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The Evolution of Mating Preferences and Major Histocompatibility Complex Genes

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ABSTRACT: House mice prefer mates genetically dissimilar at the major histocompatibility complex (MHC). The highly polymorphic MHC genes control immunological self/nonself recognition; therefore, this mating preference may function to provide "good genes" for an individual's offspring. However, the evidence for MHC-dependent mating preferences is controversial, and its function remains unclear. Here we provide a critical review of the studies on MHC-dependent mating preferences in mice, sheep, and humans and the possible functions of this behavior. There are three adaptive hypotheses for MHC-dependent mating preferences. First, MHC-disassortative mating preferences produce MHC-heterozygous offspring that may have enhanced immunocompetence. Although this hypothesis is not supported by tests of single parasites, MHC heterozygotes may be resistant to multiple parasites. Second, we propose that MHC-dependent mating preferences enable hosts to provide a "moving target" against rapidly evolving parasites that escape immune recognition (the Red Queen hypothesis). Such parasites are suspected to drive MHC diversity through rare-allele advantage. Thus, the two forms of parasite-mediated selection thought to drive MHC diversity, heterozygote and rare-allele advantage, will also favor MHC-dependent mating preferences. Finally, MHC-dependent mating preferences may also function to avoid inbreeding; a hypothesis consistent with other evidence that MHC genes play a role in kin recognition.

Keywords: Red Queen, sexual selection, host-parasite coevolution, heterozygote advantage, inbreeding avoidance, kin recognition.

When females assess potential mates, they should look for "good genes" to increase the viability of their offspring, especially when males only contribute sperm (Trivers 1972). What type of genetic benefits do males have to offer females? For choosy females to increase the viability of their offspring, there must be genetic variation affecting fitness among males. Host-parasite coevolutionary arms races potentially provide a source of endless genetic variation affecting host fitness; therefore, Hamilton and Zuk (1982) proposed that females can increase the survival of their offspring by mating with disease-resistant males. Although less appreciated, Trivers (1972) suggested that females can obtain good genes for their offspring by mating with males whose genes are compatible or complementary to their own. For example, females who mate assortatively, disassortatively, or avoid inbreeding can increase the genetic compatibility of their mates and the viability of their offspring.

One of the most widely cited examples of good genes mating preferences involves the genes of the major histocompatibility complex (MHC; Freeman and Herron 1998). The MHC is a large chromosomal region containing several closely linked, highly polymorphic genes (MHC class I and II loci; fig. 1) that play a central role in controlling immunological self/nonself recognition (Klein 1986; Janeway 1993). Several studies in mice (*Mus musculus domesticus*), and one in humans, have found females prefer to mate with males carrying dissimilar MHC genes (table 1). Mice can recognize the MHC identity of potential mates through odor cues (reviewed in Penn and Potts 1998*b*). For example, both mice and rats can distinguish individuals that are virtually genetically identical except in the MHC region (Yamazaki et al. 1979; Brown et al. 1987) and at single MHC loci (Yamazaki et al. 1983; Penn and Potts 1998*a*). How MHC genes influence odor is still unclear, but two possibilities are that MHC genes influence microbial flora (Singh et al. 1990) and concentrations of volatile acids (Singer et al. 1997). Although much work has examined how MHC-dependent mating occurs through odor cues, relatively little attention has been paid to determining why it occurs. What is the adaptive significance of MHC-dependent mating preferences?

In this article we provide a critical review of the evidence for MHC-dependent mating preferences in house mice, sheep, and humans. Although the existence of MHC-

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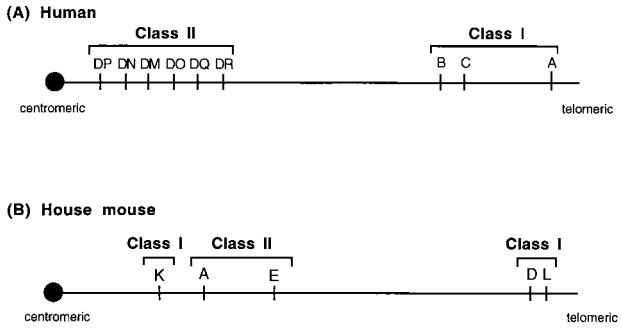

