The Major Histocompatibility Complex of the Mouse

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Summary. Like physicists striving to develop a unified field theory, immunologists are attempting to bring order to the microcosmos of defense reactions. Indications are that one of the most important constants in this microcosmos is the major histocompatibility complex (MHC) of the species. A test of any interpretation of the MHC's role in immunity is how well it explains this system's polymorphism. One of the most crucial questions an MHC hypothesis must answer is: Why are there so many alleles at this complex?

When a vertebrate recognizes a foreign substance as nonself, it initiates a complex reaction against it, summarily referred to as the immune response. Until recently, the most important class of molecules involved in this response appeared to be immunoglobulins, and immunology, to a large degree, had been the science of immunoglobulins. However, in the last decade the suspicion has grown steadily that there might be a second class of molecules, perhaps as important as immunoglobulins and certainly as interesting. These molecules were first discovered in the mouse by the Englishman Peter A. Gorer (*1*), but later other investigators found similar molecules in many other vertebrates (*2*). The molecules could be recognized for two reasons: first, because one could make antiserums against them and study them serologically; and second, because cells and tissues carrying them were destroyed (rejected) when introduced into an individual whose corresponding molecules were not exactly the same as those introduced. Because of the latter property, a property governing tissue compatibility, Gorer, Lyman, and Snell (*3*) designated the molecules as histocompatibility antigens and gave them a serial number—2. They designated the gene coding for the antigens as *H-2* (*histocompatibility 2*). When later research proved that the *H-2* consists of not one, but a series of genes, immunologists became accustomed to denoting this series as the *H-2* complex (*4*). Similar complexes in other species have different names (*HLA* in the human, *Rt-1* in the rat, *B* in the chicken, and so on [see (*2*)]. The generic name for the complexes of different species is the major histocompatibility complex (MHC). This name reflects the fact that there are many other (minor) histocompatibility systems which to immunologists—at this time at least—seem to be less important (*5*).

Originally, immunologists were interested in the MHC only because it presented a formidable obstacle to organ transplantation by controlling the strongest antigens against which the recipient mounted severe immune response, leading to rapid graft rejection. They thought that by studying the MHC they might come across ways of avoiding graft rejection and thus accomplishing successful organ transplantation. In that respect they failed. Although they were able to somewhat improve organ-transplant survival rates by matching, as closely as possible, MHC molecules of donor and recipient, they have not yet solved the rejection problem. But their interest in the MHC has paid off in a totally unexpected way. For during their studies, immunologists gradually realized that the MHC plays some important role in the immune response to antigens in general. The question remaining to be answered is: What exactly is this role? In recent years immunology has come tantalizingly close to answering this question. The situation is like that before the opening of a mystery play: The stage is ready, the spectators are filled with expectation—someone has just to lift the curtain.

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There are so many aspects of MHC research that it would be impossible in one article to discuss them all. Instead, I have selected a few topics that I consider most pertinent to interpreting the MHC's role in the immune response.

Genetic Organization

The *H-2* complex is located in the middle portion of chromosome 17, one of the shortest mouse chromosomes (Fig. 1). In the same chromosome, three other groups of loci have been identified: loci controlling embryonic differentiation (*T,t, Kb, Fu*, and *qk*); loci controlling hair growth (*th* and *thf*); and loci coding for isozymes (*Pgk-2, Ce-2, Apl, Glo-1*, and *Map-2*). At least some of these groups (in particular the *T,t* group) might form functional complexes similar to *H-2*.

The *H-2* complex (Fig. 2) is between 0.3 and 1.5 centimorgans long, depending on which loci one counts as belonging to the complex. Originally, the complex's borders were demarcated by the *H-2K* locus at the centromeric and the *H-2D* locus at the noncentromeric (telomeric) ends. These two loci are 0.3 cM apart. However, more recent studies indicate that several loci to the right of *H-2D* are functionally and biochemically related to at least some of the *H-2* loci, and could, therefore, be considered as part of the complex (*6*). In this extended version of the *H-2* map, the *H-2* borders are demarcated by *H-2K* and *Tla*, two loci which are some 1.5 cM apart.

