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Research Article

Biology of the Human Histocompatibility Leukocyte Antigen (HLA) System and a Hypothesis Regarding the Generation of Autoimmune Diseases

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Introduction

The intense interest in the HLA system over the past several decades was kindled by its relevance to the phenomenon of graft rejection. Graft rejection is very old biologically and has been shown to occur in primitive animals such as sponges and tunicates (1, 2), although it is not yet known whether the genes, protein products, and the cells that are involved in this phenomenon are the evolutionary ancestors of those involved in higher vertebrates. The term "transplantation antigen" was first used in connection with graft rejection in studies of transplantation of mouse tumors (3). Breeding studies later showed that the main barrier to transplantation in mice is encoded by polymorphic genes in a single region called the H-2 region (4). All vertebrates examined have a similarly organized region now called the major histocompatibility complex (MHC)[1] (4–6). This region encodes three major classes of proteins, the class I MHC antigens (HLA-A, -B, and -C antigens in man), the class II antigens (HLA-DP, -DQ, and -DR), and the class III antigens (some components of the complement system: C2, Bf, C4A, and C4B). Since grafting is not a physiological phenomenon in man (except for the special case of the fetus in utero), the natural function of this system cannot be related to graft rejection. Each of these sets of antigens plays an important role in some aspect of immune defenses. Graft rejection is a by-product of the polymorphism of the MHC genes and proteins, an essential element in the natural functioning of these components of the immune system. Immunogenetic studies of the human MHC, located on the short arm of chromosome 6, and of its mouse homologue on chromosome 17, provided us with a rough gene order. Because most of the autoimmune diseases linked to HLA genes are linked to class II genes (7), this discussion will focus on these genes and their products.

The class II region of the human MHC is at least twice as large as that of the mouse, based on recombination frequency (8). By cosmid cloning the class II region of the mouse MHC is 250 kilobase (kb) in size and encodes two α-chain genes and five β-chain genes. Comparable studies of the class II region of the human MHC have indicated the presence of a minimum of six α-chain genes and eight β-chain genes, representing >400 kb of cloned DNA in seven segments that have not yet been connected. These cosmids represent the largest region of the entire human genome that has been cloned. The expansion of the class II region of the human genome may have made it possible for man to respond to many more epitopes on a given antigen, i.e., it may have increased the fine tuning of the immune response. It is also conceivable that this may have enhanced the probability for genesis of autoimmunity (see below).

Linkage of autoimmune diseases to HLA alleles

The polymorphism of these genes and their products is the most striking feature of the human MHC. Serological reagents have resulted in the definition of 25–40 alleles at the HLA-A and the HLA-B loci and 12 at the HLA-DR locus, but cellular reagents have greatly extended this number so that we now believe that >100 functionally distinct alleles can be defined at each of these loci (9). For example, HLA-A2 can be subdivided into four subgroups based on recognition by HLA-A2–specific cytotoxic T lymphocytes (CTL) (10), and HLA-DR2 can be divided into five subtypes based on proliferative responses of human T lymphocytes (11). A striking feature of this system is the linkage of many autoimmune diseases to particular alleles of HLA antigens (7). In some cases the linkage is very high; 95% of patients with ankylosing spondylitis carry the HLA-B27 allele as compared with 7% of controls (relative risk > 100). However, only a small fraction of HLA-B27$^+$ individuals have ankylosing spondylitis. We do not yet know whether the occurrence of this disease is more closely related to one of the four subtypes of HLA-B27 that have so far been defined by CTL (12, 13), or even to a particular "disease" allele; many more subtypes that have not yet been distinguished by functional analysis may occur in the population. On the other hand, 59% of patients with multiple sclerosis (MS) are HLA-DR2$^+$ as compared to 26% of controls (relative risk 4). When the disease is tightly linked to an HLA allele (as in the case of ankylosing spondylitis and other B27-related diseases), it is assumed that the HLA gene/protein itself is in some manner related to the disease. However, when the degree of association is lower, as in the case of MS (DR2), rheumatoid arthritis (DR4), or juvenile-onset diabetes (DR3 or DR4 with a particularly high correlation to the DR3/4 heterozygote), several possibilities can be considered.

(*a*) The actual gene (protein) associated with the disease is in linkage disequilibrium with the gene being assayed. Since good serological reagents are available only for the DRβ gene in the class II region (see below), only linkage to this gene can be easily measured. Diseases associated with any other gene in this region in linkage disequilibrium with DRβ will have a relatively lower degree of association with DRβ. Linkage disequi-

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1. *Abbreviations used in this paper:* CTL, cytotoxic T lymphocytes; kb, kilobase; MHC, major histocompatibility complex; MS, multiple sclerosis.

