Human Leukocyte Antigen: A review Article

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Abstract

Within the last 20 years, the rapidly developing field of study has produced the human leukocyte antigen (HLA) or tissue types. Many researchers recognized the presence of a complicated sequence of transplantation antigens early in the study. Still, it was commonly assumed that these antigens would not be well-defined even in this century. Nonetheless, in the last two decades, an international nomenclature committee has discovered 124 distinct HLA antigens determined by at least seven tightly linked genes on the short arm of chromosome 6 and subsequently agreed upon. The area has evolved swiftly thanks to extensive international collaboration spurred by the potential therapeutic application of these antigens in clinical Transplantation. During this time, nine worldwide histocompatibility workshops were organized. The HLA antigens were associated with disease susceptibility to a greater extent than any other known genetic marker in man, which was of primary clinical importance in Transplantation and great basic interest in human genetics and anthropology. An unexpected bonus was discovering that HLA antigens are associated with disease susceptibility to a greater extent than any other known genetic marker in man.

Keywords: Human Leukocyte Antigen, Genetics of the HLA System , Immune Responses , Nomenclature

1. Introduction

The term immunity comes from a Latin word immunitas, which refers to Roman senators' immunity from legal prosecution throughout their terms in office. Immunity has traditionally meant protection against disease, particularly infectious diseases. The immune system is made up of molecules and cells responsible for immunity, and the immune response is their coordinated and collective response to the introduction of foreign substance. In rare cases, an exact mechanism which generally protect people from infection and remove unwanted substances can also cause tissue harm and illness. Even self-molecules can provoke immunological responses in some situations (so-called autoimmune responses) [1].

The HLA system has been discovered as the most complex and polymorphic human gene system. Even though the HLA system has only been studied for a short period, we have made remarkable progress in our short period. The study of anthroposociology, clinical medicine, fundamental medicine, and other fields might benefit from HLA research since it elucidates the structure and numerous biological roles of genes and proteins involved with the HLA system. HLA research has resulted in not only revolutionary changes in basic medical disciplines like anthroposociology, genetics, heredity, immunology, and biology but also in many clinical medicine specialties like vaccination, genesiology, ecsomatics, forensic medicine, transfusion science, oncology, and organ transplants, as well as disease-related fields of internal medicine. As a result, utilizing the suitable statistical analysis to organize and analyze HLA research data is crucial. The correct application of statistics may directly impact the scientific character, accuracy, and objectivity of HLA-related research.

Furthermore, in addition to the concepts and methods of biomedical statistics prevalent in other life sciences, statistical analysis of HLA research data has its own set of needs that incorporate contemporary bioinformatics theories and methodologies. Bioinformatics is a significant research area in biomedical statistics and a vital biomedical research subject that is expanding from macrocosm to microcosm [2]. It combines a variety of statistical methodologies, mathematics, computer technology, and biotechnology into a critical subject that is quickly becoming a significant source of biological discoveries, therefore serving a vital role in the organization and processing of relative HLA research data [3].

History

The immune system was thought to be incapable of reacting against the body's tissues in the later 19th century. At the start of the twentieth century, Paul Ehrlich suggested the idea of horror autotoxicus. Ehrlich eventually revised his concept to account for the potential of autoimmune tissue assaults. However, he still felt that some inherent defense systems would keep the autoimmune response from becoming pathological.

The discovery of a chemical in the serum of individuals with paroxysmal cold hemoglobinuria that interacted with red blood cells in 1904 cast doubt on this notion. Several illnesses might be connected to autoimmune reactions in the following decades. The authoritative character of Ehrlich's premise, on the other hand, made it difficult to comprehend these findings. Immunology shifted from a clinical to a biochemical field. The current knowledge of autoantibodies and autoimmune disorders began to expand in the 1950s.

More recently, it has been established those autoimmune reactions (sometimes known as “natural autoimmunity”) represent an essential feature of vertebrate immune systems [4]. Autoimmunity should not be confused with alloimmunity.

