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Major Histocompatibility Complex Regulation of the Immune Response

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The ability of an organism to distinguish self from nonself is determined by a cluster of genes located in the major histocompatibility complex. Recent advances in molecular genetics and cellular immunology have begun to elucidate the mechanisms responsible for immune response regulation. In this review article, the genetic organization of the murine and human major histocompatibility complexes and the manner by which their gene products modulate immune responsiveness are discussed.

INTRODUCTION

The body's recognition of a foreign substance as nonself initiates a complex cascade of events which leads to an immune response. Regulation of this immune response is controlled by a cluster of tightly linked genes encoded within the major histocompatibility complex (MHC) [1, 2]. While the MHC was originally defined as the site for control of graft rejection, it is now known that MHC genes have a variety of functions including immune response regulation, complement component synthesis, viral and tumor immunity, and cell–cell interactions [3–5]. The direct relationship between immune competence and survival may account for why this genetic region has been so highly conserved over the course of evolution and is present in remarkably similar forms in all vertebrate species [6].

Originally, surgeons and immunologists were interested in the MHC because of its important role in organ graft rejection. Largely through efforts directed at avoiding graft rejection by manipulating the MHC, the general role of MHC molecules in the immune response to foreign antigens became more clearly understood. Recent investigation has demonstrated that MHC molecules regulate the immune response in several ways. Whether this regulation is their primary function is not clear, as it seems possible that other as yet undiscovered levels of regulation of the immune response may exist. Since much of our understanding of the role of the MHC in immune regulation has resulted from studies on the mouse MHC, the structure and function of both mouse and, when available, human MHC molecules will be discussed in this review. Our emphasis will be on the role the MHC genetic locus plays in the establishment, maintenance, and defense of self.

The MHC Genes and Their Products

The murine major histocompatibility genes are contained within 2.0 centimorgans (4000 kilobases) of DNA on chromosome 17 [7, 8]. This *H-2* MHC consists of five distinct gene clusters representative of three different gene families (Fig. 1). The class I molecules, formerly termed the major transplantation antigens, are encoded in the *H-2K* and *H-2D/L* gene clusters which flank the class II and III genes on either side [9]. The class I molecules have been implicated in graft rejection, cell-mediated lympholysis reactions, and viral and tumor immunity [10]. The

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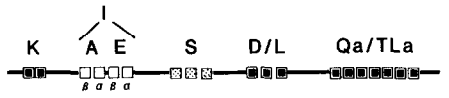

FIG. 1. Genetic organization of the murine major histocompatibility complex (*H-2*). The properties of the class I (■), class II (□), and class III (□) gene products are described in the text.

class II genes, or immune response (*Ir*) genes, important in the generation of immune responses to protein antigens, are located in the *I* region and code for the immune response-associated (Ia) antigens [7, 11]. The class III genes which encode some of the complement component polypeptides are contained in the *H-2S* locus [12]. Finally, distal to the class I, II, and III genes, located in the *Qa, TLa* region, is a cluster of 20–30 related genes, similar to the class I genes, which code for differentiation antigens expressed on certain hematopoietic cells [13, 14].

The class I histocompatibility molecules are composed of two noncovalently associated polypeptide chains: a highly polymorphic 45,000-Dalton glycoprotein coded for by the MHC *H-2K, H-2D/L* genes and an 11,600-Da non-MHC-coded protein of limited variability termed β_2 microglobulin (Fig. 2A) [15, 16]. These molecules are expressed on the membrane of all cells, but are more densely concentrated on lymphocytes [17]. The class I *H-2K* glycoprotein is composed of 346 amino acid residues and two carbohydrate moieties [18]. On the basis of its postulated structure in the cell surface membrane, the molecule can be divided into three external domains of approximately 90 amino acids each, one hydrophobic transmembrane portion, and a hydrophilic intracellular region at the extreme carboxy terminus. The greatest region of class I molecule polymorphism is concentrated within the outermost external domain [19]. This may be important in the recognition of foreign class I glycoproteins as nonself by cytotoxic T lymphocytes.

The molecules encoded by the class I genes fall into two categories by virtue of their differences in cellular distribution, extent of serologic polymorphism, and function. The class I genes contained in the *H-2K* and *H-2D/L* clusters encode the highly polymorphic transplantation molecules found on the cell surface of most nucleated cells. These class I molecules play important roles in T-cell recognition of viral or tumor antigens on infected and transformed cells. In addition, the H-2K, D, and L molecules are involved in cytotoxic T-cell killing and allograft rejection.