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librium (failure of adjacent genes to segregate in the population) is a well-known phenomenon in the HLA system (14), and the relatively low extent of correlation of MS with HLA-DR2, for example, may be due to the fact that MS is related to a gene in linkage disequilibrium with DR2 rather than to DR2 itself. In coeliac disease in which 45% of patients are HLA-DR7 and 28% HLA-DR3, 95% have been shown to carry the DQ2 allele (in linkage disequilibrium with DR3 and 7), while the remaining 5% are DR4 (15). Thus, in understanding this linkage it is extremely important to know the locations and the extent of polymorphisms of all of the genes in this region. Another striking example is the linkage of congenital adrenal hyperplasia to the HLA-B47 allele. This disease is now known to be due not to an HLA gene but to a 21-steroid hydroxylase gene, deletion of which is tightly linked to HLA-B47 (16, 17). This gene is located between the C4B locus in the class III region and the HLA-B locus in the class I region. Thus, the disease association may actually be to a gene in the MHC region that is not an HLA gene.

(*b*) Linkage of a disease to DP would be a special case, since DP genes have little or no linkage disequilibrium with DQ and DR genes. At least one "hot spot" for recombination occurs between DP-DX and DQ-DR (see below). Thus, a disease that had two forms, one linked to DP and the other to DQ or DR, would show only a low linkage to the latter.

(*c*) The presently defined alleles of HLA genes are heterogeneous, e.g., the five subtypes of DR2, and the extent of polymorphism may be very large. Thus, the diseases may be associated with only one "subtype" of a given gene/protein. Although correlation of a disease with a particular subtype would not increase the fraction of individuals who are DR2, for example, it would significantly increase the relative risk associated with that subtype.

(*d*) Promiscuous epitopes may account for the lower linkage. The epitopes of the HLA genes, i.e., polymorphic regions defining reactivity with antibodies or cellular reagents, are the functional units of these genes/proteins. However, these epitopes are not entirely fixed to one gene/protein but can be "shuffled" to other genes/proteins in this system. The mobility of DNA sequences in these genes has been well documented in several studies (18, 19). It is thus possible, for example, that a "disease" epitope in MS could be found in a DR3β allele in some individual rather than in a DR2β allele, or in coeliac disease in a DR4β allele rather than in a DQ2β allele.

(*e*) The disease itself may be heterogeneous; e.g., type 1, but not type 2, diabetes is HLA linked. Perhaps type 1 can be further subdivided, and only one subtype will be linked to MHC genes.

Structure of HLA genes and proteins

The structure of the genes and proteins in this region and their function are therefore very relevant to our understanding of these diseases. From a structural standpoint, the products of the class I and class II genes belong to a large gene superfamily that is called the Ig superfamily (Fig. 1) because the Ig genes were defined first, although surely they are one of the latest evolutionary members of this family. Both the class I and class II antigens are composed of four extracellular domains, two of which are Ig-like (20, 21). They differ, however, in that the two chains (α and β) of the class I antigens are composed of three and one domain, respectively, while those of the class II antigens are each composed of two domains. Moreover, only the heavy chain of the class I antigen spans the membrane while both chains of the class II antigen do so. Our knowledge of the precise

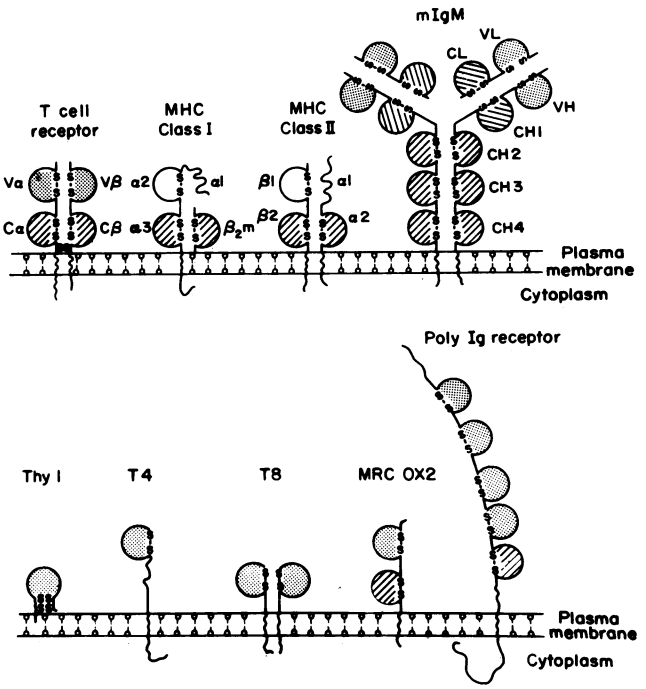

Figure 1. Schematic representation of MHC antigens and other membrane proteins with homology to immunoglobulin constant domains (▣) and variable domains (□).