In 1958, Dausset's discovery of the antibody detecting the human leukocyte antigen (Mac) (HLA-A2)1 introduced the science of human histocompatibility testing. Leukocyte

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antigens, initially tested only for organ transplantations [5, 6] and later blood transfusions, s' 7 are now known to have a strong relationship to immune responsiveness and disease susceptibility [2, 7-9]. The current and future clinical usefulness of HLA testing is based on several significant scientific observations and technologic advances such as the transformation of a mixed lymphocyte culture into a unidirectional test, and the capacity to freeze lymphocytes for reference cell type [10], the creation of the National Institutes of Health's Serum Bank as a repository for high-quality typing reagents, the miniaturization and standardization of the cytotoxicity technique [11], the discovery of parous females as the excellent source of antibody [12], and its reduction to a micro method [13], the exploration of cellularly defined antigens by homozygous typing cells (HTC) and primed lymphocyte testing (PLT) [14], and the rapidly developing identification of new leukocyte antigen systems by serologic reagents for B-cell antigens [15]. Each of the worldwide workshops on histocompatibility antigens has defined a benchmark for development. Amos of Duke University organized the first workshop to compare the number of evolving approaches for recognizing leukocyte antigens. In 1965, participants in van Rood's second workshop in Leiden, Holland, examined people from the "Leiden panel" with their procedures and sera and discovered comparable responding sera and antigens. Dr Ceppellini picked Italian families for cooperative study at the Turin workshop in 1967, finding that leukocyte antigens were regulated by a single chromosomal region and were extremely variable. In 1970, Dr Paul Terasaki's fourth workshop in Palm Springs, California, included data on family typing supplied by each scientist working in his laboratory, which was done using a standardized procedure and a panel of typing sera. With the increasing number of identified antigens, at least two segregant antigen series existed in 1970. Each worked as though a multiple allelic series regulated the corresponding antigens at closely linked loci or a single complicated genetic locus. However, fractures began to form in the foundations of previously recognized antigens like A3, B5, and B7, and the intricacy of cross-reacting antigens and "splits" began to emerge. 3 Population studies from across the world were the focus of Dr. Jean Dausset's sixth workshop at Evian, France, in 1972. It shows that race significantly impacts the frequency of histocompatibility antigens. Dr Fleming Kissmeyer-Nielsen, of Aarhus, Denmark, led the 6th international workshop, which looked at not only the serologically defined (SD) antigens of the A, B, and C loci, but also the lymphocyte-defined (LD) antigens of the D locus defined by homozygous typing cells (HTC) in unidirectional mixed lymphocyte culture. The 1977 workshop in Oxford, England, organized by Drs. Walter and Julia Bodmer focused primarily on B lymphocyte antigens (DR antigens) that may be analogous to la antigens studied in animals. Recently, the details of these systems in mice were examined [16] and are discussed later

The origins of HLA typing may be traced back to early attempts to classify leukocyte kinds. Even though red cell antigens had been known since Landsteiner's time, early attempts to use red cell type methods to identify antigens on leukocytes were plagued by technical difficulties. Walford! and Killman thoroughly examine these historical procedures and tactics. 2 Dausset described MAC as one of the first antigens characterized by leukoagglutination in 1958 [6]. Due to the inaccuracy of the leukoagglutination test, this specificity could not be clearly proven by the time of the First International Histocompatibility Workshop in 1964. At this workshop, the typing methodologies employed by several laboratories were reviewed, and Terasaki developed a microdroplet lymphocytotoxicity test, which was later adopted as a standard way of typing. [4] The advent of computer algorithms by van Rood-6 to sort out antigenic specificities greatly aided the development of HLA typing. Despite the multiple false-negative and false-positive responses contained in the information, certain specificities may be determined using these tools. Van Rood-7 convened the Second Histocompatibility Workshop in 1965. The relationship between specificities documented independently by the pioneer laboratories was seen at this workshop for the first time. These connections were later established in the workshops that followed. For the first time at this workshop, it was also stated that the MAC antigen, which Dausset first characterized, had been defined separately by five additional laboratories. Payne et al. descriptions's of LA-I, -2, and -3 [7]. Dausset's hypothesis that we were dealing with products from a single locus based on the correlations between the specificities is one of the canonical descriptions of allelism in HLA antigens, as verified by the workshop [8]. However, Cappellini's wonderfully organised Third International Histocompatibility Workshop1O unexpectedly grouped all of the identified antigens into a single locus constituted of two antigen series, as Kissmeyer had recommended. [9]. The segregation of HLA haplotypes in families could now be convincingly proven. In 1967, the official World Health Organization (WHO) Nomenclature Committee was formed due to worldwide collaboration in HLA research. Terasaki [12] convened the Fourth International Histocompatibility Workshop in Los Angeles, which established the two HLA-A and HLA-B loci as we know them today. For the first time at this meeting, all laboratories agreed to use microlymphocytotoxicity assays to standardize HLA testing. The laboratories could share antisera by mail and compare typing findings due to this standardization. The micro-test also allowed several tests with a tiny amount of reagent. For 1000 tests, one milliliter was adequate. In 1972, more than Sixty populations from across the world were typed for HLA antigens by 75 laboratories, which was perhaps the pinnacle of international collaboration. The same reagent was used by all of the foreign laboratories in these genetic investigations, allowing the serum reactivities and antigen frequencies to be compared. The book that resulted from the workshop [15] The better single source of antigen frequencies among the world's diverse populations is still available. Kissmeyer's Sixth International Histocompatibility Workshop initially discussed the HLA-C