The position of each *H-2* locus on the map is determined by typing recombinants derived from heterozygous parents in which two chromosomes 17 have broken and rejoined (have undergone crossing-over) in a particular position within the *H-2* complex. To give an example: If one were to designate alleles at individual *H-2* loci of one chromosome (haplotype) *k k k k k k k k k* (taking into account only loci from *H-2K* to *H-2D*, see Fig. 2), and alleles at loci of another haplotype *d d d d d d d d d*, then a haplotype *k k k k k k k k d* would represent an *H-2* recombinant, in which the left-hand portion of *H-2* is derived from one and the right-hand portion from another parental chromosome. In this particular new haplotype, designated $H\text{-}2^{a1}$, the crossover break has occurred between loci *H-2G* and *H-2D*. The recombinant haplotype might then become involved in another recombinational event with another haplotype, for example *s s s s s s s s s*, and a new recombinant, *s k k k k k k k d*, might arise, which might be traced back to

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three different chromosomes. In this way, multiple consecutive recombinations can convert *H-2* chromosomes into two-dimensional patchworks of the type shown in Table 1. These patchworks have become one of the most important immunological tools for the elucidation of gene-function relationships. The availability of more than 60 *H-2* recombinants is the main reason why knowledge of the *H-2* system has progressed so rapidly in recent years.

Two loci separated by recombination can be either adjacent to each other or set apart by one or more loci that we may have no notion of. Because of this uncertainty about the number of loci in a particular chromosomal segment, immunogeneticists use the term "region" to designate a segment occupied by at least one but possibly more loci. A region in which several presumably related loci have been identified can be divided into "subregions" occupied by these loci. However, the distinction between regions and subregions is so subtle and so ambiguous, that it is probably best to abandon it and use only the term region.

The current *H-2* map (Fig. 2) is divided into six regions (K, I, S, G, D, and T), with the I region divided into five subregions (A, B, J, E, and C). These region designations originally had historical connotations, but for new regions they are introduced in more or less alphabetical order. The T-region designation is introduced here for the chromosomal segment defined by the *Tla* locus.

To date, 18 *H-2* loci have been counted but some of these loci might, in fact, be identical. Thus in the I region, the current *H-2* map lists five loci, only two or three of which are definitely established as distinct. The *Ia-1* locus is clearly distinct from *H-2K* and other I-region loci, and at least one other *Ia* locus in addition to *Ia-1* exists between the A and S regions. The exact position of this last locus has not yet been agreed on, since some investigators map two loci within this region (*Ia-3* and *Ia-5*), and it is not clear who is dealing with what locus (*7*). One other I-region locus, *Ia-4*, also maps in the same chromosomal segment, but its separateness from *Ia-3* and *Ia-5* is, at least functionally, well documented. The fifth locus, *Ir-1B*, is the least firmly established of the five, since there is only one recombinant to support its existence.

The *Ss* and *Slp* loci are shown as separate on the *H-2* map in Fig. 2, but this separateness is supported so far by only tentative biochemical data (*8*); no recombinant separating the two loci is known. The existence of an *H-2G* locus separate from *Ss* and *Slp* is also uncertain, for the same reason (*9*). The existence of two loci in the D region, *H-2D* and *H-2L*, is well documented, but again, no crossover event between them has been discovered (*10*). Finally, the assignment of loci to the T region must be considered as very tentative. In particular, the identity of the *H-2T* and *Qa-1* loci is questionable (*6*).

Thus a conservative *H-2* map consists of ten loci; a nonconservative map contains at least 18 loci. Some investigators have suggested that each region might, in fact, contain a cluster of many loci, of which only one would be expressed (*11*). At present, however, there is no experimental evidence to support such a hypothesis (*12*).

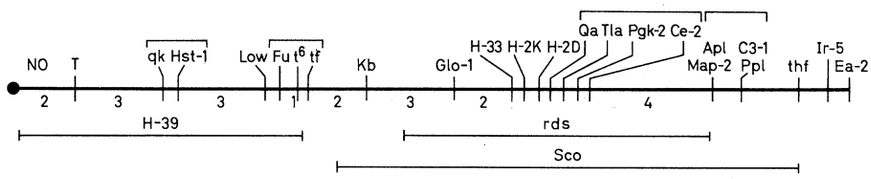

Fig. 1. Genetic map of chromosome 17. The loci, from left to right are: centromere (•), brachyury (*T*), quaking (*qk*), hybrid sterility-1 (*Hst-1*), low (Low), fused (*Fu*), anury (t^6), tufted (*tf*), histocompatibility-39 (*H-39*), knobbly (*Kb*), kidney catalase (*Ce-2*), histocompatibility-33 (*H-33*), histocompatibility-2K (*H-2K*), histocompatibility-2D (*H-2D*), Q antigen (*Qa*), thymus-leukemia antigen (*Tla*), phosphoglycerate kinase-2 (*Pgk-2*), retinal degeneration-slow (*rds*), plasma protein (*Plp*), complement component 3-1 (*C3-1*), scopolamine modification of exploratory activity (*Sco*), acid phosphatase-liver (*Apl*), glyoxylase-1 (*Glo-1*), α-mannosidase processing-2 (*Map-2*), thin fur (*thf*), immune response-5 (*Ir-5*), erythrocyte antigen-2 (*Ea-2*). Brackets indicate that the order of loci within the bracket is unknown; segments indicate that the locus has not been mapped precisely and can lie anywhere within the limits of the segment.