Figure 1: The MHC is a large chromosomal region (around 2,000 kb in mice and 3,500 kb in humans) containing over 200 coding loci that control the immune system, growth, and reproduction. The term "MHC genes" usually refers to the highly polymorphic "classical" loci that encode class I and II antigen-binding molecules. Class I and II MHC genes arose by tandem duplication events and are inherited as a unit (haplotype) since they are closely linked in many species. *A*, Human MHC encodes six antigen-presenting molecules, and the polymorphism, which is still incompletely characterized, varies from one to 179 alleles per locus (41 on average; Parham and Ohta 1996). *B*, In house mice, there are five antigen-presenting molecules with over 100 alleles per locus in local populations (Duncan et al. 1979; Klein 1986).

dependent mating preferences is sometimes treated with extreme skepticism (especially in humans), we show that there is good evidence for this behavior in house mice. We also provide a review of the potential functions of MHC-dependent mating preferences and suggest some novel hypotheses. The MHC-dependent mating preferences may enable females to produce disease resistant offspring or avoid inbreeding (Brown 1983; Alberts and Ober 1993; Potts and Wakeland 1993; Brown and Eklund 1994). There are two ways that MHC-disassortative mating preferences can increase the resistance of an individual's progeny against parasites. First, MHC-disassortative mating preferences produce MHC-heterozygous offspring that may be resistant to multiple parasites. Second, we show that MHC-dependent mating preferences alter the immune system of an individual's offspring, potentially providing a "moving target" against rapidly evolving pathogens. These good genes hypotheses are not mutually exclusive as MHC-dependent mating preferences may perform all of these functions.

MHC-Dependent Mating Preferences

House Mice

Several studies have found MHC-dependent mating preferences in both male and female house mice (table 1). A serendipitous observation of mice that are virtually genetically identical except in the MHC region (MHC-congenic strains) suggested that mice prefer to mate with MHC-dissimilar individuals. Subsequent experiments by Yamazaki and his colleagues (1976) indicated that male congenic mice prefer to mate with MHC-dissimilar females in four of the six MHC-congenic strains tested (one strain showed MHC-similar preferences, and one showed no preferences). Subsequent experiments eliminated the possibility that MHC-disassortative mating was due to mutations at other loci that might have accumulated among the congenic lines by testing the mating preferences of F_2 segregant mice (produced by crossing two congenic lines, intercrossing the F_1 heterozygotes, and testing the F_2 MHC-homozygous progeny; Yamazaki et al. 1978). Another laboratory study found that female mice prefer to mate with MHC-dissimilar males, and estrus females preferred the odor of MHC-dissimilar males (Egid and Brown 1989).

Several studies indicate that house mice learn the MHC identity of their family during early ontogeny (familial imprinting) and avoid mating with individuals carrying familial MHC genes. First, Yamazaki and his colleagues noted that the MHC-dependent mating preferences of male mice appeared to be altered when they were exposed to MHC-dissimilar mice as pups (Beauchamp et al. 1988). To test this hypothesis, Yamazaki and his colleagues (1988) removed pups at birth and reared them with MHC-dissimilar (cross-fostered) or MHC-identical (in-fostered) parents. When presented with a simultaneous choice, cross-fostered males avoided mating with females carrying MHC genes of the male's foster family even though this meant mating with MHC-similar females. This effect was not due to the fostering procedure because fostering did not reverse the mating preferences of in-fostered control males reared with MHC-identical parents. Second, this cross-fostering experiment was successfully replicated with a second strain of male MHC-congenic mice (Beauchamp et al. 1988). Third, another laboratory experiment with MHC-congenic mice found that cross-fostering altered the mating (first mount) preferences of one of two strains of female mice tested compared with unfostered mice (Eklund 1997*a*). Finally, we recently found that cross-fostering reverses the MHC-disassortative mating preferences of wild-derived female mice living in seminatural conditions (Penn and Potts 1998*c*). Taken together, these cross-fostering studies provide strong experimental evidence for MHC-dependent mating preferences and familial imprinting.