and- D loci. There, it was demonstrated that the C locus could be recognized individually. Mixed lymphocyte culture (MLC) tests suggested that there may be a fourth locus (D) that is intimately tied to the HLA complex. The D locus and a novel DR locus characterised by serologic approaches were established during the Seventh International Histocompatibility Workshop in 1977, held under the guidance of Bodmer [10]13. Homozygous typing cells were used to identify the D locus specificities. Individuals who tested positive for specificity did not react to the homozygous typing cells of that specificity in these tests. As a result, a person's cells that do not respond with DW2 homozygous cells might be categorized as DW2 specificity positive. Most importantly, B cells were successfully typed for their DR specificities despite severe technical challenges. B lymphocytes are extracted from blood samples and then tested for DR antigens using the standard microcytotoxicity assay. Because B cell isolation procedures were first problematic, most of the responses were comparable to those employed in the early days of leukoagglutination assays. However, during that workshop, specificities for the DR locus were determined. The letter "R" in DR stands for "related" because this locus was identical to or comparable to the D locus discovered using MLC methods. A complete account of the serology and genetics of HLA loci and their specificities was published in a paper derived from the Eighth International Histocompatibility Workshop held in Los Angeles in 1980 [13]. Under the chairmanship of Albert and Mayr, the Ninth International Workshop was held. [13] When assessing papers on HLA and illness connections, keep in mind that the HLA antigens that are now known have developed over the previous 15-20 years. The findings of the cell exchange procedure presented in Tables 2.1 and 2.2 may be the best assessment of the development of these antigens. Lymphocytes from four persons were sent to over 200 laboratories throughout the world for HLA typing on a monthly basis for the last ten years.

Nomenclature

The WHO HLA Nomenclature Committee gave new terminology for the 59 SD antigens of the A, B, and C series, the 11 LD antigens of the newly identified D series, and the seven additional DR antigens following the 1977 workshop. The region or system designation for the histocompatibility antigens remains HLA, formerly written HL-A. The original interpretation of HLA was human leukocyte locus A" but is now considered more appropriately as the human lymphocyte antigen system since antigens of all four of the known loci of this system have been detected on lymphocytes. The five loci thus far defined within the HLA system have been given the designations A, B, C, D, and DR. The A, B, C, and DR series of antigens are serologically defined and thus sometimes designated SD. In contrast, the D locus antigens, which initially and primarily were detectable by mixed lymphocyte culture reactions, have been designated as cellularly defined (CD) or lymphocyte defined (LD) [17]." Antigens of each of these loci that have official World Health Organization acceptance are now designated as HLA-A, HLA-B, HLA-C, HLA-D, and HLA-DR with the appropriate Arabic number for the antigen specificity. If an antigen is only provisionally accepted, a "w" is inserted between the locus letter and the antigen number, e.g., HLA-Bw22. For reference to the older literature, it should be recalled that the A locus was previously known as the first locus, and before that, the LA locus; the B locus was previously known as the second or the Four locus; the C locus was previously known as the third locus or as the AJ locus; and the D locus was known as the mixed lymphocyte culture (MLC), the mixed lymphocyte reaction (MLR), the LD, and briefly as the "a" locus. The DR antigens, which initially were thought to be simply the serologic equivalents of HTC-derived D antigens are now felt to represent the gene products of a distinct, nearby locus, DR. An example of a genotype for an individual written in terms of the two haplotypes for that individual would be as follows: HLA-A2, B12, Cw5, DRw4/HLA-A3, Bw22, Cwl, DRw2. If there is an undetected antigen in a family study, then the unknown specificity may be designated with the capital letter designating the locus to which it belongs in conjunction with a hyphen afterwards indicating the blank or undesignated antigen [18]. A complete listing of all the recognized HLA specificities, and further details of the precise forms for writing genotypes and phenotypes in either extended or abbreviated fashion have been published." More extensive listings of the older nomenclature and equivalents of current antigen specificities are also available [19]. It should be appreciated that the first human leukocyte antigen was described only about 20 years ago and that the number of accepted antigens has increased rapidly within the last few years. In 1967, there were only six accepted specificities, HLA-A 1, 2, 3, and HLA-B5, 7, and 8; whereas in 1970, the number almost doubled to 11 specificities, HLA-A1, 2, 3, 9, 10, 11, and HLA-B5, 7, 8, 12, and 13. The current listing of 77 specificities represents a dramatic increase in the number of antigens to be considered in the use of this system. Part of the increase in the number of these antigens is due to "splits" of previously intact specificities such as A9 splitting into Aw23 and Aw24, while others represent new antigens, e.g., B37. Still there are serologic similarities extending beyond single antigens so that cross-reacting groups (CREGS) are a well-accepted phenomenon [2]. Another important set of antigens, not yet as well defined in man, are the so-called immune response antigens detected in the mouse and other species of inbred animals.