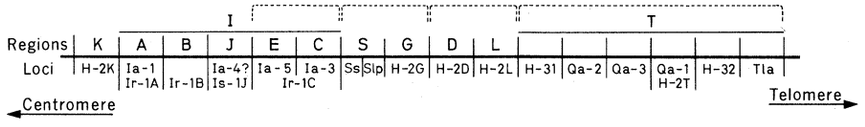

Fig. 2. Genetic map of the *H-2* complex. Brackets indicate that the order of loci within the bracket is unknown.

Table 1. Representative *H-2* recombinants and their genotypes. Symbols: ., allele not determined; *x*, allele of unknown origin; |, position of crossing-over.

Strain	*H-2* haplotype	Parental *H-2* haplotypes	Alleles at regions
			K A B J E C S G D T
A/J	*a*	*k/d*	*k k k k k|d d d d x*
A.AL	*a1*	*k/d*	*k k k k k k k k|d d*
HTG	*g*	*d/b*	*d d d d d d d|. b b*
D2.GD	*g2*	*d/b*	*d d d|b b b b b b b*
HTH	*h*	*a/b*	*k k k k k d d|. b b*
B10.A(1R)	*h1*	*a/b*	*k k k k k d d|. b b*
B10.A(2R)	*h2*	*a/b*	*k k k k k d d|. b b*
B10.A(4R)	*h4*	*a/b*	*k k|b b b b b b b*
HT1	*i*	*b/a*	*b b b b b b b|. d x*
B10.A(3R)	*i3*	*b/a*	*b b b b|k d d d d x*
B10.A(5R)	*i5*	*b/a*	*b b b|k k d d d d x*
AKR.M	*m*	*k/q*	*k k k k k k k k|q x*
C3H.OL	*o1*	*d/k*	*d d d d d d|k k|k b*
C3H.OH	*o2*	*d/k*	*d d d d d d d d k b*
A.TL	*t1*	*s/a1*	*s|k k k k k k k d d*
B10.S(7R)	*t2*	*s/a*	*s s s s s s s s|d x*
B10.HTT	*t3*	*s/t1*	*s s s s|k k k k d d*
B10.S(9R)	*t5*	*s/a*	*s s|. | k k d d d d x*
B10.AQR	*y1*	*q/a*	*q|k k k k d d d d x*
B10.T(6R)	*y2*	*q/a*	*q q q q q q q|. | d x*

Phenotypic Expression

According to their phenotypic expression, *H-2* loci can be grouped into at least three classes, with loci within each class more closely related than loci of two different classes. These classes can be designated arbitrarily by Roman numerals I through III (*13*).

Class I loci (*H-2K* and *H-2D*) code for membrane-bound glycoproteins with a molecular weight of 44,000 (*5*). The glycoprotein molecule consists of a single polypeptide chain some 350 amino acids long, to which two carbohydrate side chains are attached (*14, 15*) (Fig. 3). In the membrane, the molecule is noncovalently associated with a shorter polypeptide, 100 amino acids long (molecular weight of 12,000) and encoded by a gene that is not part of the *H-2* complex. This shorter chain also exists in the serum and some other fluids as a free molecule of β_2 microglobulin (*16*). The amino acid sequence of human β_2 microglobulin is

known (*17*) and the sequencing of the 44,000-dalton chain is nearing completion (*15*) (Table 2). The *H-2K* and *H-2D* molecules show a strong homology in their primary structure—a homology as strong as that between two alleles at the *H-2K* or *H-2D* loci (*18, 18a*). Clear-cut homology also exists among class I molecules of different species (*18, 18a, 19*) (Table 2), pointing to a common evolutionary origin for the corresponding genes.

Class I molecules can be detected serologically by producing antibodies against them, or histogenetically by generating lymphocytes that are cytotoxic for *H-2K*- or *H-2D*-bearing target cells (*4, 5*).