manner in which these antigens function is far too primitive to relate these structural differences to the differences in function of class I and class II antigens (see below). The structure of a typical gene in this family, the DRα-chain gene, is shown in Fig. 2 (8, 21). Its exons faithfully represent the domains of the protein structure, and the manner of its transcription to form mRNA, subsequent translation and posttranslational processing to form the mature protein, is also illustrated. The cDNA clones originally obtained by a variety of methods were used to probe λ-phage libraries in order to obtain the genes and cosmid libraries to obtain gene clusters. Five such clusters have been obtained (8) (Fig. 3): (1) the DP cluster (110 kb encoding SXβ, SXα, DPβ, and DPα; (2) the DX cluster (35 kb) encoding DXβ and DXα; (3) the DQ cluster (50 kb) encoding DQβ and DQα; (4) the DR clusters encoding DRβ and a DRβ pseudogene (70 kb); and (5) DR(MT)β and DRα (140 kb). The product of the DRβ gene in cluster 4 is responsible for the generation of antibodies used in typing DR alleles.

Each of the DRβ genes appears to be preceded by a repeated element that includes the signal sequence and upstream promoter sequences (22). Three additional copies of this repeat occur between the DR(MT)β gene and the DRα gene, which are 90 kb

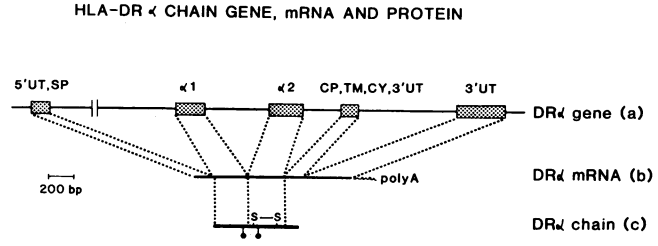

Figure 2. Structure of the DRα chain gene, mRNA, and protein.

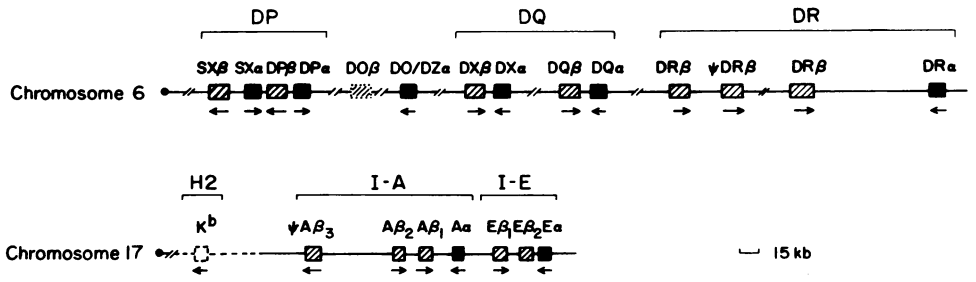

Figure 3. Comparison of the human HLA-D and murine I regions. A schematic representation of the arrangement of the genes encoded within the human HLA-D region on chromosome 6 is shown. A similar map is presented for the murine I region, which is located on chromosome 17.

apart. It is not known whether these additional copies are followed by β-chain genes that have diverged too far to be detected by cross-hybridization, by fragments of degenerated DRβ-chain genes, or by unrelated genes that have come under the control of similar promoter elements. The answer to this question will obviously have some relevance to our thinking about the meaning of linkage of autoimmune diseases to the DRβ gene. In addition to the twelve genes in these five clusters, an additional α-chain gene has been obtained as a phage and cDNA clone (DO-DZα) (20 kb) (23, 24), and an additional β-chain gene has been obtained as a cDNA clone (25); it is unknown whether these are related as a gene pair. The promoter sequences as far as 2 kb upstream of the transcription initiation site may function in the regulation of class II antigen expression. They include sequences important for γ-interferon induction, for example, and are presumably also involved in the normal control of expression of the class II antigens (26). In addition to these *cis*-acting regulatory sequences, *trans*-acting factors, which are essential for gene expression and may be encoded elsewhere in the genome, have been detected (27, 28) and appear to be involved in the bare lymphocyte syndrome, an immunodeficiency syndrome in which class I and/or class II antigens cannot be expressed on lymphocyte surfaces (29, 30).