Individual laboratories applied new names to the specificities (antigens) uncovered in the early phases of HLA research. Because several antigens were found separately in various regions of the globe, it was evident that a universal and standard nomenclature for the HLA antigens was required [20]. In 1969, the WHO established a Nomenclature Committee that published its first report in 1970. Since then, the HLA nomenclature committee has convened after each international workshop to update and assign new names for the antigens based on the data gathered at the workshop. These naming conventions, which have been in place since the beginning, have allowed the field's orderly and quick development.

Immune Responses

The word immunity comes from the Latin word

immunitas, which alludes to the legal Roman senators' immunity throughout their tenure in office. Immunity has traditionally meant protection against disease, particularly infectious diseases. The immune system is made up of molecules and cells responsible for immunity, and the immune response is their coordinated and collective response to the introduction of foreign substance. Although the immune system's primary role is to defend against infectious germs, it may also trigger immune responses to non-infectious foreign substances and damaged cell products [20]. Furthermore, under rare circumstances, the same processes that ordinarily defend persons from infection and remove unwanted substances can also cause tissue harm and illness. As a result, a broader definition of the immune response includes any reaction to microorganisms or molecules identified as alien, regardless of the pathologic or physiologic consequences of such a reaction. Even self-molecules may provoke immunological responses (so-called autoimmune responses) in particular circumstances. Immunology is the scientific study of immune responses in general and the cellular and molecular events that occur when an organism comes into contact with bacteria and other foreign macromolecules. Historians frequently credit Thucydides of Athens, who lived in the fifth century BC, as the first to mention immunity to a disease he named plague (but that was probably not the bubonic plague we recognize today) [21]. The ancient Chinese habit of making infants immune to smallpox by having them inhale powders derived from the skin lesions of patients recuperating from the disease suggests that the idea of protective immunity may have existed long earlier. In its present form, immunology is an experimental discipline in that explanations of immunologic phenomena were based on experimental observations and findings. A capacity to modify the immune system's activity under controlled settings has been critical to the evolution of immunology as an experimental field.

Edward Jenner's successful vaccine against smallpox was the first unambiguous example of this manipulation, and it remains one of the most spectacular ever documented. Jenner, an English physician, noted that milkmaids who had recovered from cowpox never got smallpox, which was more dangerous. He injected the material from a cowpox pustule into the arm of an 8-year-old child based on this finding. The illness did not develop when this youngster was purposely vaccinated with smallpox [22]. In 1798, Jenner published his seminal dissertation on vaccination (Latin vaccinus). It resulted in a broad acceptance of vaccination as a technique of producing immunity to infectious illnesses, and vaccination is now the most effective infection prevention method. The declaration by the World Health Organization in 1980 that smallpox had been eliminated globally through a vaccination campaign was an eloquent monument to the value of immunology. There has been a dramatic shift in our knowledge of the immune system and its functioning since the 1960s. Thanks to genetically altered animals (especially transgenic and knockout mice), x-ray crystallography, recombinant DNA methodology, immunochemistry, and advances in cell culture techniques, immunology has evolved from a primarily descriptive science to one in which diverse immune phenomena can be explained in structural and biochemical terms (including monoclonal antibody production) [22]. The discovery of medicines targeting distinct components of the immune system based on fundamental science and drastically modifying the path of human inflammatory illnesses and malignancies has been one of the most critical developments in immunology since the 1990s.

