expression of class I mol. on cell membrane).

**Class II antigens**
They are glycoprotein in nature consist of two chains, one α- heavy chain with mol. wt. 33,000 dalton & one β - light chain with mol.wt. 25000 dalton, each chain consists of:
- two extra cellular domains α1, α2 & β1, β2 respectively
- a trasmembranous region
- a cytoplasmic tail

Heavy chain α 1 domain & light chain β 1 domain form the antigen binding groove of class II MHC mol.
MHC-II molecules present on cell membrane of APC (monocytes, macrophages, dendritic cells, B-lymphocytes), & activated T-cells. They are specialized in binding to exogenous Ags. They present processed antigenic peptide to Th cells.
**Function of HLA Ags:**
Both *class I* & *class II* MHC molecules are important in controlling immunological responses by a process known as **MHC restriction**.
- Class I Ags are involved in MHC restriction of cell mediated cytotoxicity.
  - Class I MHC mol. are specialized in binding to endogenous Ags (viral Ag, tumor Ag.).
  - During I.R., class I Ag function as regulator of interaction of cytotoxic T-cell with target cell. The cytotoxic T-cell recognize non-HLA cell surface Ag in connection with class I HLA-Ag → Kill target cell.
- Class II MHC mol. are specialized in binding to exogenous Ags.
  - The *class II* Ags play a role in antigen presentation by APC (macrophages, dendritic cells, B-cells) to T-cells.
  - The epitope of the Ag is presented to its homologous receptor on the T-cell, thus triggering activation of T-cell.
**Assembly of endogenous peptides with MHC-I (cytosolic pathway):**
Peptides presented by MHC class I molecule are generated from cytosolic proteins (endogenous Ags).
Endogenous Ags proteins are processed & degraded by proteolytic activity of proteasomes in the cytoplasm, and then these peptides are of about 8-15 amino acids are transported by TAP (Transporter Protein) into endoplasmic reticulum.

Inside ER, peptide loading involves other protein named calnexin. These proteins promote & guide the assembly of stable MHC class I molecule - β2 - microglobulin - peptide complexes. These fully assembled molecules are transported to golgi apparatus then to the cell surface.

**Assembly of exogenous peptides with MHC-II (endocytic pathway):**
Exogenous Ag enter the cell by endocytosis & form early endosome. MHC class II mol. are found in the ER complexed to a peptide called invariant chain (Ir). After that they are transported through the golgi compartment where they are loaded with peptide derived from exogenous Ag to form late endosome then the fully assembled class II - peptide molecules are transported to the cell surface.
Cytosolic pathway

Endocytic pathway
Genetic control of immune responsiveness:
Immune response is under the control of the following groups of genes:

1- **Cell interaction (CI) genes:**
A/ Control most effective macrophage-Lymphocyte Interaction.
B/ Control most effective T-T & T-B , Lymphocyte Interaction.
C/ Code for molecules active in enhancing & suppressing immune response.
D/ Control most effective lysis of virus-infected & neoplastic target cell by cytotoxic T-Lymphocyte.

2- **Immune response (Ir) & Immune suppression (Is) genes:**
A/ Ir genes determine the ability of an individual to respond to a given Ag determinant.
These genes occur in the HLA-D region in human.
B/ Is genes control stimulation of specific suppressor T-lymphocyte.

**HLA system & disease:**

*Diseases associated with HLA system have the following criteria:*
1- They are of unknown cause, with hereditary pattern of distribution.
2- Association with immunological abnormalities.
3- They have little or no effect on reproduction.

**The positive association between diseases & HLA-alleles can be divided into:**
1- Those ass. with class - I HLA-Ag.
   ex. Ankylosing spondylitis + HLA-B27
       Psoriasis      + HLA-CW6
       Myasthenia gravis + HLA-B8
2- Those ass. with class II Ag:
ex. Rheumatoid arthritis + HLA-DR4
Autoimmune thyroiditis + HLA-DR3

Theories explaining HLA-Disease association:
1- HLA-Ags could act as a receptor for certain microorganisms, toxins,… foreign substances which cause dominant susceptibility to infection, then HLA- disease ass. would result.
2- A molecular mimicry or cross reactivity (immunologic similarity) between Ag of microorganism & HLA-Ag ,this results in either an immune response against the invading m.o. or formation of auto-antibody which attach the host cells. e.x. Rheumatic fever.
3- HLA-Ag act as marker for Ir or Is genes.
e.. hyper-responsiveness to collagen is associated with HLA-DR4 & appear to be secondary to lack of collagen specific supp. T-cell, (due to state of equilibrium- disequilibrium between Ir & Is genes).

Nonclassicali MHC molecules:
- Recently discovered mol. encoded in MHC system.
- They have relatedness to classical MHC mol. but with restricted cell type expression.
- Function → unknown, but may:

* Involved in the presentation of few peptides to the immune system.
* Required for Ag processing & presentation.

- Non-classical MHC-I mol.
  HLA-E , HLA-F , HLA-G
- Non-classical MHC-II mol.
  HLA-DM, HLA-DN