Laboratory studies on MHC-dependent mating preferences in mice have been criticized by Hughes and Hughes (1995); however, most of their criticisms are misleading. They correctly point out that the mating preferences observed by Yamazaki et al. (1976) may have been

Table 1: Evidence for MHC-dependent mating preferences

	Mating preferences		Odor preferences		
	Male	Female	Male	Female	References
House mice:					
1.	+				Yamazaki et al. 1976
2.	+				Yamazaki et al. 1978
3.	+				Yamazaki et al. 1988
4.	+	−			Beauchamp et al. 1988
5.	−				Eklund et al. 1991
6.		+		+	Egid and Brown 1989
7.		−			Manning et al. 1992*a*
8.		+			Potts et al. 1991
9.				+	Ninomiya and Brown 1995
10.		+			Eklund 1997*a*
11.		−			Eklund 1997*b*
12.		+			Penn and Potts 1998*c*
Sheep:					
13.	−	−			Paterson and Pemberton 1997
Humans:					
14.				+	Wedekind et al. 1995
15.		+			Ober et al. 1997
16.	−	−			Hedrick and Black 1997
17.			+	+	Wedekind and Füri 1997

Note: Modified from Penn and Potts 1998*b*.

due to male preferences, female preferences, or both (e.g., females may have been more receptive to MHC-dissimilar males). However, contrary to Hughes and Hughes (1995), this ambiguity does not challenge the central finding by Yamazaki et al. nor could it have been eliminated by separating the two stimulus females during experiments (i.e., controlling female-female interactions only eliminates the possibility that intrasexual competition masks preferences when no preferences are found). There is no reason to suspect that intrasexual competition would create a spurious MHC-dependent mating pattern. Furthermore, Hughes and Hughes (1995) fail to recognize that cross-fostering experiments provide direct experimental evidence for mating preferences in male mice (Beauchamp et al. 1988; Yamazaki et al. 1988). Hughes and Hughes (1995) suggest that the odor preferences of female mice for MHC-dissimilar males observed by Egid and Brown (1989) were due to a preference for unfamiliar rather than MHC-dissimilar odors. However, this is not an alternative explanation because a preference for unfamiliar (or nonfamilial) odors may be the proximate mechanism that results in MHC-dissimilar matings.

Still, there are some valid reasons to be cautious about the evidence for mating preferences from laboratory studies (Manning et al. 1992*a*). First, the assays for mating preferences in laboratory studies have been indirect, relying on sperm plugs, association, and first mount preferences. Yet, sperm plugs are not always present, and mounts and intromissions are nonejaculatory copulations that may function as courtship behavior rather than mate choice in rodents (Dewsbury 1988). Second, most of this work has been conducted on inbred, laboratory mice, and since not all strains show MHC-dependent mating preferences (Yamazaki et al. 1976; Eklund et al. 1991; Manning et al. 1992*a*; Eklund 1997*a*), these results cannot be extrapolated to wild mice. Third, female MHC-dependent mating preferences have only been found in the laboratory when male dominance has been controlled (Egid and Brown 1989), leaving the possibility that mating preferences do not create selection in natural conditions where dominance occurs.

Not all laboratory studies have found MHC-dependent mating preferences (table 1). No evidence for MHC-disassortative mating preferences was found in two strains of male laboratory mice (Eklund et al. 1991), and for females, no evidence for MHC-disassortative mating preferences was found in one laboratory strain (Beauchamp et al. 1988), semiwild (Manning et al. 1992*a*), or wild female mice (Eklund 1997*b*). Still, there are many reasons to be cautious about overinterpreting the negative evidence from experimental studies. First, most laboratory studies have been based on small sample sizes (e.g., Eklund 1997*b*). However, to demonstrate the null hypothesis of no mating preference, one needs a large sample size determined by a power analysis (Cohen 1988). Without such an analysis, there is nothing one can conclude. Second,

when female mating preferences were tested by Beauchamp et al. (1988), male-male interactions were not controlled; therefore, females probably mated with the most dominant male. Third, laboratory strains may show no MHC-dependent mating preferences, perhaps because inbreeding avoidance behaviors are selected against during domestication (Manning et al. 1992*a*). Finally, laboratory experiments create artifacts and unnatural circumstances that may abolish mating preferences. Consider the following examples: housing females in isolation from males or artificially inducing estrus may abolish choosiness; the assessment of mates may require more time than what is allowed in brief mate-choice assays; collaring and tethering males controls dominance interactions, but females may avoid the male most easily stressed from the artificial restraint. Inconsistent results in laboratory mate choice experiments are not surprising—such inconsistencies have plagued mate choice experiments in mice for more than 3 decades (reviewed by D'Udine and Alleva 1983). These caveats about laboratory studies underscore the importance of examining the behavior of animals under natural social conditions.