Fundamental Facts Concerning HLA Antigens

The HLA antigens are glycoproteins which can be found in the serum, saliva, and urine of man. The antigens exist on the surface of all tested cells in the human body 5 with the possible exception of the mature erythrocyte and trophoblast. They exist on the reticulocyte but appear to be virtually extinguished on the mature erythrocyte, although some evidence indicates that certain antigens can still be present in small quantities here also." Furthermore, they might exist as single haplotypes on the surface of human sperm. HLA antigens have been found in the cellular portion of the renal glomerulus but not in the glomerular basement membrane component [21]. The HLA antigen is made up of two noncovalently bound polypeptide chains, one heavier with a molecular weight (MW) of about 33 KD and the other lighter with a MW of about 11 KD, according to studies, the HLA antigens were extracted from the cell surface membranes of grown lymphoblastoid cells using papain [22]. The 11 KD polypeptide is identical to the β-2-microglobulin protein, which shares structural similarities with the IgG heavy chain's CH3 region [23]. Molecules of beta-2-microglobulin appear to be more numerous (6 x 107 molecules) than the 33,000-dalton HLA molecules (4.5*104) on the cell surface of the human lymphocyte.29 Although the heavy and the light chain are closely related anatomically on the cell surface of lymphocytes, " the genetic control for these two polypeptide chains appears to be different. The heavy chain of the HLA molecule is under genetic regulation on the 6th chromosome, whereas that for beta2-microglobulin is on the 15th chromosome [23]. The other major lymphocyte antigen system currently under intense investigation is that on B lymphocytes [24]. Biochemical studies on these so-called la antigens derived by papain treatment have shown that they also have two noncovalently-bound polypeptide chains, one about 30,000 and the other about 23,000 Dalton, but no beta-2-microglobulin. In order to avoid confusion between the HLA antigen system and other antigen systems unique to a certain cell type, it should be stated here that although platelets, neutrophils, and lymphocytes all have HLA antigens, in addition, lymphocytes have non-HLA antigen systems, 32 neutrophils have three known systems (NA, NB, and 9),33 and platelets have specific systems (PLA, PLE, and KO). Other cells may have differentiation antigens as well which are characteristic of their own histologic type [25]. Antibodies to HLA antigens are generally of the IgG class but IgM antibodies have also been reported. The IgM antibodies in particular seem to have a greater reactivity at lower temperatures and comprise some of the

autocytotoxins seen in diseases such as lupus erythematosus.35 Within the HLA system there is suggestive evidence that certain antigens may be stronger transplantation antigens than others. Both clinical and experimental studies are compatible with the concept that HLA-A2 is a relatively strong histocompatibility antigen36' 39 and conversely, that HLA-A1, 3, and 11 are weaker [26]. The proximity of the B locus to the D locus has made the B-series antigens appear stronger, a point borne out in several clinical studies though not in all.From the results of immunization studies, the C-series antigens appear to be weak.46 Skin-graft studies would suggest that D-locus antigens are more important than any of the SD antigens. [27]"8 A clinical bone marrow success in which only the D-locus antigens were matched and all [27]the SD antigens were incompatible also support this possibility, although recently, a D-locus incompatible, SD-identical graft has also been successful [28].

