A BRIEF REVIEW OF THE HLA SYSTEM

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The HLA system is a highly polymorphic genetic system located on the short arm of the 6th chromosome. It encodes for cell membranes glycoprotein molecules called HLA antigens, also known as histocompatibility or transplantation antigens. The letters HLA originally stood for His-tocompatibility Leukocyte system A because this genetic system was first discovered on leukocytes, but these three letters are now meant to stand for Human (Histocompatibility) Leukocyte Antigens.

Historical Background

Half a century ago, Peter Gorer, an English pathologist, showed that an antigen, which he named as Ag-II, was responsible for rejection of tissues derived from donor mouse that is not geneticallyidentical with the recipient[1-3]. George Snell, an American working independently on the problem of graft rejection, named the gene mediating graft rejection in mice as Histocompatibility (or H) gene[4-6]. In a subsequent collaborative study by Gorer and Snell[7], the H-gene was found to be closely linked to Ag-II on mouse chromosome 17, and the two were renamed as Histocompatibiity-2 (H-2) gene. This gene was subsequently found to be genetically “complex’ (H-2 gene complex), and to encode for “transplantation antigens” that trigger the rejection of tissues derived from any donor which is not genetically identical with the recipient[6-8]. The late Sir Peter Medawar[9], while investigating failure of skin grafting from one person to another as a treatment of severely burned soldiers and civilians in the second World War, noted that skin grafts from a brother to his severely burned sister stimulated a reaction in the sister that resulted in a more rapid rejection of subsequent grafts. He later showed in animal experiments that the accelerated rejection of subsequent grafts was very specific to the particular donor[10]. He noted that tissue transplantation was under the control of immunological mechanisms which distinguish self from non-self, just like the immunity against microbes. Jean Dausset[11,12] from France was able to show the presence of histocompatibility system in man in 1958 by demonstrating the existence of first such antigen, which he named Mac (now renamed HLA-A2) This work evolved from his earlier demonstration of the existence of anti-leukocyte antibodies reacting with foreign leukocyte antigens[13,14]. Subsequent world-wide studies have demonstrated marked polymorphism of the human leukocyte antigen (HLA) system, and the presence of homologous histocompatibility systems in other vertebrate species, e.g., GPLA in the guinea pig, RLA in the rabbit, DLA in the dog, RhLA in the rhesus monkey, ChLA in the chimpanzee, etc. All of these histocompatibility systems are equivalent and highly polymorphic, and have been assigned a generic label, the Major Histocompatibility Complex, or MHC[12,14,17].

The HLA System

The total genetic information characterizing the HLA system of an individual is located in the MHC region on the short arm of the 6th pair of chromosomes (one paternal and one maternal) [8,12]. The responsible genes on chromosome 6 have been attributed to four HLA loci that have been designated by the letters A, B, C, and D; the D locus is. now called the D region and is subdivided into al least three subregions called DR, DO, and DP[18-20]. These genes are inherited in a simple Mandelian fashion as a series of codominant alleles, and they encode for glyco-proteins molecules expressed on cell membranes. [A gene is an inherited unit located at a locus on a chromosome, while an allele is an alternate form of the gene at a locus, arising by mutation and other mechanisms.1 The various HLA alleles are assigned the letter(s) signifying the locus followed by a number signifying the allele (Table). For example, HLAB27 implies an HLA allele number 27 belonging to the locus B, and HLA-DR4

means an allele number 4 belonging to the DR locus. The HLA— B27 implies an HLA allele number 27 belonging to the locus B, and HLA—DR4 means an allele number 4 belonging to the DR locus. The HLA—D specificities are detected by mixed lymphocyted culture (MLC) test, while the rest are detected serologically. The HLA—A and HLA—B specificities are numbered in the order of their official recognition by the HLA nomenclature committees, but all specificities belonging to the other HLA loci have been assigned numbers from 1 upwards (Table).

