The main histocompatibility complex

It is a genetic system that is primarily responsible for distinguishing one's own from another's (M ajor H istocompatibility C omplex). In humans, the main histocompatibility system is the HLA complex (H uman L eucocyte Antigen) - a large complex of genes that determine surface molecules (antigens) located in the plasma membrane of cells.

Basic information

Antigens behave as transplant , ie. that they cause tissue rejection in incompatible transplants. The HLA system is homologous to the H-2 locus in mice (the system on which the principle of histocompatibility was first discovered) and is located in a certain section of the short arm of chromosome 6. It contains genes for histocompatibility antigens, complement components and probably Ir-genes (immune response genes - genes responsible for the intensity of the immune response).

The main physiological function of MHC molecules is to present antigens or their fragments to cells of the immune system, especially T-lymphocytes (antigen presentation is the first prerequisite for the development of an immune response and thus defense against attack by microorganisms). Using these molecules, the cells of the immune system cooperate with each other. There are other loci within the HLA complex, or in its immediate vicinity. It is mainly one polymorphic enzyme (glyoxalase - GLO) and two diseases (21-hydroxylase deficiency - *congenital adrenal hyperplasia* and *olivopontocerebellar ataxia*).

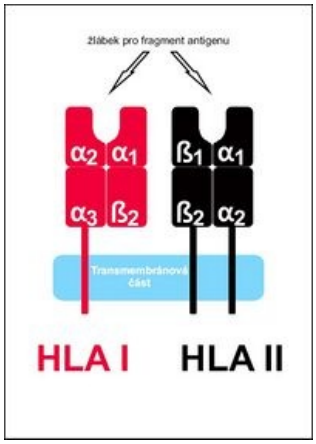
Distribution

We know 5 HLA complexes: HLA - A, HLA - B, HLA - C, HLA - D, HLA - DR (D-region related - in relation to area D). Each of them has a number of alleles (today at least 20 alleles are known for HLA - A, 40 alleles for HLA - B, 8 and more for the other three). A set of HLA genes on one chromosome forms a haplotype , so an individual has two haplotypes (from each parent) and 5 determinants in each.

The order of areas in the MHC is different for different animal species. HLA genes are so tightly bound that they act as a unit. The probability that 2 siblings will have the same haplotypes is 1/4. A large number of alleles at each of the five loci allows for HLA variability. If the HLA system is highly polymorphic, it can be used as the sole genetic marker in population research or in determining paternity.

Immunologists divide the gene products of the HLA system into:

1. *class I molecular products* : HLA antigens - A, B and C (order in the centromere direction is: B, C, A),
2. *class II molecular products* : HLA-D and DR antigens (B-cell antigens),
3. *class III molecular products* : complement components (C2, C4, factor B).



All I. class genes lie in one area, II. classes in another region of the complex, their order in the direction from the centromere is II → III → I. Among a considerable number of genes are pseudogenes . For each of the genes I. and II. class there is a multiple allele . Allelic forms of MHC molecules differ in the structure of the binding site and thus in the ability to bind peptides. The polymorphism here represents a selection advantage related to the basic role of MHC molecules, i.e. antigen presentation.

Recombinations between genes in HLA are observed, but not very common. Function of MHC molecules: presentation of antigen to T-lymphocytes, which enables mutual cooperation of cells of the immune system .

T-lymphocytes recognize

- foreign antigens in complex with MHC molecules themselves, leading to an immune response,
- own antigens in complex with own MHC molecules, leading to tolerance,
- foreign MHC molecules (transplantation reactions).

Class I molecules

HLA class I They are expressed on *all somatic nuclear cells* . They consist of the heavy chain α (44 kDa), which is non-covalently associated with the light chain β2-microglobulin . Alpha-chains (α1, α2, α3) are glycoproteins with 3 functional regions: external, transmembrane and cytoplasmic. The α-chain genes consist of 8 exons and 7 introns. Exon 1 encodes an untranslated region 5 and a leader sequence L. The other 3 exons carry information for α1 α2 α3 external domains. Exon 5 encodes the transmembrane region. The remaining exons are the cytoplasmic region and the 3´ region, which is not translated again.

β2-microglobulin is a soluble protein composed of 99 AMK. The β2-m gene does not lie in the HLA complex, but is located on chromosome 15. It consists of 3 exons and 2 introns. Most individuals of the same species and different species have identical β2-m molecules. This means that its primary structure is highly conserved in evolution. Both

chains form dimers on the cell surface.

HLA molecules - A, B, C are classical transplant antigens, highly polymorphic. Upon closer analysis, other genes were identified - E, F, G with lower polymorphism, their function is not sufficiently known. HLA - G are expressed on the trophoblast, they play a role in suppressing the mother 's immune response against the fetus .

Molecules II. classes

They do not have as wide a tissue distribution as class I. They are expressed on antigen presenting cells (dendritic cells, B-lymphocytes, monocytes and activated macrophages). *They are heterodimers composed of one heavy α-chain and one light β-chain . Both chains are glycoproteins. They consist of external, connective, transmembrane and cytoplasmic regions. The extracellular part consists of two domains: α1, α2, β1, β2. The α1 and β1 domains are variable, α2 and β2 are constant.*

The genes for α- and β-chains consist of 5 or 6 exons; Exon 1 determines the 5´ region (which is not translated) and the leader sequence. Exon 2 and 3 encode 2 external domains, exon 4 transmembrane region, exon 5 and 6 cytoplasmic region and 3´ region, which is not translated again. Both chains are non-covalently bound by the interaction of other external domains. Inside the cell, they are synthesized separately. After synthesis, they are associated with the third chain γ. When this complex reaches the plasma membrane, the γ-chain is dissociated and only the double-stranded complex is exposed on the membrane.

Molecules III. classes

The loci encoding the complement components C2, C4, Bf and TNF (tumor necrosis factor), Hsp (heat shock protein), 21-hydroxylase enzyme and others are stored here.

MHC and disease incidence

In patients with some diseases, some alleles of the HLA loci occur more frequently than in groups of healthy patients. The association of these diseases with certain HLA alleles is evident. Many of these diseases affect the joints, endocrine glands and skin .

One of the strongest associations is M. Bechtěrev (ankylosing spondylitis) - it occurs together with the HLA-B27 allele, it affects and gradually immobilizes the joints of the spine and limbs, especially the hip joint .

Links

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Source

- ŠTEFÁNEK, Jiří. *Medicine, diseases, study at the 1st Faculty of Medicine, Charles University* [online]. [feeling. February 11, 2010]. < http://www.stefajir.cz >.