Genetics of the HLA System

The A, B, C, D, and DR series of HLA antigens are controlled by linked but distinct loci on the sixth chromosome. The gene at each locus has multiple alleles, the products of which are the antigen specificities [29]. The HLA alleles are codominant. The unit of inheritance of these antigens is designated a haplotype which represents the contribution of one parent to the offspring. A haplotype will have no more than one antigen from each series, currently giving a total of five. The phenotype of an individual who has inherited one haplotype from each parent will have a total of ten antigens, two from each series. An example of a family with all of the antigens detected in each series. In this family, the parents each have two different haplotypes. This is the typical situation in a random population with four different haplotypes occurring in the two parents. Among their children, there is a 25% chance of two of the children being a 2-haplotype identical match, a 25% chance of a 0-haplotype match, and a 50% chance of a 1-haplotype match. The details of this are described in Figure 2. If the family is one in which the parents share a single haplotype, then in addition to the HLA-identical sibling pair, there is now the possibility of identical parent-child matches [30]. Furthermore, the sharing of a parental haplotype that may be especially found in the marriages of first cousins can lead to offspring who are homozygous for all of the antigens of the A, B, C, and D series. The homozygosity of the D-series antigen renders such an individual's cells useful as "LD typing cells" or HTC as described earlier. The affinity of two antigens from separate series is called "linkage disequilibrium" when they are coupled with a higher degree of frequency than would be predicted based on their independent frequencies in the population [31]. A number of such associations have been shown in Caucasians. Examples of these associations between antigens of the A and B series are A29-B12, A2-B12, A3-B7, and A1-B8; between antigens of the B and C series, Bw35-Cw4, B40-Cw3, B27-Cw2, Bw22-Cwl, and B5-Cwl; between antigens of the B and D series, Bw35-Dwl, B8-Dw3, B7-Dw2, and B15-Dw4; and between antigens of the A, B, and C series, Aw23, B12, and Cw4. The clinical usefulness of linkage disequilibrium lies in the fact that if one is unable to specifically identify a D or DR series antigen, one increases the probability of identifying it by finding the B- or the D-series antigen with which the missing antigen is in linkage disequilibrium. Individual HLA antigen frequencies and the sum of the frequencies of antigens defined in each of these series can vary significantly according to race. For example, in Caucasians, approximately 98% of the antigens in the A series, 90% of those in the B series, and 50% of those in the C, D, and DR series have been identified. However, in Blacks, Orientals, and other races, fewer of the antigens in these series are identified than in the Caucasian population [32]. Therefore, other antigens, in addition to those found in Caucasians, may exist in these other races and still must be identified. An example of individual antigen frequencies changing with race can be seen with Al and B8; these are among the most frequent antigens found in Caucasians but are not found in Japanese.3 ' 65 The Fifth International Histocompatibility Workshop was devoted to the study of racial influences on HLA." The A, B, C, and D loci are in reverse, skip order: D, B, C, and A, according to genetic mapping of the histocompatibility loci on the sixth chromosome. The DR locus is probably closest to the D locus. Also mapping in this chromosomal region, called the Major Histocompatibility Complex (MHC), are the genes, which control the levels of C2 and C4; the structural gene for C2; properdin factor B, also known as glycine-rich betaglucopeptide (Bf); and the Chido and Rodgers blood groups now known to be components of C4. Data concerning the locus for C6 being in the MHC are conflicting [33]. The la antigens may well be controlled by several genes at loci distributed throughout the MHC and intermingled with the HLA loci. Although not yet formally assigned to this region, immune response genes and genes conferring susceptibility to certain diseases have been placed in the MHC in man. Also closely associated with D-locus gene products is the lymphocyte Fc receptor [34].

ANIMAL STUDIES AS THE BASIS OF THE RELATIONSHIP OF DISEASE SUSCEPTIBILITY AND IMMUNE RESPONSIVENESS WITH HISTOCOMPATIBILITY, IR, AND IA ANTIGENS immune responsiveness (IR) and disease susceptibility (DS) has its basis in studies of inbred strains of mice and guinea pigs.12 The most extensive studies have been done in mice. Lilly first found that a gene which conferred resistance to Gross leukemia virus (Rgv-1) appeared to be linked to the H-2 histocompatibility complex. Similarly, an H-2 association was found for Friend, B/T, and radiation leukemia virus, mammary tumor virus, lymphocytic choriomeningitis (LCM), and autoimmune thyroiditis. [35] Recently, Smith has reported that there are H-2 related differences in the spontaneous occurrence of tumors in inbred mice 9 months or more in age.6 This first area of disease susceptibility in the form of autoimmunity, virus infection, and viral oncogenesis being related to histocompatibility antigens was expanded into a second area by numerous studies which showed that the immune responsiveness to approximately 20 different natural and synthetic antigens was controlled by genes linked to H-2 histocompatibility genes [36] In mice, the major histocompatibility complex (MHC) is located on the 17th