The second category of class I genes includes the *Qa-2,3, TLa,* and *Qa-1* which encode for less polymorphic molecules present on certain hematopoietic cells. The function of these molecules is not known [20]. Whereas some of the *TLa* genes code for hematopoietic differentiation antigens found on thymocytes early in development and on leukemic cells, the Qa antigens are located on many different types of lymphoid cells [21–23]. The DNA sequence of these *TLa* and *Qa* genes has been shown to exhibit striking homology to the class I transplantation molecules. Moreover, *Qa-2,3* genes from different mouse strains are as homologous to the genes encoding the transplantation molecules as they are to one another [24].

The class II molecules are encoded by the *I* region of the murine MHC [25]. The *I*-region genes include the Aβ, Aα, Eβ, and Eα genes which code for the four polypeptides that form the Aα:Aβ (I-A) and Eα:Eβ (I-E) molecules expressed on the surface of B lymphocytes, dendritic cells, and macrophages (Fig. 2B) [26, 27]. The α chains range

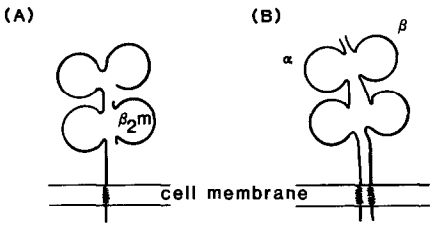

FIG. 2. Schematic representation of the major histocompatibility complex gene products. (A) Class I molecule with its three external domains associated with β_2-microglobulin. (B) Class II molecule composed of one α and one β chain each with two external domains.

in molecular mass from 30,000–33,000 Da and contain two carbohydrate moieties while the β chains contain only one carbohydrate group and range in molecular mass from 27,000–29,000 Da [28]. Each class II polypeptide is composed of two external domains of about 90 amino acid residues in length, a transmembrane region, and a short cytoplasmic portion [29]. In contrast to the class I molecules where one chain (β_2 microglobulin) does not insert into the membrane, both class II α and β chains are transmembrane structures. By comparison of amino acid and nucleotide homologs between the α and β chains, the α chains have been shown to be more tightly conserved whereas the β chains are more polymorphic [30]. This β-chain polymorphism may be important in the recognition of class II molecules in the generation of immune responses to foreign antigens.

The Function of MHC Molecules

Earlier studies on the organization of the murine MHC have referred to *Ir* genes, subregions, and loci which regulate the immune response and restrict T-cell interactions [31]. With recent advances in molecular genetics, this nomenclature has been altered to reflect the expression of physical genes located in the MHC. Therefore, the assignment of *Ir* genes to subregions and loci within the *H-2I* region has evolved into the notion that foreign antigens associate with determinants (epitopes) expressed on the I-A or I-E molecules to form complexes which can be recognized by T cells to initiate the cascade of events culminating in cell-mediated and antibody-mediated immunity [32, 33]. In this fashion, immune responses to protein antigens are genetically restricted.

The manner by which the class I and II molecules regulate the immune response has been the subject of many recent articles [34, 35]. Although this issue has been extensively investigated, the mechanisms of regulation are far from completely understood. Whereas some investigators view the class I or class II molecules as "restricting" the T-cell response to viral or protein antigens [36, 37], others claim that the diversity in immune response patterns resides in the T-cell repertoire and is independent of the expression of class I or II gene products [38, 39]. Most probably, the immune response patterns observed in any given individual result from a combination of class I and II molecules and T-cell repertoire contributions.

Among the functions regulated by the class I molecules are graft rejection, viral and tumor immunity, and cell-mediated lympholysis (CML) reactions. Recognition of foreign class I molecules on donor tissue cells by the host immune system results in profound graft rejection mediated by both humoral and cellular pathways. Class I molecules have been shown to play a role in the immune response to viral and tumor-associated antigens by forming complexes which can be recognized by T lymphocytes [40]. Triggering these T lymphocytes results in lysis of cells expressing this complex. Finally, CML reactions are regulated by class I molecules, in that recognition of foreign class I molecules by the host immune system culminates in the generation of cytolytic T lymphocytes. This assay is used clinically to detect class I molecule incompatibilities between graft donor and recipient.