The rules for α/β-chain association are not presently known and certainly may be relevant to our thinking about autoimmune diseases. Three possibilities that should be considered are: (1) an α-chain can only form a heterodimer with its closely related β-chain, e.g., DQα with DQβ; (2) closely related α-chains can form heterodimers with each other's β-chains, e.g., DQα with DXβ and DXα with DQβ; or (3) any α-chain can form a heterodimer with any β-chain, although such products may be formed only in small amounts and as low affinity interactions. A particularly relevant case is the question of interaction within a family itself. The DPβ, DQβ, DRβ, and DR(MT)β-chain genes are polymorphic, but among the α-chain genes only DQα is also polymorphic. One peculiarity of the polymorphism is that the DQα polymorphism is in linkage disequilibrium with the DR(MT)β-chain gene polymorphism, i.e., DQ2α and DR(MT2)β with DR3, 5, (6) and 8, and DQ3α and DR(MT3)β with DR4 and 7. By contrast, DQβ is in linkage disequilibrium with different sets of DRβ alleles: DQ1β with DR1, 2, and 6, DQ2β with DR3 and 7, and DQ3β with DR4, 5, and 8. Notice that these disequilibria would be identical if DR3 and DR4 switched in either series. DR3 and DR4 are the two alleles related to type 1 diabetes and the DR3,4 heterozygotes are especially at risk (7). The high risk of the DR3,4 heterozygotes could be particularly explicable if *trans*-association occurred so that a DQ2α, DQ3β, and/or a DQ3α, DQ2β heterodimer could be formed. This class II product could then be involved in the genesis of type 1 diabetes.

Biology of the HLA system

Several additional factors need to be considered in a hypothesis relating to the origins of autoimmune diseases in addition to (*a*) the linkage to a particular class II allele. These include: (*b*) the data that suggest that some of these diseases at least may involve the interaction of two susceptibility genes, only one of which would be an MHC gene (31, 32); (*c*) the repeated suggestion supported by animal models that viruses may play some role in the genesis of at least some of these diseases (33, 34); (*d*) the relatively low extent of concordance in monozygotic twins (although higher than in dizygotic twins or families) (35, 36); and (*e*) the specificity of the disease process in many instances for a particular target tissue, e.g., β cells of the pancreas in type 1 diabetes, myelin in MS, joint lining in rheumatoid arthritis, etc. Before attempting to fit these ideas into a hypothesis regarding the genesis of autoimmune diseases, one aspect of the biology of class II antigens should be emphasized.

In a broad sense it has been thought that class II MHC antigens function primarily as restriction elements in the presentation of foreign antigens by antigen-presenting cells to helper T cells in the genesis of the humoral immune response (antibodies) (6), and that class I antigens function primarily in the presentation of viral antigens to precursors of cytotoxic T lymphocytes in the genesis of the cellular immune response (37). Allorecognition by CTL is regarded as a "crossreaction" of CTL generated in this latter manner (38). However, after human class II antigens were purified in biochemical quantities, they were inserted into liposomes and found to be able to stimulate the generation of class II–directed CTL in a secondary xenogeneic immune response employing primed mouse spleen cells (39), as had previously been demonstrated for human class I antigens (40). Similar studies using human peripheral T cells demonstrated that class II antigens could also act as stimulators for the generation of alloimmune human cytotoxic T cells directed against class II alloantigen targets (41, 42). More recently it has been shown that class II antigens can also act as restricting elements for some viral antigens and in the case of measles virus, for example, they are used preferentially as the restricting element rather than class I antigens (43). The phenotype of these class II–directed CTL is $T3^+$, $T4^+$, and $T8^-$, while class I antigen-directed CTL are $T3^+$, $T8^+$, and $T4^-$ (41, 42, 44). Thus, it was suggested that T4 and T8 are markers, not for the function of the T cell subset but for the class of MHC antigens with which that subset must interact in its immune function.