chromosome and consists of five major regions: K, I, S, G, and D . The H-2K locus appears analogous to the human HLA-B locus, and the H-2D to the HLA-A locus. The gene products of these loci function as transplantation antigens, weak stimulators in MLC, targets in cytotoxicity, and possibly as a means of immune surveillance [37]. The S-region genes control the production of certain serum proteins including complement and therefore seem related to the complement component genes mapped in the human major histocompatibility complex (MHC). It is the I region that has unfolded with the greatest complexity and has the genes that primarily regulate the immune response to thymus-dependent antigens, antigens that stimulate T cells in the MLC and GVH reaction, and B cell production of la antibodies [1]. Recently, an I region locus has been found that controls surface determinants on suppressor T cells [7].The major MLC locus analogous to the D locus in man is located in the I region in the mouse. Within the I region there are sets of marker loci: Ir and la." Ir antigens are immune response antigens that appear to be expressed primarily on T cells and are identified by variable degrees of antibody response to particular antigens and sensitivity to viral oncogenesis [38]. La antigens are I-region-related antigens usually present on B lymphocytes and were detected by serology. Within the I region are the subregions 1-A, 1-B, 1-J, 1-E, and 1-C, in which the Ir- and la-marker loci are Ir-lA and Ia-1; Ir-lB and Ia-2; Ia-4, Ir-lC and Ia-5; and Ia-3, respectively. Ir-lA is located near the K end of the MHC, and Ia-3 toward the D end. The Ir-lA gene has the strongest, but not the sole, control of MLC reactivity and thus resembles the HLA-D locus of man. Rgv-1 may be an Ir gene located near the K end of the I region and therefore in or near the la subregion. A potentially important locus recently described in mice is the Ia-4 locus of the 1-J subregion that controls suppressor cell activity and unlike other la loci, has its gene products expressed predominantly if not exclusively on T cells [7]. Unfortunately, no comparable locus has yet been defined in man, though such a locus probably does exist in the MHC and could modify immune responsiveness. The immune responses to natural and synthetic antigens have been mapped with several of the la loci. Until very recently, it was assumed that only one histocompatibility-linked Ir genewas required to control the immune response to a single antigen. But it has been found that the immune response in mice to certain synthetic antigens is controlled by two dominant histocompatibility-linked Ir genes [2] The response is generally greater in the cis than in the trans position. McDevitt has expanded this scheme to include five such systems that require a gene in the A subregion and the C subregion complementing each other in the cis or trans position to give an immune response [8]. The parallel of this in man would be the requirement for one haplotype with both Ir genes or two haplotypes each with an Ir gene probably marked by D-locus antigens. Thus, from elaborate experiments in animals, the evidence that two Ir genes are necessary for the response to an antigen is compatible with the findings in human diseases that suggest the necessity of at least two Ir genes for disease susceptibility [39].

POSSIBLE MECHANISMS OF HLA AND DISEASE ASSOCIATIONS: SEX PREVALENCE

Which may be responsible for histocompatibility antigens being associated with diseases is that different diseases may have different mechanisms and that a disease might have one initiating and another sustaining mechanism. Furthermore, some of these mechanisms blend into one another, e.g., virus receptor and altered self-hypothesis. The major mechanisms proposed for HLA and disease association are as follows. First, there may be molecular mimicry, or cross-reactivity, between a pathogen and a histocompatibility or disease-association antigen so that normal immune surveillance mechanisms fail to eliminate the pathogen because it resembles a "self" antigen [40]. There is preliminary and rather tenuous evidence for this mechanism in AS where cross-reactivity between B27 and Klebsiella antibodies has been demonstrated.1 Other indications of cross-reactivity include those between HLA antigens and the streptococcal M-antigen that remains controversial, between transplantation antigens and streptococci, and between allogeneic and autologous platelets in posttransfusion purpura [41] Second, a form of molecular mimicry which is nonimmunologic and actually more like competitive inhibition has been hypothesized by Svejgaard. His concept proposes that "if an HL-A antigen has some incidental resemblance to the binding site of a cellsurface receptor molecule for a given hormone, there could be competition between the receptor and the HL-A antigen molecule." The wide tissue distribution of HLA antigens could offer significant interference with ligand (hormone)-receptor interactions despite the stronger affinity between the latter two. The H-2 control of serum testosterone levels and sensitivity of target organs to testosterone are two pieces of evidence presented in support of the hypothesis. Third, the antigen in question may actually be a receptor for a microbial pathogen or other pathogenic substance. There is no direct evidence for this mechanism, and there is considerable negative evidence from work with measles, lymphocytic choriomeningitis (LCM), and vaccinia virus [42]. The conditions in which there has been some suggestion of this mechanism have been [36] AS with B27 as the presumptive microbial receptor because of its greater than 90% occurrence with AS in Caucasians, [42] gluten sensitive enteropathy because of the response of BS-positive patients to alpha gliadin7 (see Gluten Sensitive Enteropathy [Chapter 7, Section VII.I]), and [42] vesicular stomatitis virus (VSV)-infected cells because of a 50% decrease in HLA concentration. However, in the latter case, the effect of VSV on HLA is most likely based on inhibition of protein synthesis.6 A fourth possibility focuses on the histocompatibility restriction for lymphocytes cytotoxic to virus-infected target cells. The major work leading to this concept has been done by Doherty and Zinkernagel who found that cytotoxic T cells from mice acutely infected with LCMV interact only with H-2 compatible virus-infected cells.8 That this was not an isolated phenomenon was shown by similar H-2 restrictions for T-cell helper activity and for lymphocytes cytotoxic to trinitrophenylated lymphocytes, minor