Class II genes are of two types, *Ia* and *Ir*. The two well-defined *Ia* genes—one in the A region and the other in either the E or the C regions—code for membrane-bound glycoproteins consisting of two noncovalently associated polypeptide chains, α (molecular weight of 35,000) and β (molecular weight of 28,000), and an unknown number of carbohydrate chains (*20*).

Only limited amino acid sequence data are available for Ia molecules (*18a, 21*) (Table 3). The data allow one to draw certain tentative conclusions about the homology relationships of the various *Ia* genes. First, no homology has been found among the four chains and between the class I and class II chains. Second, the β chains appear to be more variable than the α chains among the different alleles. Third, the α chain encoded by the E/C-region locus shows strong homology to the so-called p34 molecules encoded by the human HLA complex; the β chain shows moderate homology

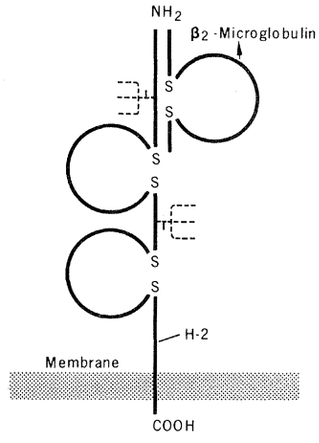

Fig. 3. An artist's view of a membrane-bound *H-2* molecule.

with the human p29 molecule and with the guinea pig MHC molecule carrying antigens 4 and 5. However, because of the limited data available, these conclusions must be viewed with caution. It is possible that hitherto unrevealed homology relationships exist in other parts of the Ia molecules for which no data are available. Also, the *Ia* gene–Ia molecule relationship is unclear. It remains to be established whether both chains in the two molecules are controlled by the *H-2* complex and, if so, how many genes in what region of the complex code for the individual polypeptides.

Although *Ia* gene products were originally detected serologically with antibodies, they were later shown to be responsible for the activation of lymphocytes in mixed lymphocyte culture (*22*) and the generation of cytotoxic lymphocytes (*23*).

The *Ir* genes regulate immune response as measured by antibody production, delayed-type hypersensitivity, or proliferation of thymus-derived (T) lymphocytes in vitro (*24*). These genes can either enhance or suppress the response. In a typical case, one mouse strain can be shown to produce high levels and another strain can be shown to produce low levels of antibody to a given antigen. When the two strains are crossed and segregating populations analyzed, one finds, in the simplest case, that the antibody level is controlled by one or two genes mapping in the I region. Four *Ir* genes have been described, three enhancing and one suppressing immune response. The enhancing genes map in the A, B, C, or E regions; the suppressor gene maps in the J region. These genes are quite specific in that the same gene can apparently distinguish between two closely related antigens and effect a high response to one and a low response to the other antigen.

The relation between *Ia* and *Ir* genes is unclear. The two types of gene map in the same positions, and all attempts to find an *Ir* gene product distinct from *Ia* gene products have failed.

Class III genes code for serum proteins Ss (serum serological) and Slp [sex-limited protein (*25*)]. Both the Ss and Slp proteins have a molecular weight of 200,000 and consist of three covalently linked polypeptide chains, α (87,000), β (78,000), and γ (33,000). These molecules are the C4 component of the classical complement pathway. The three chains are derived by cleavage from a single precursor chain and are thus presumably encoded by a single gene. Small

Table 2. The NH_2-terminal amino acid sequences of class I molecules of different species [compiled from (*15, 18, 18a, 19*)]. Symbols: ., not determined; —, amino acid shared with K^b; ( ), uncertain assignment.