The letter “w” (for workshop) indicates that the specificity is not yet felt to be completelywell-defined, and the letter "w" is dropped when the specificity is eventually fully accepted. Note, however, that all HLA—C specificities will retain the letter “w” to avoid confusion with complement factors, since, as will be discussed later, genes for some of the complement components, such as C2 and C4, also reside in the HLA region. Many original broad specificities have been split[19], and it is optional to list the broad specificity in parenthesis after a split (i.e., narrow specificity). For example, HLA—A23, which is a split of HLA—A9, could be written as HLA—A23, which is a split of HLA—A9, could be written as HLA-A23(9) or HLA-A23. The HLA glycoprotein molecules occur into distinct varieties called class I and class II molecules[16-20]. The HLA class I molecules are the classical transplantation antigens, and they are encoded by genes at the highly polymorphic HLA—A, B, and C loci (Table). The A locus is associated with a segregant series of 24 alleles, the B locus with 50 alleles, and the C locus with 11 alleles (Table). Thus there are a total of six class I HLA alleles (3 inherited from each parent) in an individual, and depending on whether the individual is homozygous or heterozygous there are at least three and up to six different class I HLA molecules detectable on the cells of the individual. The class I molecules are expressed on nucleated cells as well as on platelets. The class II molecules are encoded by genes at DP, DO, and DR loci, and have a more limited distribution, being found especially on monocytes and B cells, and on activated T cells. The HLA class! molecules are composed of an MHC-encoded heavy chain (molecular weight of approximately 44,000 deltons), also called the alpha-chain, which is non-covalently bound to a much smaller (molecular weight of approximately 12,000 daltons) non- MHC-encoded, light or beta-chain [18]. The heavy chain is organized into three extracellular functional domains (designated as alpha 1, alpha 2, and alpha 3), a transmembrane part, and an intra-cytoplasmic tail (Figure).

Each The majority of peripheral T lymphocytes bear cell-surface antigen receptors (called the T cell receptors or simply TCR) comprised of two chains (alpha and beta) that are disulfide- linked, i.e., the TCR are alpha-beta heterodimers. In an immune response, the T cells do not recognize antigens that are unaltered [i.e., not processed by macrophages or other antigen presenting cells (APC)J; they only recognize processed (degraded) fragments of protein antigens bound to HLA molecules on the surfaces of other cells. HLA class I molecules are involved in immune recognition of foreign antigens since they function as peptidebinding proteins that present processed peptide fragments of antigens to the TCR[16,17] on the surface of cytotoxic T cells (CTL). The three-dimensional crystallographic structure of a class I molecule (HLA-A2) has now been determined by x-ray diffraction[21]. It reveals that the beta-2-microglobulin and the alpha 3 do-main of the heavy chain are associated with one another next to the cell membrane, forming a macrophages or other antigen presenting cells (APC)1; they only recognize processed (degraded) fragments of protein antigens bound to HLA molecules on the surfaces of other cells. HLA class I molecules are involved in immune recognition of foreign antigens since they function as peptidebinding proteins that present processed peptide fragments of antigens to the TCR[16,17] on the surface of cytotoxic T cells (CTL). The three-dimensional crystallographic structure of

