Classical HLA Antigens

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Key Words: MHC, HLA

The Major Histocompatibility Complex (MHC) in Primates

Collections of genes similar to those found in the human and mouse MHCs have been identified in a variety of species including amphibians and birds¹. In most cases, with the possible exception of fish, class I and class II genes are linked. Indeed, in chickens some class I and class II genes may be found next to each other. Comparing the MHC regions of different species it is clear that there has been scope for differential evolution and different strategies have been used to solve problems. The extreme case is of mice with many thousands of copies of class I genes². The question arises as to whether MHC genes are linked because of historical precedent, there having not been sufficient time for them to have become distributed, or whether linkage of MHC genes has been maintained because of a selective advantage. It will be difficult to address this question until large stretches of genomes of diverse species have been compared for synteny.

It is assumed that MHC molecules have derived from the same genes with immunoglobin and T cell receptor molecules. These genes, which encode MHC molecules during their development, have grouped together to form small chromosome region as a result of continuous duplications and mutations³.

According to an hypothesis, the MHC Class II region is the first emerging gene region. There is evidence that decendent MHC molecules are similar to the structure of Class II molecules and that Class II molecules consist of them. Another hypothesis says that the MHC Class I gene region has emerged from the recombinations of heat-shock proteins (HSP70) with peptide connecting domains and immunoglobin like domains. However, the nature of the first MHC genes could not yet been explained. Investigations done with amphibians have shown that the connections of Class I, II and III gene regions within MHC regions have been existing for 370 million years⁴⁻⁶.

The MHC gene region, exists on the 6° chromosome (6p21.31) and occupies 4 Mbp. The longest haplotypes are (110-160 kb) DR53 group haplotypes. Jan Klein did the first definiton as Class I, II, III in 1977⁷. Nowadays,
the 0.3 Mbp region on the Class III HLA telomeric terminal, has been proposed to be called as the Class IV region.

The Human MHC
The human major histocompatibility complex spans about 4 Mbp of DNA at 6p21.3. It contains 300 genes, about 20% of which are involved with the immune system. The MHC is conveniently divided into regions, according to gene families: class I (telomeric), class II (centromeric) and class III. The length of the class I region is not known and linkage disequilibrium extends for several Mbp in the direction of the telomere.

The 4 Mbp MHC has been cloned in overlapping yeast artificial chromosomes (YACs) and mapped by pulse field gel electrophoresis. There is considerable coverage by overlapping cosmid clones. The complete DNA sequence of some regions has been determined. This information and many more details are maintained on database.

Analysis of sequences from each region show that there is a clear boundary between class II and class III in terms of mean GC content with a difference (GC%) of 11.8%. The class III region also contains the highest gene density. The class I region contains the HLA-A, B and C loci as well as a number of class I-related sequences such as the M region genes and the even more distantly related MICA and B genes.

Polymorphism
HLA class I and class II products are the most polymorphic human proteins described so far. Alleles at class I and class II loci occur in non-random combinations on “ancestral haplotypes” or “supratypes”. Some haplotypes contain distinctive sets of alleles, deletions, duplications and other rearrangements. It is possible that the positioning of antigen-processing genes such as the TAPs and LMPs within the MHC may help to maintain successful combinations of alleles in cis. Rat TAP/class I allelic combinations illustrate this point well. There are other explanations for keeping combinations of loci together on extended haplotypes, such as co-regulation of expression or gene conversion. Maintaining class I or class II genes together may also be advantageous for permitting sequence exchange and it is clear that recombination is restricted to “hot spots” in the MHC, such as between the two TAP genes. Recombination is rare in some other regions, between DQ and DR, for example.

Classical HLA antigens are coded within the HLA-A, -B, -C region of Class I genes and the HLA-DR, -DQ, DP region of Class II genes. All the Class I genes are of 3-6 kb length and Class II genes of 4-11 kb length. Other genes within the Class I region except for the genes coding classical antigens are HLA-E, -F, -G, -H, -J, -K, -L and only HLA-E, -F, -G among them is expressed. The gene density of the Class II region is quite a lot and a part of them are not related to the immune system. There are other gene regions like HLA-DM, -DN, -DO, -TAP1, TAP2, LMP2 and LMP7 within the Class II region, encoding classical antigens.