Species (MHC)	Molecule	Amino acid position																										
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Mouse (*H-2*)	K^b	—	Pro	His	Ser	Leu	Arg	Tyr	Phe	Val	Thr	Ala	Val	Ser	Arg	Pro	(Gly)	Leu	(Gly)	(Glu)	Pro	Arg	Tyr	Met	Glu	Val	Gly	Tyr	Val
	K^d	Met	.	—	.	Leu/Val	—	—	.	.	—	.	.	.	—	—	.	Leu/Val	.	.	—	—	(Phe)	.	.	.	.	—	.
	K^k, K^q	(Gly)	—	—	—	—	—	—	—	His	—	—	—	—	—	—	.	—	.	Lys	—	—	Phe	.	.	.	.	—	.
	D	Met	.	—	.	—	—	—	—	Val	—	—	—	Thr	—	—	.	Phe	.	.	—	—	Tyr	.	.	.	.	—	.
	D^d	.	—	.	.	.	—	—	.	.	.	—	—	.	—	—	.	Leu	.	.	—	—	Tyr	.	.	.	.	—	.
Rat (*Rt-1*)	B4	.	.	.	.	Leu/Ile	—	—	—	Tyr	.	—	—	.	.	.	.	.	.	.	.	.	Phe	Ile	Ala	—	.	—	Val
Man (*HLA*)	A2	Gly	Ser	—	—	Met	—	—	—	Phe	—	Ser	—	Ser	—	—	—	Arg	—	Glu	—	Arg	Phe	Ile	Ala	—	—	—	.
	B7	Gly	Ser	—	—	Met	—	—	—	Tyr	—	Ser	—	Ser	—	—	—	Arg	—	Glu	—	Pro	Phe	Ile	Ala	—	—	—	.
	B12	Gly	Ser	.	—	Met	—	—	—	Tyr	—	Ala	—	Ser	—	—	—	.	—	Glu	.	.	Phe	Ile	Ala	.	.	.	.
	B14	Gly	Ser	.	—	Met	—	—	—	Tyr	—	Ser	—	Ser	—	—	—	.	—	Glu	(Ser)	Asx	Phe	.	.	.	.	.	.
Guinea pig (*GPLA*)	B.1	.	.	—	.	Leu	—	—	—	Tyr	.	Ala	—	.	.	—	.	.	.	.	.	.	Phe	Val	.	.	.	—	.
Chicken (*B*)	9	.	Leu	—	.	Leu	—	—	Ile	Phe	.	Ala	.	.	.	—	.	(Pro)	.	Leu	.	.	Phe	Val	.	—	.	—	—
	10	.	Leu	—	.	Leu	—	—	Ile	.	.	Ala	.	.	.	—	.	.	.	.	.	.	Phe	Val	.	.	.	—	.
	2	.	.	—	.	Leu	—	—	Phe	Tyr	.	Ala	—	.	.	—	.	.	.	.	.	.	Phe	Val	.	.	.	—	.

Table 3. The NH_2-terminal amino acid sequences of class II (Ia) molecules of different species [compiled from (*19, 21*)]. Symbols: ., not determined; ( ), uncertain assignment.

Species	Molecule	Amino acid position																									
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Mouse	A_α^b	.	.	.	Ile	.	Ala	.	.	.	.	.	Tyr	.	.	.	Val	Tyr	.	.	.	.	.	.	.	.	Tyr	.
	A_α^k	.	.	.	Ile	.	Ala	.	(Val)	.	.	.	Tyr	.	.	.	Val	Tyr	.	.	.	.	.	.	.	.	Tyr	.
	A_β^b	.	.	.	.	Arg	.	.	Val	Tyr	.	.	.	.	.	.	Tyr	.	.	.	.	.	.	.	.	.	Tyr	.
	A_β^k	.	.	.	.	.	.	.	Val	.	.	.	.	.	.	.	Tyr	.	.	.	.	.	.	.	.	.	Tyr	.
	EC_α^d	Ile	.	.	.	.	.	Ile	Ile	.	Ala	.	Phe	Tyr	Leu	Leu	.	.	.	.	.	.	Phe	.	Phe	.	Phe	.
	EC_α^k	Ile	.	.	.	.	.	Ile	Ile	.	Ala	.	Phe	Tyr	Leu	Leu	.	.	.	.	.	.	.	.	.	.	.	.
	EC_β^d	Val	.	.	.	.	Pro	.	Phe	Leu	.	Tyr	Val	.	.	(Leu)	.	.	Phe	Tyr	.	.	.	.	.	(Val)	.	Phe
	EC_β^k	Val	.	.	.	.	.	.	Phe	(Leu)	.	Tyr	.	.	.	.	.	.	Phe	Tyr	.	.	.	.	.	.	.	(Tyr)
Man	p^{34}	Ile	Lys	Glu	Glu	Arg	Val	Ile	Ile/Leu	Glu	Ala	Glu	Phe	Tyr	Leu	Asn	Tyr	Asp	Phe	Gln	Gly	.	.	.	.	.	.	.
	p^{29}	Gly	Asp	Thr	Pro	Glu	Arg	Phe	Leu	Glu	Gln	Val	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Guinea pig	4,5	Ile	Tyr	.	Pro	.	.	Phe	Leu	Phe	.	Phe	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

differences in the γ chain of the Ss protein (detected by a rabbit antiserum to mouse serum) and the Slp (detected with an alloantiserum) have recently been reported (*8*) suggesting that the two proteins might be controlled by two genes.

