A Major Incompatibility System in Mice—The H-2 Complex

William C. Davis

Department of Veterinary Microbiology and Pathology, College of Veterinary Medicine, Washington State University, Pullman 99164.
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Introduction

The histocompatibility-2 gene complex (H-2), the mouse homologue of the major histocompatibility complex (MHC), is a cluster of codominantly expressed genes that has remained closely linked throughout the evolution of the higher vertebrates (12,34). The recent finding that it is involved in determining acceptance and rejection of tissue grafts, susceptibility to certain viral (10,37,40,41) and bacterial pathogens (3), and regulation of the immune response (11,15,17–19,27,35) has made it the focus of intensive investigation.

Results of studies on the H-2 complex are relevant to delineation of the genetic mechanisms of plant disease resistance in several ways: first, progress in the analysis of this gene system may provide insight into the general problem of characterizing gene fine structure in eukaryotes and an indication of how gene complexes have evolved. Second, they may lead to understanding of the properties of cell molecules that serve as specific receptors for identification of antigenic substances present on parasites or other foreign substances and the cellular responses elicited by their interaction with their ligands. Third, technical advances in serological and biochemical techniques may prove to be of equal value in the identification and characterization of specific gene-mediated products in both plants and animals.

The purpose of the present review is to provide a brief synopsis of what is known about the specificity of cellular recognition and response in the context of the immune response in vertebrates and the role of the MHC in regulating its expression.

The Immune Response

Vertebrate immunity differs uniquely from that of plants in that (i) in a set of highly specialized cells have evolved that interact with substances antigenically foreign to the host and also with mutant host cells that have developed malignant potential; and (ii) as a part of this evolution, the cells involved have developed the capacity to respond more rapidly upon second exposure to the same antigen (memory response).

The immune system is redundant; it has two major components, cell-mediated and humoral immunity. When the host encounters an antigenic substance it can respond in one of three ways: either by producing specific antibody (humoral immunity), by developing specific cell-mediated immunity, or by both producing antibody and developing cell-mediated immunity (27). As noted in Fig. 1, these forms of immunity develop along separate but interrelated pathways. The principal cells involved are macrophages (25,39), which play an important but passive role, and lymphocytes, which act as the antigen-specific effector, regulator, and memory cells (15,39). The macrophage is involved in the concentration and presentation of antigen and the secretion of molecules (monokines) that possess the capacity to regulate lymphocyte activity by potentiating or inhibiting cellular differentiation and proliferation (39). Detailed studies of the functional properties of lymphocytes and the constellations of antigenic membrane markers that distinguish each cell type have revealed two major classes, thymus independent B cells and thymus dependent T cells. Both cell types arise from bone marrow, but the thymus is essential for T cell differentiation. B cells and their differentiated progeny (memory cells and plasma cells) are responsible for the secretion of antibody (humoral immunity) (26). T cells are responsible for immune regulation (15), (a function of subclasses of T cells: T helper [T_h] and T suppressor [T_s] cells) and cell-mediated immunity (a function of another subclass, T effector cells [T_e]).

The specificity of the response in both major classes of lymphocytes is mediated through membrane receptors. For B cells, it is now evident that the receptors are a membrane-bound form of conventional antibody and, depending on the stage of differentiation of the cell, may be represented as any one of the major classes of antibody (ie, on virgin B cells by IgM ± IgD and on memory B cells by IgG, IgA or IgE ± IgD). For T cells, it remains unclear as to the molecular composition of the receptor molecule. Current evidence indicates that the specificity of the receptor site per se is determined by the same V regions (variable regions) as found on classic antibody molecules. In addition, evidence exists for a second type of molecule, which interacts specifically with antigen, that bears no apparent resemblance to the antibody molecule. The latter has been identified as a cell-associated constituent of the cell membrane and as a secreted molecule. It functions in regulation of the immune response. How specificity is encoded in this molecule has not been elucidated. As part of their role in the immune response T lymphocyte subpopulations also synthesize a number of low molecular weight products that function in immune regulation as cell membrane associated or secreted molecules and as effector molecules (lymphokines) (39).