A hypothesis for the generation of autoimmunity

My hypothesis for the development of autoimmunity will take account of the five observations relating to these diseases stated above: (1) their linkage to class II MHC alleles; (2) the possibility of involvement of a second gene; (3) the possible role

of viruses in development of these diseases; (4) discordancy in monozygotic twins; and (5) tissue specificity. In this hypothesis, some virus infection (e.g., measles virus in the case of MS (45), or Coxsackie virus or rubella (34) in the case of juvenile-onset diabetes) sets the stage by initiating the development of class II–restricted virus-specific CTL. It should be emphasized that the virus may be a ubiquitous agent and might infect any cell, not necessarily the target cell for the disease (e.g., myelin sheath or β cell of the pancreas). The resultant class II–restricted CTL would have a broad specificity, as is illustrated both by the ability of these CTL to function in allorecognition and in another context by the very large number of foreign antigens that can be presented by a limited number of class II antigens to helper T cells. As a result of this broad specificity, these class II–restricted, virus-specific CTL may crossreact with a determinant on some surface protein on normal cells (e.g., a protein in the myelin sheath or a protein on the surface of the pancreatic islet β cells); an identity in a sequence as small as 5–8 amino acids would be sufficient as a recognition site. The recent discovery of a sequence with 8 identities in 12 residues (including five consecutive residues, random probability = 20^5) between A-gliadin, a wheat protein known to activate coeliac disease, and the 54-kd E1b protein of adenovirus type 12, may be the first example of this relationship (46). Conceivably some environmental agent other than a virus (e.g., gliadin or some other dietary component) may itself provoke the primary immune response. The essential element would be any agent that can provoke a pauciclonal expansion of a CTL bearing a T cell receptor idiotype with a cross-reactive potential for some normal tissue component (or even in some cases a pauciclonal B cell proliferation resulting in an immunoglobulin bearing a particular disease-associated idiotype, as in the production of rheumatoid factor). Only some class II HLA alleles as restricting elements will result in generation of this cross-reactive CTL, thus explaining the linkage to an HLA allele (e.g., the DQ2 allele in coeliac disease or the DQ3α, DQ2β product in the case of juvenile-onset diabetes). Indeed it is not yet known whether a particular polymorphism of a class II gene, i.e., a special disease allele, may be related to some autoimmune processes, but it should be emphasized that this need not be an essential feature of these diseases.

However, autoimmunity is relatively rare, although infection with viruses such as adenovirus, measles, rubella, and Coxsackie is nearly 100% in the human population. Thus, the second gene involved in the genesis of these diseases may determine a polymorphism for another element involved in the system. There are two obvious possibilities: (1) a polymorphism for one of the chains of the T cell receptor, or (2) a polymorphism for the target antigen; i.e., these CTL may recognize in the crossreaction only an infrequent variant of the target protein. There are many other possibilities of course, e.g., a gene determining susceptibility to repeated virus infection perhaps even related to an Ig allotype (31), but some factor involving either the T cell receptor (which recognizes the cross-reactive epitope) or the target protein would immediately provide a firm basis for the tissue specificity in autoimmunity. Although this article has focussed on the role of CTL, a similar discussion would apply to the role of autoantibodies in the genesis of other autoimmune diseases. At least two (and possibly three) genes have been implicated in the development of diabetes in the genetically susceptible BB rat, one an MHC gene and the second a gene determining a lymphopenia, apparently the consequence of some abnormality in T cell development (32, 47). Is it possible that the latter is a defect in T cell receptor rearrangement, leading to limited pauciclonal T cell development in which a particular T cell receptor idiotype with autoimmune potential is dominant?

Finally, monozygotic twins are no longer identical after the maturation of the immune system. Generation of the repertoire of CTL by rearrangement of the T cell receptor genes (48, 49) (as well as Ig genes) is a stochastic process that will result in the generation of a different set of CTL directed against the same foreign antigen and with different potentials for cross-reaction. Thus, chance may play a prominent role in the potential for any individual to develop an autoimmune disease, either a chance mutation of a single amino acid in the gene for some surface protein or for one of the chains of the T cell receptor, or a chance rearrangement of a T cell receptor gene resulting in a potential for recognition of a cross-reactive tissue antigen. Both the familial occurrence and the sporadic nature of autoimmune diseases are consistent with this hypothesis. It is not necessary to postulate a chance encounter with some virus or other environmental agent to explain the discordancy in monozygotic twins. Our knowledge of the nature and size of V, D, and J region families of the α- and β-chains of the T cell receptor that determine the specificity of the receptor is rapidly increasing. However, the paucity of information about the target proteins represents a large gap in our knowledge in this field. Only in the case of myelin basic protein, implicated as the target antigen in experimental allergic encephalitis (a possible model for MS), do we have any information at all.

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