More recently, genes coding for other complement components have also been shown to be linked to the MHC in various species: C3 in the mouse (*26*), Bf in the guinea pig (*27*), man (*28*), the rhesus monkey (*29*), and C2 in man (*30*).

Very little is known about the expression of the other *H-2* genes which cannot be classified into one of the three classes described above. For this reason, I will not consider these genes further.

Polymorphism

One of the most remarkable properties of *H-2* loci is their genetic polymorphism, that is, the existence in a population of several alleles at individual *H-2* loci in frequencies that cannot be explained by recent mutations. In this property, the *H-2* loci differ sharply from almost all other genes. For example, if one screens mouse populations for genes controlling allozymes (isozymes), one finds that about 60 percent of the loci are invariant (monomorphic), that is, only one allele can be found in a population at each of these loci (*31*). The remaining 40 percent of loci are polymorphic in that two, very rarely three, alleles can be found at these loci. Usually one of the three alleles is considerably more frequent than the other two. Most mice are homozygous at the polymorphic loci (that is, they carry the same allele at the two genes in the homologous chromosomes); usually less than 10 percent are heterozygous at these loci.

With the *H-2* loci, the situation is drastically different. In our studies of class I loci in wild mice captured in Michigan or Texas (*32*), we found that the two populations contained at least 20 alleles at each of the two loci (there were probably more alleles, but we could detect only those coding for antigens that we could identify with our battery of reagents; the frequency of the "blanks" that did not react with any of our antiserums was 20 percent and it is unlikely that all the blanks were encoded by the same allele). The most frequent class I locus allele present in the wild population was found in only 12 percent of the mice. Most other alleles were present in frequencies of less than 2 percent. Corresponding to this high polymorphism among wild mice was a high degree of heterozygosity. Homozygotes at the class I loci were extremely rare; more than 90 percent of the mice were heterozygous (*33*).

Some of the alleles found among wild mice closely resembled—in terms of serological reactivities—those found among inbred strains of laboratory mice. However, many new alleles were also found among wild mice. Since the allelic products of class I loci differ by many amino acid substitutions (Table 3), they cannot be derived each from another by a single mutation. Thus, the presence of such highly diverse alleles among wild mice represents a true polymorphism that cannot be explained by a transient, local appearance of recent mutations.

In total, 56 alleles at the *H-2K* locus and 45 alleles at the *H-2D* locus have been found so far in the house mouse (*34*). This number of alleles at the two loci can occur in 2500 combinations and the indications are that most of these combinations do exist among wild mice. Considering the high degree of *H-2* heterozygosity and the fact that there are many more loci in the *H-2* complex, the variability of natural populations at this complex is extraordinary.

Our studies concerning the polymorphism of the class II (*Ia*) loci indicate that these loci indeed contribute considerably to the overall variability of the *H-2* complex (*35*). Although individual Ia antigens appear to be somewhat more frequent among wild mice than are class I antigens (Ia antigens detected with the most specific of our antiserums occur with frequencies of about 15 percent, which is higher than the frequency of the most frequent private class I antigen), the occurrence of different combinations of these antigens indicates the presence of a large number of alleles. However, there seems to be a conspicuous difference in the degree of polymorphism between the *Ia* loci of the A and E/C regions. While *Ia* of the A region appears to be as polymorphic as the class I loci, we have found only five alleles at the E/C region *Ia* locus. Whether this difference is real or merely an artifact of the serological methods used in this study remains to be determined.

Formally, the polymorphism of the *H-2* loci can be explained in one of two ways: It is so high either because it is tolerated by the species (that is, the different alleles provide neither selective advantage nor disadvantage for the animals) or because natural selection favors the presence of so many alleles in the population. The former is the neutralist, the latter the selectionist view of the *H-2* polymorphism. Which view is correct is not known, but to argue that the spectacular multitude of *H-2* alleles in nature has no functional meaning does not seem very sensible. (Among other things, such an argument would lead to the supposition that there is no other neutral gene system in nature, since no other system is as polymorphic as *H-2*.) More likely, *H-2* polymorphism exists because it is needed for *H-2* to do whatever it does in the cell. What *does* the *H-2* do?

Function

Despite (or perhaps because of) the broad pleiotropism of the complex [more than 60 traits are affected by *H-2* loci, see (*12*)], clues to the function of *H-2* are rare. The strongest clue was discovered by Zinkernagel and Doherty 4 years ago (*36*). The essence of their discovery is this.