By far, the most extensive information available on the molecules involved in immunity and the basis for their specificity is on antibody. Results of investigations have shown that B lymphocytes from higher vertebrates such as mice and humans can synthesize five major classes of immunoglobulin, IgG, IgM, IgA, IgD, and IgE (see ref 26 for detailed description of each type of molecule). The basic unit of each molecule contains four polypeptides: two identical 23,000 dalton L chains (L = light chains) and two identical 50,000–70,000 dalton H chains (H = heavy chains). The variation in molecular weight of the different H chains is attributable to the different forms of the chains that characterize each class of Ig molecule. Synthesis of the molecules is

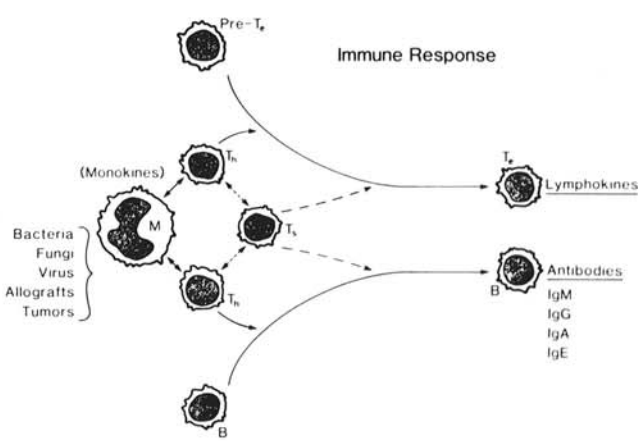

Fig. 1. Schematic representation of the events leading to an immune response and the cells involved. M = macrophage, B = B lymphocyte, Th = T helper lymphocytes, Ts = T suppressor lymphocyte, and Te = T effector lymphocyte.

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determined by three linkage groups of genes present on different chromosomes; two sets control the synthesis of L chains (κ and λ) and one set, the synthesis of H chains (26,37,38). The unique feature of these gene clusters is that each set forms a group of two kinds of genes, one responsible for synthesis of an invariant portion (constant C region) of the peptide and the other responsible for a synthesis of the highly variable portion (variable V region). Each set is represented by a few unique C region genes and multiple unique V region genes. When the peptides are formed, one C region gene combines with one V region gene to form a single peptide. When the whole antibody molecule is assembled, the peptides align to form two identical units each comprised of one H and one L chain. The association and folding of the V regions of each pair imparts a specific configuration to the antibody receptor site. Although not yet clearly defined, the specificity of the T cell receptors is assumed to be imparted by a similar if not identical mechanism. The evidence suggests that the V region genes of antibody are part of the receptor molecules of T cells (15,33). What is important for the discussion here is that the specificity of the reactive receptor molecules can be accounted for by variations in amino acid sequence and folding of the variable regions of the receptor molecules and that individual clones of T and B lymphocytes bear receptors of a single specificity when at a functional state of maturation. What is required for a specific response is a reaction with the cognate antigen and activation by interaction with regulatory T cells and macrophages.

Recent Advances

One of the major questions under investigation concerns the mechanism(s) of immune regulation. It is apparent that contact between most antigens and their cognate receptors on B and T cells does not cause cell activation, proliferation, and differentiation to a functional stage. As shown in the schematic (Fig. 1) a more complex interaction between macrophages, lymphocytes, and antigen is required. At this juncture the evidence indicates that macrophages collect and present the antigen to helper and/or suppressor T cells, which in turn potentiate or inhibit activation of immunocompetent B and T cells. These initial cell interactions are accompanied by the synthesis and release of a number of molecules with antigen-specific and antigen-nonspecific immunoregulatory activity. The mechanisms are only partially understood. However, two major findings have accelerated the pace of research and have begun to provide a more detailed understanding. The first is that a number of the principal genes involved in expression and regulation of immunity has been found to be linked to the major histocompatibility complex (1,2,6,17,18,35). This finding has permitted an immunogenetic analysis of factors controlling immunity and an opportunity to identify the molecules involved in immune regulation. The second finding is that it is possible to develop a continuous source of monoclonal antibody to virtually any antigen. This technological breakthrough has afforded a way to bypass the problem of using complex immune sera to isolate and characterize antigenic molecules, especially molecules with similar physical properties and a common phylogenetic origin.