Class II immune response-associated molecules have been shown to regulate the interactions between macrophages, T cells, and B cells necessary for the generation of immune responses to foreign antigens [41, 42]. These Ia molecules form complexes with processed foreign antigen on the surfaces of macrophages and B cells [35] which when recognized by T lymphocytes allow for the establishment of cellular- (T lymphocyte) and antibody- (B lymphocyte) mediated immune reactions [43, 44]. In order for the T cells to perform their effector functions, they must recognize foreign antigen in the context of a class I or class II molecule; this recognition in association with an MHC molecule is termed *H-2* restriction. Recognition of the same foreign antigen in the context of a

different class I or class II molecule will not trigger the T cells to initiate an immune response.

The ability to initiate the cascade of events culminating in cell-mediated and antibody-mediated immune reactions depends upon successful interactions between macrophages (antigen-presenting cells) or target cells and T lymphocytes. This interaction requires recognition by specific receptors on T lymphocytes of processed protein antigens or viral antigens in association with class II and class I molecules, respectively [45]. Failure to initiate T-lymphocyte proliferation can result from an unsuccessful macrophage/target cell–T-lymphocyte interaction either due to (1) the lack of appropriate T lymphocytes in the T-cell repertoire to recognize the macrophage/target cell MHC molecule + antigen complex [46, 47], (2) the inability of the macrophage/target cell to form the required complex necessary to trigger T-cell proliferation [48], or (3) specific immune suppression [49, 50]. In many cases of nonresponsiveness, it is difficult to determine whether nonresponsiveness is due to a defect in the macrophage/target cell or the T-cell repertoire.

There are certain immune responses to antigens for which suppression has been demonstrated to account for nonresponsiveness. The failure of certain mouse strains to respond to some polypeptide antigens [51, 52] is clearly due to the activation of suppressor T lymphocytes whereas nonresponsiveness to other proteins is the result of concurrent activation of helper T cells by the I-A molecule + antigen complex and suppressor T cells by the I-E molecule + antigen complex [53]. In cases of nonresponsiveness where no T-cell suppressor activity has been detected to account for the failure to initiate an immune response, the defect is localized to the level of the macrophage/target cell–T-lymphocyte interaction [54]. The two perspectives on this issue differ primarily in their assignment of the level of the immune response defect—the "determinant selectionists" argue that nonresponder macrophages/target cells fail to present antigen in an immunogenic form to responding T cells [37] whereas others claim that no antigen-presenting cell defect exists in nonresponders, but rather that nonresponsiveness results from holes in the T-cell repertoire due to T-cell deletions during immunological maturation [55–57]. To date, no experiments have been performed which unambiguously resolve this conflict.

Functional Pleiomorphism of MHC Products

According to the traditional model, the MHC is a chromosomal segment which contains a number of regions, subregions, and loci coding for different immunologic traits. This concept of separate loci, each controlling distinct traits, has been recently replaced by the idea that the phenotypic expression of each individual MHC gene is pleiomorphic in that a single MHC gene product can modulate several functions [1]. Therefore, immunologic traits such as allograft rejection, cell-mediated lympholysis, mixed lymphocyte reactivity, and regulation of T-cell activation all represent different manifestations of the same MHC molecules. The different manifestations arise from the activation of distinct subsets of effector T lymphocytes, each capable of different effector functions. Whereas recognition of a foreign transplantation molecule leads to the generation of cell-mediated lympholysis by the activation of cytotoxic T lymphocytes, the same molecule can evoke allograft rejection through the recruitment of other T-lymphocyte subsets.

The ability of a single gene product to regulate a seemingly diverse set of reactions can be explained in the following manner: The recognition of any foreign antigen, whether it be a soluble polypeptide, MHC molecule, or MHC molecule associated with viral/tumor antigens, requires the activation of helper T lymphocytes. These helper T cells are turned on by antigen-presenting cells (macrophages) which express membrane complexes composed of self-class II molecules and processed foreign antigen. Once triggered,

these "common denominator" lymphocytes can activate cytolytic T lymphocytes resulting in the destruction of target cells expressing that foreign antigen. Alternatively, they can activate other helper T or B lymphocytes to trigger the events which culminate in an antibody-mediated immune response [58, 59]. All of these reactions probably occur simultaneously but the ability to dissect out the individual interactions is biased by the assay system employed. The induction of a CML reaction by host cytolytic T lymphocytes does not preclude the generation of a mixed lymphocyte reaction in the same test tube; it is only that the detection system used focuses attention on a single reaction.