a class I molecule (HLA-A2) has now been determined by x-ray diffraction[21]. It reveals that the beta-2-microglobulin and the alpha 3 domain of the heavy chain are associated with one another next to the cell membrane, forming a cushion on which the alpha 1 and the alpha 2 domains of the heavy chain reside. The alpha land alpha 2 domains of the class I molecules form the antigen binding sites. This site looks like a pocket or a groove, that has a floor (consisting of eight anti-parallel ribbon-like beta-pleated sheets) bounded by two long alpha helices, where the peptide antigen is non-covalently bound[21]. Most CTL bear the cell surface phenotype marker CD8 (formerly called T8), and are restricted in antigen recognition by class I HLA molecules. Studies of virus specific killing have demonstrated that cell mediated cytotoxicity requires that the sensitized CTL recognize both the virus specific antigen and the self class I HLA molecules on the target cell, before lysis of target cell would occur[16,17]. Thus, the sensitized CTL perform an important immune function by limiting intracellular viral replication through lysis of infected cell recognized by the presence of viral antigen bound to self class I HLA molecule on the cell surface of the infected cells[16,17]. Each HLA molecule has a single binding site for the processed peptide antigen. The extensive polymorphism that is so characteristic of the HLA system in the general population (Table) is associated with variation of the amino acid residues that form the peptide-binding site of the HLA molecules. This helps diversify in the general population the interactions of HLA molecules with peptide antigen fragments and TCR. Because an individual has a few HLA molecules but is exposed to an infmite number of antigens, an HLA molecule must be capable of binding to very many different peptides. Therefore, the specificity of the immunological response is provided by the phenomenal diversity of the TCR in every individual. The HLA Class II Molecules are encoded in the HLA-D region, which is subdivided, as discu.ssed earlier, into three major subregions, DR, DO, and DP. These molecules are composed of two non- covalently associated glycoproteins of approximately 34,000 (alpha chain) and 29,000 daltons (beta chain), respectively[13-15] . Each chain is organized into two extracellular functional domains, a transmembrane portion, and an intracytoplasmic tail (Figure). The sites of the genetic polymorphic variations of class II molecules are primarily located in the outermost domains of the beta and/or alpha chains[16,17]. Both the alpha and the beta chains are encoded in the HLA-D region, and the molecules are divided into three major subgroups according to the three HLA-D subregions (DR, DO and DP) encoding them. The DR locus is associated with a segregant series of 18 alleles, the DO locus with 9 alleles, and the DP locus with 6 alleles[19] (Table). The tissue distribution of class II HLA molecules is relatively limited, being found especially on certain cells of the immune system, such as B lymphocytes, macrophages, and activated T cells. Antigens precessed by antigen presenting cells (APC), such as macrophages and B lymphocytes, are presented by the class II molecules on the cell surface of the APC, where these processed antigen peptide fragments are recognized by CD4 (formerly called T4) bearing T cells through their TCR. These CD4 bearing T lymphocytes tend to be specialized for secretion of various lymphokines (interleukins) that help activate other cells, notably B cells and macrophages, and therefore these cells are also known as helperT cells. Thus, the class II molecules play a central role in antigen recognition and effective collaboration between immunocompetent cells for an efficient immune response[15,17] . For most protein antigens the interaction between the TCR and the peptide-HLA class II protein complex leads to interaction between T cells and B cells that results in a vigorous antibody response by the B cell specific for the same antigen. HLA class II molecules are not required for T-cell- independent antibody response to antigens, where the activation of a resting B cell starts with the binding of the antigen to cell-surface form of immunoglobulin on the B cell surface. The genes encoding for some of the complement components of the classical (C2 and C4) and the alternate (properdin factor B [BfJ) pathways also reside in the HLA complex, located between the HLA class I and class II regions[16-18]. . There are two loci for C4, coding for C4A and C4B (previously recognized as Rodgers and Chido blood group antigens, respectively). The molecular products of these

complement genes are grouped together as the class III molecules. Moreover, the genes for steroid 21-hydroxylase (210H) enzyme are also located in the HLA complex[18,22], but there is no evidence to suggest that such a location has some special physiologic advantage. These genes occupy approximately 120 kiobase (Kb) sequence between HLA-B and DR loci, and are represented as C2-Bf-C4A-210H(A)-C4B-210H (B). More recently, the gene for Tumor Necrosis Factor (TNF) has also been located in the HLA region between B locus and class III complement! 21-hydroxylase gene cluster[22,23]. Two TNF genes have been identified, one encodes for TNF-alpha (also called cachetin) and the other encodes of TNF-beta (also known as lymphotoxin). Both these molecules have similar biological activities and share a 28% sequence homology. In addition, these two molecules share a common receptor. TNF-beta is secreted from mitogen stimulated T lymphocytes and is a glycosylated protein of 171 amino acids. TNF-alpha is derived from activated monocytes and has a size of 157 aminoacid residues. The various bioactivities of TNF have been well summarized by Sherry and Cerami[23].

HLA and Disease AssociationsThe discovery of the HLA polymorphism has inspired many studies of possible associations with human diseases. Tiwari and Terasaki[24] have nicely summarized the known HLA and disease associations. Two of the most remarkable associations are between HLA-B27 and ankylosing spondylitis[20,24-29]. and between HLA-DR2 and narcolepsy[30-32] Some of the other diseases associated with HLA include rheumatoid arthritis, systemic lupus erythematosus, myasthenia gravis, coeliac disease, and insulin-dependent diabetes mellitus, just to name a few[24,29] . It is hoped that further advances in the HLA field will unravel the etiology and pathogenesis of many rheumatic, autoimmune and other diseases of “undetermined etiology.” it is worth pointing out in the end that the discovery of the MHC, and the subsequent understanding of its biologic function, resulted in the 1981 awards of Noble Prize in Medicine and Physiology to Snell[4], Dausset[12], and Benacerraf[15] for their pioneering work in this field.

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