Briefly, the technique, first described by Köhler and Milstein (20) in mice, involves the fusion of antibody-producing B cells (that are incapable of sustained cell proliferation in vitro) with cell culture adapted lines of myeloma cells (plasma tumor cells (24,28). Myeloma cells incapable of synthesizing DNA by the salvage pathway (mutants induced by culturing in the presence of 8-azaguanine or 6-thioguanine), are fused with spleen cells from specifically immunized mice by using polyethylene glycol. The cell mixture is then cultured in selective growth medium (HAT = hypoxanthine, aminopterin, and thymidine) (23) that inhibits DNA synthesis. Only hybrid (B-myeloma) cells that have regained the capacity to use the salvage pathway grow; their colonies develop while unfused B cells undergo a few cycles of division and die. Cultures producing the antibody of interest are then cloned and used as a source of antibody.

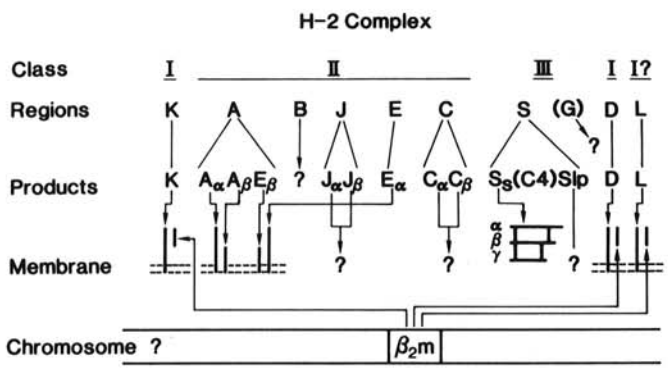

Fig. 2. The H-2 complex, classes of regions showing biochemical and/or functional relation of gene products, and composition of known gene products. The existence of a G region or locus is in question.

The H-2 Complex

Historical. The most extensive information available on the composition of the MHC is on the mouse homologue of the MHC, the H-2 complex. The complex was discovered in the late 1930s as a result of its prominent role in determining the fate of transplanted tumor and normal tissue grafts exchanged between unrelated mice (see reviews 11,16,17,19,35). The gene products of the H-2 differed from those determined by other H loci in that they were found to be antigenically highly polymorphic and readily detected by the vigor of the graft rejection response they elicit and their capacity to elecit antibodies detectable by hemagglutination, complement fixation, and leukocyte cytotoxicity reactions (16). Other H loci were detectable only by histogenetic means, with no single locus eliciting a rejection response comparable to the H-2. In the course of investigation of the H-2 complex a large series of inbred strains of mice was developed to provide a genetic library comprised of all the known H-2 haplotypes (specific sets of linked H-2 loci on a given chromosome). Studies with these strains revealed the H-2 is not a single locus, but rather a series of closely linked genes that control the synthesis of histocompatibility antigens, the expression of the immune response and the synthesis of certain serum proteins.

Currently, the H-2 complex is recognized as a 0.3–0.5 cM segment of the 17th chromosome. The exact dimensions have not been defined and may be extended to include additional loci as more information becomes available. Various investigators have estimated that it may contain a few or several hundred genes (19). It is involved in the following immunological phenomena: (i) the induction of B cell differentiation leading to the production of antibodies; (ii) the induction of T cell differentiation leading to the development of regulatory and effector activity that can be detected by (a) blast transformation in the mixed lymphocyte reaction in vitro and graft vs host reaction in vivo (b), cell-mediated lymphocytoxicity (CML) in vitro, graft rejection, and delayed-type hypersensitivity reactions (DTH) in vivo; (iii) regulation of the immune response to a variety of antigens; and (iv) control or synthesis of components of complement. At this juncture, genetic studies show the complex can be divided into regions on the basis of genetic recombination, with each region being defined by at least one marker gene, and the regions grouped into classes according to evidence for a common genetic origin and/or similarity in composition or function (19). Three classes of regions are recognized: Class I regions containing the loci that code for the serologically defined transplantation antigens present on erythrocytes and lymphocytes; Class II regions containing loci that code for serologically and histogenetically defined cell membrane antigens present on B cells, macrophages, and subpopulations of T cells and loci regulating the immune response; and Class III regions containing loci that are directly or indirectly involved in the synthesis of several components of complement.