histocompatibility antigens, male y antigen, and numerous viruses (Rous sarcoma, ectromelia, vaccinia, parainfluenza, murine sarcoma, and SV40). Explanations for the H-2 restriction phenomenon include the dual recognition (or "intimacy") and the altered self (or "interaction") hypotheses [43]. The former theory requires matching of H-2 determinants on the effector T cell and target cell in order for recognition of the target cell to occur. According to the changed self-hypothesis, target cells homozygous for the H-2 gene complex display at least two unique virus-associated antigens, which is more plausible (four in heterozygotes). Different clones of immunological T cells produced in virus-infected animals of the same H-2 type identify these features. Each antigen is an "interaction antigen" coded for in part by the viral genome and in part by genes that map to H-2D or H-2K [44]. The alteration of the cell surface might occur by a conformational change, a hidden or neoantigen, a complex formed between antigen and virus, a biochemical alteration in the antigen, or derepression of other histocompatibility antigens. Consequently, the heterozygous state of an individual and the polymorphic state of the entire histocompatibility system in a population would tend to be protective mechanisms whereby a broad diversity of viruses and possibly other infectious agents can be successfully repelled by H-restricted cytotoxic lymphocytes. A fifth and highly promising mechanism is linkage and linkage disequilibrium between the HLA loci and Ir loci for disease susceptibility [45]. The vast majority of such disease associations are with HLA-B and D-series antigens. Svejgaard has pointed out that because Ir genes are dominant, the lack of an adequate Ir determinant could produce a recessive susceptibility to certain infections, whereas an "autoaggressive" Ir determinant could cause a dominant susceptibility to autoimmune disease.' However, the modification or production of disease by suppressor cells controlled by an la locus must now be considered [2].Almost as a corollary of the linked Ir gene mechanism is the sixth mechanism of linked complement and properdin genes. These factors which mediate many forms of immune injury could be important ancillary factors in disease susceptibility but do not seem sufficient by themselves to account for the total phenomenon. Finally, HLA antigens may act as differentiation antigens that can alter cell-cell interaction. An example of this would be the D antigens that are present only on B cells. This mechanism rests heavily on the tissue distribution of these antigens, but there is relatively little data on the density, distribution, and kinetics of HLA antigens in different tissues. The well-known sex prevalence of certain diseases such as AS and Reiter's disease in males and of myasthenia and chronic active hepatitis in females, all of which have strong HLA associations, suggests that some influence on disease may be afforded by the combination of both sex and HLA antigens. How this influence of sex may be effected is uncertain, but several possibilities exist. First of all, there may be genes capable of determining the level of male or female hormones which may be one of the elements in the development of the disease. Second, it may be that cell-surface receptors for sex hormones may lie in a close proximity to certain HLA antigens associated with that disease and thereby influence the way in which that antigen operates in establishing susceptibility to a disease [46]. These two mechanisms are also described by Svejgaard's nonimmunologic competitive binding hypothesis and its supporting evidence.* Third, the presence of the HY antigen may enhance the development of maleassociated diseases and its absence promote the development of female-associated diseases, possibly through related la genes or steric interference."

Autoimmunity is an organism's immune response to its healthy cells, tissues, and other typical bodily elements. An "autoimmune disease" is defined as a disease caused by this type of immune response. Prominent examples include Multiple sclerosis (MS), dermatomyositis (DM), ankylosing spondylitis, polymyositis (PM), rheumatoid arthritis (RA), Addison's disease, idiopathic thrombocytopenic purpura, Graves' disease, Hashimoto's thyroiditis, eosinophilic granulomatosis with polyangiitis, Sjögren syndrome, systemic lupus erythematosus (SLE), Henloch Scholein Purpura (HSP) sarcoidosis, diabetes mellitus type 1, post-infectious IBS, and celiac disease. Steroids are often used to treat autoimmune disorders. [47].

Autoimmunity is defined as the existence of antibodies or T cells, which react with self-proteins and are found in all people, even those in good health. If self-reactivity produces tissue damage, it leads to autoimmune disorders [45].

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