The MHC region consisting of a series of immunologic and nonimmunologic functional genes, was first discovered by Peter Gorer through transplantation investigations on rats in 1937. The products of these molecules were first defined by Jean Dausset (HLA-A2) in 1958, and the same year Van Rood and his colleagues defined HLA-BW4 and BW6 antigens and antibodies which occurred against leucocytes within the serums of people having blood transfusion and in that of women with multiple deliveries. Since the first tissue antigens were found in leucocytes, they were called as human leucocyte antigens (HLA). In the following years, with the exploration of the fact that they exist in all body cells except erythrocytes this group of antigen system was called MHC molecules or MHC antigens. MHC
is a general name and every type has its own MHC sign. MHC molecules are the basic determinants of graft rejection. Thus, individuals, expressing the same MHC molecules, accept each others tissue grafts while individuals with different MHC gene regions develop graft rejection. Only 20 years after the exploration of this locus, was the significance of MHC understood in immune response. Hugh Mc Devit and his colleagues found out in their research on rats in the 1960s, that no antibodies emerge when immunisation was done with simple polipeptides and that the immune response is an autosomal dominant characteristic in the mapping of the MHC region. Besides, the genes controlling the immune response are called Immune response genes (Ir). They showed in their research that the Ir genes control the activation of Th (T helper) lymphocytes which are necessary for the antibody response of protein structured antigens.

MHC Class I Molecules
The Class I molecule consists of the \( \alpha \) chain connecting to the \( \beta_2 \) microglobulin in a non covalent way. The alpha chain includes three extracellular domains namely \( \alpha_1 \) (N terminal), \( \alpha_2 \) and \( \alpha_3 \). The \( \alpha_3 \) domain within MHC Class I molecules is of protected nature and comprises the region reacting with the CD8 molecule within the T lymphocytes. The Beta 2 microglobulin is stabilized by one disulphide connection within its structure. Class I molecules are not expressed in the cell membrane in case of a nonexistence of \( \beta_2 \)-microglobulin. Alpha-1 and alpha-2 domains form a platform together with 8 anti-parallel \( \beta \) strands and 2 anti-parallel \( \alpha \) strands. They are generally expressed in the nucleocells. Nevertheless, the expression levels differ among cells. While expressed in top levels within lymphocytes, the expression of Class I molecules in fibroblasts, muscle cells, hepatocytes, sperms, oocytes, placental and central nervous system cells is very low or trivial. HLA-C molecules appear in the cell surface 10 times less, than HLA-A and -B molecules. However, HLA-C molecules are also functional and are the first target points recognised by NK (Natural Killers).

MHC Class II Molecules
Class II molecules are heterodimers consisting of the non-covalent connection of the heavy \( \alpha \) chain and the light \( \beta \) chain. There are domains of \( \alpha_1 \) and \( \alpha_2 \) within the alpha chain and domains of \( \beta_1 \) and \( \beta_2 \) within the beta chain. They comprise the hollow region between the alfa-1 and alfa-2 domains, where the peptide fragments are connected. Class II molecules are expressed in a rather limited number of cells like the dendritic cell, macrophage, B and active T lymphocyte.

HLA Molecules in the Antigen Presentation
The seperation of protein molecules into peptide parts and the presentation of the antigen to T cells, comprises an important part of immunity. Class I molecules play a role in the presentation of peptides of endogenous source to CD8 (+) T lymphocytes while Class II molecules play a role in the presentation of peptides of exogenous source to CD4 (+) T lymphocytes. The peptides are first subject to degradation and peptide fragments are connected to HLA Class I and II molecules within the cell. These molecules come to the cell surface together with the connected peptide.

There are two big ways providing the destruction of proteins within cells. The first one is the lysosomal proteolysis occuring in lysosomal acidic medium while the other one is the ubiquitine proteasome destruction way. Proteins, marked with a great number of ubiquitine are destructed by proteasome consisting of many sub-unitic protease.
complexes. ATP energy is used for the connection of ubiquitine and its marking.

Endogen proteins are connected with ubiquitine and are directed towards the proteasome. LMP2 and LMP7 encode the peptides comprising the components of the proteasome complex. The production of LMP sub-units, change the proteolytic function of the proteasome in a way beneficial for the peptides to be connected to Class I molecules. The proteosome takes place in the digestion of most of the cytoplasmic proteins with short life. Here, the endogen proteins falling down towards short peptides with 8-10 aa of length, are transferred to the ER over the TAP heterodimer. TAP molecules, provide the transportation of different elements as oligopeptides and bigger proteins between membranes. TAP1 / TAP2 molecules form a complex in the ER membrane which transport peptides from the cytoplasma to the lumen. The transported peptides, are loaded to the Class I molecule. These structures, which separate from the endoplasmic reticulum, come to the golgi complex and then carried to the cell membrane through transporter vesicles and are finally presented to the cytotoxic T lymphocytes.

Proteins of exogen source (like bacteria), are taken into the cell in an endocytic way and by joining with the lysosome, they are transformed into small peptides with the influence of lysosomal enzymes. Class II molecules that are recently synthesized in the ER, are connected with the invariant chain (li) molecule and are transported to the lysosome through vesicles resulting in a fusion. The li molecule within the lysosome is transformed into a small peptide and when there is a peptide bond for the HLA-DM molecule, there exists an exchange of the li molecule and the exogen peptide. The Class II molecules are finally carried to the cell membrane and presented to CD4 (+) T lymphocytes.

REFERENCES