Composition and function of H-2 gene products. As shown in Fig. 2 and Table I, Class I is comprised of three loci, one of which has only recently been described (19). Each locus determines the synthesis of an antigenically complex glycopeptide with a molecular weight of 45,000 daltons. These are present in the cell

membrane in noncovalent association with a smaller 11,500 dalton peptide (β_2 microglobulin). Though some evidence exists for the association of these products with other membrane molecules, they are independent of each other and any one of them can be displaced laterally in the cell membrane without influencing the distribution of the others (8). The implication is that the Class I products function independently. The polymorphism of the individual allelic products is reflected in their antigenic complexity. Each product is characterized by at least one allele-specific antigen (private antigen) and a variable number of antigens that may be coded for by two or more alleles (public anitgens). Up to 30 of such antigens may be coded for by one allele. That this antigenic complexity is not an artifact has been established through the use of monoclonal antibodies (19). It is estimated that there are in excess of 100 unique alleles for the K and D regions. Because of the relatively recent discovery of the L region, only five of its alleles have been identified and no estimate is available on the extent of its polymorphism. The evidence indicates that the Class I regions have a common genetic origin (19).

The reason for the exceptional polymorphism of Class I loci and the biological function of their gene products is not yet clear. Transplantation studies have shown that the products are responsible for the strong rejection response and related phenomena detected by the MLR and CML assays in vitro. However, it is evident these reactions reflect a more significant role in cell function. An indication of this has been noted in studies of certain viral infections and cellular response to transplantation antigens. The data indicate that part of their function involves the immunological recognition of self and the recognition of foreign antigens in the context of self (5,10,18,19,38,41).

Class II is comprised of regions that have been grouped provisionally on the basis of their function in the regulation of the immune response. The first loci recognized as belonging to this class, Ir (immune response genes), were found to affect the antibody response to a variety of natural and synthetic antigens (high and low antibody responses) (35). Subsequent studies revealed that a number of loci exist in this region and could be defined as separate entries by crossover and/or one of several other distinguishing characteristics: (i) reactivity in the mixed lymphocyte reaction (MLR), (ii) graft rejection, (iii) immune regulation (Ir = helper cell associated activity; Is = suppressor cell associated activity) and (iv) control of synthesis of serologically defined Ia products (immune response associated antigens). Whether the same or different genes are responsible for the various phenotypically defined activities is under intensive investigation. At present, five regions are recognized; *A, B, J, E,* and *C*. Of these, products (immune response associated antigens [Ia]) have been characterized only for two regions, *A* and *E*. The *A* and *E* products are glycoproteins (57,000–63,000 daltons), each comprised of two peptides, one (Aα and Eα) between 31,000 and 34,000 daltons and one (Aβ and Eβ) between 26,000 and 29,000). Interestingly, three of the genes coding for the peptides map to the *A* region (Aα,Aβ and Eβ) and one to the *E* region (Eα). A *J* region Ia product has been defined serologically, but because it is present only a small subpopulation of T lymphocytes, it has not yet been possible to characterize it (19,30). The *B* region, defined by Ir gene control of antibody synthesis to

TABLE 1. The H-2 major histocompatibility complex (MHC) in the mouse

H-2 class	Regions and/or loci	Product and tissue distribution	Composition and molecular weight	Selected traits
I	K,D,L	Cell membrane molecule present in most tissues in mature mice	45,000[a]	Strong histocompatibility antigen Antigens that elicit MLR[b] and CML[c] reactions in vitro Associative recognition of foreign antigens in context of self-recognition.
II	A	Cell membrane molecule present on B cells macrophages and sub-population of T cells (Th)	Aα~33,000 Aβ~28,000	Strong histocompatibility antigen Antigens that elicit MLR and CML reactions in vitro and the GVH[d] in vivo Immune response (Ir) activity Immune response associated antigens
	B	Unknown	Unknown	Immune response (Ir) activity
	J	Cell membrane molecule present on a subpopulation of T cells (Ts) and macrophages (?)[e]	Unknown	Weak histocompatibility antigen Immune response associated antigens (Ia) Immune response suppressor (Is) activity Antigens that elicit weak MLR activity
	E	Cell membrane molecule present on B cells and macrophages	Eα~33,000 Eβ~28,000	Immune response associated antigen (Ia) Immune response (Ir) activity
	C	Cell membrane molecule present on a subpopulation of T cells (Ts?)	Unknown	Weak histocompatibility antigen Immune response suppressor (Is) activity Immune response (Ir) activity Antigens that elicit weak MLR and CML activity
III	Ss	Serum protein	~185,000 Forms 3 chains α 95,000 β 78,000 γ 33,000	C4 complement activity (initiates the complement cascade)
	Slp	Serum protein	~185,000	Unknown