When infected by certain viruses [for example, vaccinia or lymphocytic choriomeningitis (LCM) virus], mice generate effector lymphocytes which can destroy—either in vivo or in vitro—virus-infected cells. This destruction is virus-specific, meaning that effector lymphocytes generated in vaccinia-infected mice destroy vaccinia-, but not LCM-infected cells, and vice versa. Zinkernagel and Doherty discovered a second level of effector-cell specificity, controlled by class I *H-2* genes. Thus an effector lymphocyte sensitized against vaccinia-infected H-2^a cells destroys vaccinia-infected H-2^a cells but not, for example, vaccinia-infected H-2^b cells. In other words, cell killing by effector lymphocytes is restricted by the *H-2* system, and more precisely by the *H-2K* and *H-2D* loci, since genetic mapping studies have shown that other *H-2* loci do not restrict effector cell specificity.

The explanation put forward for this restrictive killing is that a maturing effector lymphocyte learns to recognize viral antigens in association with (or in context of) *H-2K* and *H-2D* molecules of the sensitizing (antigen-presenting) cell. But when does this learning occur? Can any cell in the body teach a lymphocyte what antigens to recognize and in what context? Or, is there a special organ—a sort of "school" for lymphocytes—in which this teaching occurs? The answer is that the learning occurs—as Niels Jerne predicted several years ago (*37*)—in the thymus, the bilobal, pyramid-shaped organ resting on the pericardium beneath the breast bone and above the trachea.

The thymus consists of two main structural components: the epithelial reticular cells derived from the epithelium of the third branchial pouch, and lymphocytes derived from the bone marrow (or, in the earlier stages of life, from the fetal liver, spleen, and yolk sac). In a series of experiments, Zinkernagel and his co-workers have demonstrated that it is the thymus epithelium that dictates the *H-2* context of antigen recognition by lymphocytes (*38*). Thus in a chimeric mouse whose thymus epithelium is of an H-2^a type and whose bone marrow (the source of immature lymphocytes) is of an H-2^b type, lymphocytes learn to recognize virus-infected cells in association with H-2^a, and not in association with H-2^b. The great debate in contemporary immunology is whether this recognition occurs via two receptors (one for the viral antigens and another for the *H-2* molecules) or via a single receptor which recognizes both the viral antigens and the *H-2* molecules at the same time. Since no solid data exist to tip the balance of argument one way or the other (the debate probably will not be resolved decisively until someone actually isolates and characterizes the receptor or receptors) and since the debate is not directly pertinent to the questions discussed in this article, I shall not discuss it here further.

Studies of chimeric mice have led to another important discovery, namely, that effector lymphocytes probably do not act alone (*39*). At some stage of their functional activity, these cells require the help of other cells—appropriately referred to as helper lymphocytes. These cells also learn, from thymus epithelium, how to recognize viral antigens in an *H-2* context, but, in contrast to effector cells, the helper lymphocytes are restricted by class II (that is, I-region) molecules. Thus a cooperation in the restriction of the specificity of lymphocytes involved in cellular immune response to viral infections occurs between *H-2* loci: class I (*H-2K* and *H-2D*) loci restrict the specificity of effector lymphocytes and class II (I-region) loci restrict the specificity of helper lymphocytes. Almost nothing is known about the nature of this cooperation, but one can postulate that the class II molecules provide—through the helper cells—a specific proliferative signal necessary for the expansion of the effector-lymphocyte population, and class I molecules then provide the effector signal leading to target-cell lysis.

Interpretation

How can these new findings be used to develop a coherent interpretation of the *H-2* system? The main stumbling block to a unifying *H-2* hypothesis has been the apparent specificity of *Ir* genes. This block can now be removed if we extend the interpretation of associative recognition to cover the events occurring during B (bone marrow-derived) lymphocyte activation. Two facts have been known for some time: First, that antibody synthesis requires participation of T lymphocytes (helper cells), and second, that the interaction of helper and B lymphocytes is somehow controlled by *Ir* genes. Several pieces of evidence now indicate that this interaction occurs on the same principle as the interaction between effector and helper cells in the generation of a lytic cellular response. One can therefore speculate that helper cells involved in antibody response are restricted in their specificity by class II molecules (*40*). In other words, they are taught by the thymus epithelium to recognize antigens in the context of class II molecules and when they then interact with B lymphocytes their activity is restricted by these molecules. The specificity of *Ir* genes is then a result of this restriction. According to this hypothesis, there are no special *Ir* genes in the *H-2* complex, distinct from *Ia*. *Ia* genes *are* the *Ir* genes, and the specificity of the *Ir* genes reflects the fact that a class II molecule is recognized together with an antigen. Because of this restriction, individuals differ in the receptor repertoire of their helper-cell populations. And because this repertoire is dictated, to a large extent, by class II molecules, individuals carrying different class II molecules have different T-cell-receptor repertoires (*41*).