A Model of MHC-Restricted Immune Responsiveness

One hypothesis to account for the nature of nonresponsiveness would propose that the role of the class I and II molecules are to direct the establishment of the T-cell repertoire. This is not to suggest that these molecules do not provide the context for recognition of foreign antigens, but rather that their primary role is to instruct the maturing immune system as to which T-cell clones must be eliminated to prevent self-destruction. Based on this hypothesis, nonresponsiveness to antigen X in a particular mouse strain would result from the elimination of T-cell clones which recognize the self-I-A molecule + antigen-X complex, presumably due to the resemblance between the complex formed by the association of the self-I-A molecule + antigen-X and some other self-determinant expressed in the developing mouse [60–62]. Supportive evidence for this suggestion comes from studies in which mice have been neonatally tolerized to foreign antigens [63–64]. This model would predict that the failure of the neonatally tolerized mice to respond to that foreign antigen later in adult life is due to the elimination of that clone of T cells reactive to the self-I-A molecule + foreign antigen complex during the establishment of the T-cell repertoire. Other studies demonstrating the existence of T-cell clones with dual reactivity for self-MHC molecules + antigen and nonself-MHC molecules lend credence to this argument [65]. The attractiveness of this model is that it combines both antigen-presenting cell defects and holes in the T-cell repertoire to account for nonresponsiveness.

Inasmuch as the number of class II molecules appears to be limited (perhaps two in mice and six in man), the tremendous amount of diversity observed must be created by other means. To begin with, the entire extracellular portion of the class II molecule is available for associations with processed antigens. Studies using monoclonal antibodies and T-cell clones suggest that there exist multiple distinct determinant clusters on each class I and class II molecule and that these individual sites may be used to activate different populations of T cells in the response to foreign antigens [66]. Furthermore, the ability of the class II molecule α and β chains to freely associate in a heterozygous mouse creates four hybrid class II molecules in addition to the original four parental ones [67]. It has been shown that MHC heterozygotes have an additional level of immune response diversity due to the recognition of foreign antigens in the context of unique hybrid class II molecules unavailable in the original parents [68]. The number of discrete class II molecules which could be created in any typical heterozygous human being with three α and three β chains would be 36. Assuming that each molecule expressed at least three distinct determinant clusters for association with antigen brings the total number of possible associations with any given processed antigen to well over 100. This conservative figure suggests that the avenues for the creation of immune response diversity with a limited number of class II molecules are potentially great. Other mechanisms for the creation of immune response diversity include mutation, genetic recombination, and gene conversion involving the MHC genes [69–71]. The extent to which these are operative in nature is not known.

The Human Major Histocompatibility Complex

The major histocompatibility complex in man, although similar to that described for the mouse *H-2* complex, has proven more difficult to study. Located on chromosome 6, the *HLA* complex encompasses about 3 centimorgans of DNA (6000 kilobases) and contains at least three class I and three class II gene loci which code for immune polypeptides homologous to the transplantation antigens and immune response-associated molecules in the mouse (Fig. 3) [72]. The *HLA-D/DR* region, analogous to the *I* region of the mouse, is located between the centromere and the *HLA-A, B,* and *C* class I loci. It has been shown to consist of a number of closely related genes which code for a series of α (33,000 molecular weight) and β (28,000 molecular weight) polypeptide chains that comprise the class II molecules. The minimum number of class II genetic loci and molecules in humans is three: *HLA-DR* which codes for proteins homologous to the murine I-E class II molecules, *HLA-DS* which encodes class II molecules with striking homology to the murine I-A molecules, and *HLA-SB* for which no murine homolog has been identified [73]. Each locus codes for its own set of α and β chains. *HLA-D/DR* gene products have been identified by mixed lymphocyte reaction analysis (HLA-D) as well as by serological methods using alloantisera (HLA-DR). *HLA-SB* gene products were originally detected by mixed lymphocyte reaction and later by serological analysis. The relationship between these serologically and MLR-defined specificities is not clearly determined.