[a] A single 11,500 dalton peptide (β2 microglobulin) is associated noncovalently with each class I peptide.
[b] MLR: When lymphocytes from unrealted individuals are mixed in vitro, MHC antigens stimulate cellular proliferation which is referred to as the mixed lymphocyte reaction.
[c] CML: Both in vitro and in vivo stimulation by MHC antigens results in the development of T effector (Te) cells that can kill target cells bearing the appropriate antigens. This type of killing is referred to as cell-mediated lympholysis.
[d] Graft versus host reaction: when immunologically impaired animals are injected wtih immunocompetent lymphoid cells from unrelated donors, the donors react against the host; ie, a graft-vs-host reaction.
[e] A question mark indicates additional evidence is needed to firmly establish the presence of a given antigen on a particular cell type.

some antigens, is serologically silent. Questions remain as to whether a *C* region Ia product has been identified. Some evidence suggests that a product with immunosuppressive activity can be detected with anti-C antiserum (29,30).

Serological analysis of Ia products indicates that the extent of antigenic polymorphism is more limited than for Class I region products and that most of the antigenic variation detected is attributable to antigenic variation in the *A* region-determined Ia molecule. Studies with inbred and wild mice suggest that a minimum of 20 alleles exists for the genes coding for the *A*-Ia molecule (19). At this juncture, investigations of the *E*-Ia molecules suggest less antigenic variation and fewer alleles. A point of considerable interest is that both private (allele specific) and public (antigens coded for by more than one allele) have been identified for *A* region molecules.

It remains to be determined whether the genes coding for the Ia molecules are also responsible for the phenotypic traits characteristic for each region and also whether studies will show the loci designated as Class II to have a common genetic origin.

Class III is comprised of regions controlling the synthesis of components of the complement system, a series of proteins that serves to amplify the functional activity of specific complement fixing antibodies. The paucity of genetic markers has made it difficult to elucidate exactly how many loci exist in this group and the nature of their control (ie, whether they are structural or regulator genes). In the mouse, the first gene (*Ss*) to be detected was shown to affect the concentration of a serum protein; a second gene (*Slp*) was found to code for another serum protein with similar molecular properties (9,19). Subsequent studies showed the Ss protein defined by Ss to be the complement component, C4 (9). The identity and function of the Slp protein remains to be elucidated. Some evidence suggests that genes within the H-2 complex or present on the 17th chromosome influence the synthesis of several other components of complement (19).

The MHC and Disease Susceptibility

For most species, information on the MHC is still fragmentary and only broad inferences can be drawn as to its overall composition. However, it is evident that the three major classes of regions represent important elements since they have been identified in many species of mammals (12) and also in birds (chickens) (2,4,31,32). Further, several lines of investigation have provided evidence that shows a common phylogenetic origin for a number of the gene products, especially products of the Class I region loci (21). Why the various loci have remained closely linked during evolution of vertebrates has not been elucidated, but it has been suggested that it is most likely related to the requirement for the integrated function of the genes (1,16). Possibly, studies of recombinant DNA will clarify this point. What is of immediate interest from comparative studies is the finding that the MHC is not only directly involved in expression of the immune response but also in susceptibility to a number of diseases. The first recognition of this resulted from studies with inbred mice. It was shown that susceptibility to virus (Gross virus)-induced leukemia was associated with the inheritance of specific H-2 haplotypes. Resistance to leukemia was found to be dominant (22). Subsequent studies revealed similar associations with other leukemia viruses, vaccinia virus infection of the skin, and also tumors induced by methylcholanthrene (41,42). Results from other lines of investigation demonstrated that a limited number of generations of selected breeding was sufficient to develop populations of mice that were uniformly good or poor responders to several bacterial pathogens. Analysis of the progeny revealed that 10–18 gene systems might be involved and also that 20% of the effect could be linked to genes associated with the H-2 complex (3). Studies on the relation of these patterns of inheritance of response to pathogens revealed that good responders were more susceptible to infection by some of the pathogens (*Salmonella, Yersinia, Pasteurella pestis*). *Ir* genes per se were found to be associated with the response of mice to infection with a specific virus (choriomeningitis virus) (10). By far, however, the most convincing evidence of the association of the MHC with disease susceptibility has been obtained in studies of humans. Prompted by the meager findings in mice, extensive studies have been conducted to establish the extent to which variations in disease susceptibility are associated with the human MHC counterpart, the HLA (human lymphocyte antigen) (1,7,36). These endeavors have demonstsrated that the observations in mice are not unique but rather are indicative of a major role for the MHC in "host defense." Investigators have established that a variety of diseases are associated with the occurrence of specific genotypic markers and also provided sufficient data to gain insight into some of the types of associations to be encountered. Specifically, the investigations completed have shown that (i) in most instances in which an association is encountered, the MHC represents only one of several gene systems influencing the development of clinical signs of the disease. No instance has yet been found in which an MHC gene product associated with the occurrence of the disease has been identified in all patients. This most likely indicates that genes linked to the marker gene account for the disease association and also affirms that additional genetic and environmental factors are essential for manifestation of the disease; (ii) the effect of the "disease susceptibility gene" is usually dominant; (iii) the "disease susceptibility genes" are either an integral part of the MHC or are tightly linked to the MHC. The finding that many of the disease susceptibility genes show a strong linkage relationship with a Class II region locus has favored the former possibility and led to the hypothesis that the diseases detected are attributable to the effect of *Ir* and *Is* genes; and (iv) the occurrence of the MHC marker gene in apparently unrelated diseases can reveal the existence of larger disease syndromes that may have a common genetic basis (1,36). The major finding that has permitted the use of the MHC as a marker system for the detection of linked "disease susceptibility genes" is the antigenic polymorphism of Class I region products and the infrequency of crossover between the marker genes and the disease susceptibility genes. This has resulted in a linkage disequilibrium in the population; ie, the occurrence of the diseases of interest in association with a limited number of marker genes in higher frequency than expected.