The restriction by class II molecules means that there will be some antigens for which a given individual will not have the necessary receptors or will have only receptors with low affinity. Such an individual will then appear as a low responder to a given antigen. Another individual, with different class II molecules, and hence a different T-cell-receptor repertoire, might have the appropriate receptors and would therefore be a high responder to this antigen. Since the difference in T-cell-receptor repertoires will be dictated by class II molecules, the response itself will appear to be controlled by the class II (*Ia*) genes.

This interpretation thus provides an answer to the question posed in the summary of this article. If there were no *H-2* polymorphism, all individuals in a given species would carry the same repertoire of T-cell receptors. Consequently, they would all have the same "blind spots" in their repertoires, that is, they would all be unresponsive to certain antigens. If these antigens happened to be carried by some pathogenic organism, the end result would be that the entire population would be defenseless against this organism. The very existence of the species would thus be endangered. *H-2* polymorphism prevents the occurrence of such a catastrophe. It assures the existence in a population of at least some individuals with the right *H-2* alleles and the right T-cell repertoire to enable activation of defense reactions to any pathogen. *H-2* polymorphism thus provides a

means of generating diversity in the immune response at the population level, in addition to the diversity generated at the cellular level within an individual.

This method of diversity generation, in fact, was probably used by most lower organisms before the development of more sophisticated defense mechanisms by vertebrates (*13*). An important question then arises: Why does the system of associative recognition exist at all? Would it have not been simpler for an organism to develop a system recognizing antigens directly and independently of other molecules (as is, in fact, the case with the antibody molecules and the B-cell receptors)? One possible explanation for the existence of associative recognition is that the system provides a linkage between recognition and effector mechanisms and thus engenders a specificity in effector function (*42*). If one were to assume that class I molecules are the source of a lytic (destructive) signal and class II molecules the source of a regulatory signal, then, to assure the specificity of these signals, it might be necessary for the effector (regulatory) cell to recognize the antigen in the context of such molecules.

The mysterious presence in the MHC of genes coding for some complement components may also be tied to this speculation. Mediation of cell destruction might have been the original function of the ancestral *H-2* genes. This ability has apparently been preserved in all MHC genes, although some of the genes (class II) do not use it under physiological conditions. The linkage of complement genes would be, according to this interpretation, a relict of the past. Some of the class III genes remain linked to MHC because of their origin and not because this linkage has any functional meaning. These genes have become specialized to secrete effector molecules that were originally membrane-bound. Through this process, they have lost their dependence on T-cell receptors and have linked up with a different set of receptor molecules—the secreted immunoglobulins. Because of the conditions in which they carry out their effector function, they have become free from their original involvement in recognition and, as a result, have lost their strict specificity.

Conclusion

I began this article by comparing the situation of contemporary immunology to that of modern physics. I close with a quotation from one of the creators of modern physics, Max Planck. In 1933, in his "Where is science going?" Planck wrote (*43*): "We are living in a very singular moment of history. It is a moment of crisis, in the literal sense of the word. In every branch of our spiritual and material civilization we seem to have arrived at a critical turning point. . . . Many people say that these symptoms mark the beginnings of a great renaissance but there are others who see in them the tidings of a downfall to which our civilization is fatally destined. . . . Formerly it was only religion . . . that was the object of sceptical attack. Then the iconoclast began to shatter the ideals and principles that had hithertho been accepted in the province of art. Now he has invaded the temple of science. There is scarcely a scientific axiom that is not nowadays denied by somebody. And at the same time almost any nonsensical theory that may be put forward in the name of science would be almost sure to find believers and disciples somewhere or other. In the midst of this confusion it is natural to ask whether there is any rock of truth left on which we can take our stand and feel sure that it is unassailable and that it will hold firm against the storm of scepticism raging around it." If one were to substitute the word "civilization" in this quotation with "immunology"—what a perfect description of the current situation in biology these words would constitute! Yet, it is precisely this feeling of living in a "singular moment of history" which makes even the present chaos so exciting!

References and Notes

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