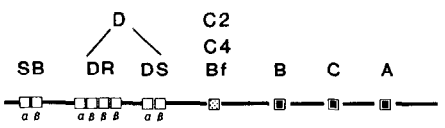

FIG. 3. Genetic organization of the human major histocompatibility complex (*HLA*). The properties of the class I (■), class II (□), and class III (□) gene products are described in the text. The exact order and number of DR1 DS α and β genes are not known to date.

There is considerable data from many investigators that demonstrate that the structure and function of the human class II molecules are identical to their mouse homologs [74–76]. Presentation of defined protein antigens by human mononuclear cells to immune T lymphocytes can be inhibited with anti-*HLA-D/DR* sera, illustrating the requirement for human class II molecules in the activation of antigen-reactive T cells. Some of the defined human class II molecule specificities have been associated with altered immune response capabilities in normal individuals [77] as well as with the ability to respond to certain antigens [78]. Lastly, correlations have been found between particular *HLA-D/DR* alleles and a variety of human diseases, suggesting that the products of these genetic loci play important and varied roles in disease susceptibility.

A number of serologically-detected specificities have also been associated with the *HLA-D/DR* region [79]. These include the MB and MT series which are found to be strongly associated with certain defined *HLA-D/DR* specificities. For example, the MT-1 specificity defined by alloantiserum has been localized to *HLA-DS* molecule determinants which are closely linked to certain *HLA-D/DR* molecule determinants. On the other hand, the serologically defined MT-2 specificity detects determinants present on both *HLA-DS* and *HLA-D/DR* molecules and is therefore termed a "supertypic specificity." Further study will begin to elucidate the relationships between these specificities and defined molecular epitopes on human class II molecules.

The class I *HLA-A, B,* and *C* genes code for the major transplantation antigens which, along with human β_2 microglobulin, are expressed on the surface of all cells [80]. As with the human class II molecules, the structure and function of the human class I molecules are identical to their mouse homologs [81, 82]. Functional studies investigating the contribution of human class I and class II

molecules to genetic regulation of the immune response have not progressed as rapidly as they have in the mouse. However, recent advances in molecular biology which allow the introduction and expression of cloned chromosomal *HLA* genes in mouse fibroblast cells provide the experimental system necessary to address these functional questions [83].

Overview of MHC-Mediated Functions

In discussing the genetic control of the immune response, it is important to consider the gene families on the murine chromosome 17 in a unified manner. Four gene families reside on this chromosome and their association is conserved from species to species [84]. These gene families, the *T/t*, *TLa/Qa*, class I transplantation, and class II immune response gene clusters, are related to one another in that they all provide cell surface recognition structures required for cell–cell interactions. The *T/t* gene complex located upstream from the *H-2* complex encodes a series of codominantly expressed antigens which operate as mediators of cell–cell recognition in the early developing embryo [85, 86]. These t antigens are found in the early embryo and not on adult tissues, with the exception of sperm and certain teratomas, and associate with β_2 microglobulin as class I molecules do. When homozygously expressed, t mutants result in dramatic cell–cell interaction defects which lead to premature death of the developing embryo. The assumption is that these mutations specify abnormal cell surface components both on sperm and on embryonic cells. In the case of embryonic cells, *T*-locus products appear sequentially and transiently and may govern processes necessary for cell–cell communication during the early stages of embryogenesis.

These clusters of related genes may represent a "supergene" family which code for molecules important in cell–cell interactions: The *T*-locus molecules provide cell surface elements necessary for the establishment of self during early embryogenesis and are later replaced by the class I and II molecules which continue to provide cell surface markers of self into adult life [87]. Although the functions of the TLa and Qa antigens have not been determined, it is likely that they also serve as cell surface recognition structures for cell–cell communication.

The similarities between these four gene families are suggestive of the existence of a supergene family which provides a series of self markers to be used as recognition structures in a surveillance system designed at maintaining self [84]. Whereas the class I and class II molecules are part of an immune surveillance system aimed at distinguishing between self and nonself after the establishment of self, the T-locus molecules may represent cell surface structures expressed transiently and sequentially in the establishment of self early in embryogenesis. Insomuch as the adult faces a foreign environment that is constantly changing, the developing embryo creates an internal milieu which is constantly in flux and becomes foreign to its previous self as it matures. The manner by which this supergene family exerts its influence on the establishment, surveillance, and maintenance of self is critical to an understanding of the basic processes of life [88]. A better appreciation of these mechanisms may provide insights into clinical solutions for the correction of autoreactive diseases and developmental abnormalities.

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