Discussion

In this brief review, emphasis has been on insight gained toward understanding the complex interplay among the genes, molecules, and cells of the immune system that maintain homeostasis between the individual and the external environment. Although seemingly overly complex and redundant, the evolution of the gene systems controlling immunity has introduced such flexibility that a host has available multiple potential routes of response to foreign substances. Thus, if the host is genetically impaired or encounters a pathogen that has successfully avoided one mechanism of recognition and response, the pathogen may still be eliminated by an alternate response.

Analysis of the mechanisms of specificity and regulation of the immune response remain the two areas of intensive investigation. How specificity is encoded in membrane receptors of antigen-specific cells appears to have been solved. Antibody molecules are the receptors on B cells. The specificity of these molecules is coded for by variable region genes represented in three distinct gene clusters. How the genes function in the synthesis of the antibody molecule is not totally understood, but investigations with recombinant DNA technology have provided considerable insight (14,37,38). The receptors on T cells appear to be V region gene products associated with a larger molecule deeply embedded in the cell membrane. Whether this represents an as yet undescribed peptide or a form of known immunoglobulin molecules has not been established.

The problem of the genetic control of immune regulation remains less well understood. However, the finding that a number of genes with immunoregulatory activity are linked to the MHC has afforded an opportunity to use an immunogenetic approach to identify the cells and products involved in regulation. The analysis of the respective gene products and their sites and modes of action have provided a broad profile of the cellular interactions and molecular events that follow interaction of antigen-specific

membrane receptors with their antigens. Results of additional studies reveal that the MHC also plays a role in controlling some aspects of susceptibility to disease.

Whether the advances in the understanding of immunity in vertebrates provide insight into the genetic mechanisms of host-parasite responses in plants remains an open question, but there are areas of interest where answers to questions would be of mutual benefit. One area especially is the composition of the gene complexes controlling resistance to certain parasites. It would be valuable to know whether gene complexes in plants show tight linkage, whether the genes have arisen by duplication, whether the complexes are comprised of more than one type or class of genes, and whether gene function requires close association of the genes. In addition, it would be interesting to know how specificity is encoded in the receptor molecules. Although it would seem that the genetic system in plants should not be as complex as that in vertebrates, it is apparent that a genetic mechanism capable of responding to subtle changes in the makeup of plant pathogens has evolved. It should prove to be an interesting gene system.

Perhaps the most useful information to emerge from recent investigations of the immune response relevant to the study of host parasite relations in plants is that it is now possible to prepare specific monoclonal antibodies to virtually any antigen through the hybridization of normal antibody-producing lymphoid cells with tissue culture-adapted lines of myeloma cells. This technological advance provides an exceptional approach to the difficult task of identifying the receptor and regulator molecules involved in recognition of parasites and the elicitation of a host response. In addition, it provides a way to detect antigenic changes in the gene products of both pathogens and hosts associated with increased resistance or susceptibility to infection by a given pathogen.

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