To determine how selection maintains the diversity of MHC alleles, Potts and his colleagues (1991) studied wild-derived mice carrying four MHC haplotypes in large, seminatural enclosures. They genotyped the progeny born in the enclosures and found fewer MHC homozygotes than expected from random mating (27% fewer homozygotes on average). The MHC-homozygote deficiency was not due to susceptibility to infectious agents since the deficiency was present in utero, implicating abortional selection or mating preferences. Informative matings in the laboratory indicated that MHC-similar pregnancies were not aborted at a significant rate, whereas genetic and behavioral data from the enclosures indicated that the female mice were selectively mating with MHC-dissimilar males. The selection from mating preferences was sufficient to maintain the diversity of MHC genes found in wild populations (Hedrick 1992). Furthermore, we recently found that the MHC-disassortative mating preferences of female mice living in seminatural enclosures can be reversed by cross-fostering (Penn and Potts 1998*c*). This supports laboratory studies showing familial imprinting in inbred, laboratory strains of mice (Beauchamp et al. 1988; Yamazaki et al. 1988; Eklund 1997*a*), as well as the original finding of MHC-dependent mating preferences in wild-derived mice (Potts et al. 1991).

The study by Potts and his colleagues (1991) has received some criticisms. First, Hughes and Hughes (1995) suggest that the results were created by the unnaturalness of the populations in the enclosures, such as a lack of age structure and dispersal. However, they fail to specify how such conditions could possibly create a spurious MHC-disassortative mating pattern. Second, Hedrick and Black (1997) suggest the results could have been due to an artificial homogeneity of background genes; however, the background genes of these mice were semiwild, not homogeneous as claimed by Hedrick and Black. Third, Hughes and Hughes (1995) suggest that females avoided MHC-similar males because MHC-similar males were simply mistaken as close kin. Again, this is not an alternative explanation because a preference for nonkin may be the proximate mechanism that controls MHC-dissimilar mating preferences (or vice versa). Finally, Hughes and Hughes (1995) point out that the observed mating preferences may not have been due to classical MHC genes (highly polymorphic class I and II loci) but rather to some other locus within the MHC region. This is entirely possible since there are many coding genes within the MHC region, including olfactory-like receptor genes (Fan et al. 1995). Still classical MHC genes are strong candidates since they are the only polymorphic loci known in this region, control variation in individual odor, and, as we will show, provide many potential indirect benefits.

Feral Sheep

A recent study investigated whether feral Soay sheep (*Ovis aries*) living on a Scottish island display MHC-dependent mating preferences (Paterson and Pemberton 1997). This population does not show a deficiency of MHC homozygotes; however, it does show an even distribution of alleles indicating balancing selection. Paterson and Pemberton (1997) genetically typed between 887 and 1,209 newborn lambs with five microsatellite markers and used a likelihood-based approach to analyze the mating patterns of the ewes. Although they found no evidence for MHC-disassortative mating preferences, their analysis could only detect strong mate selection ($s > 0.33$). Thus, weak selection from mating preferences could still account for the evolutionary maintenance of MHC diversity. The authors do not say if these sheep avoid inbreeding, which matters because inbreeding avoidance mechanisms may have been selected out during domestication (Manning et al. 1992*a*). If some species do not have MHC-dependent mating preferences, then perhaps this behavior only occurs in species at a particular risk of inbreeding depression as a result of low dispersal.

Humans

There is some evidence that humans have MHC-dependent mating preferences. Wedekind and his colleagues found that humans prefer the body odor of MHC-dissimilar individuals (Wedekind et al. 1995; Wedekind and Füri 1997). In the first study, Wedekind et al. (1995) MHC

typed 49 women and 44 men and asked the women to rate the attractiveness of the odors of T-shirts worn by three MHC-similar and three MHC-dissimilar men. Women generally preferred the odor of MHC-dissimilar men, describing them as "more pleasant." Moreover, the scent of MHC-dissimilar men was twice as likely to remind women of their mate's odor. Surprisingly, the preferences of women taking oral contraceptives were reversed, as they preferred the odor of MHC-similar men. Wedekind et al. (1995) suggested that, since steroid contraceptives mimic the effects of pregnancy, pregnant females may be attracted to MHC-similar individuals, who are likely to be close kin and potential reproductive helpers. This kin-recognition hypothesis was prompted by evidence that female house mice prefer communal nesting partners that are sisters or have similar MHC genes (Manning et al. 1992*b*).

This "T-shirt study" has received several criticisms. First, odor preferences, despite the title of the original paper, only provide indirect evidence for mating preferences. A subsequent study found that men were just as likely to prefer men's as women's odors (Wedekind and Füri 1997), which does not support the mate preference assumption. Second, preferences for T-shirt odors may not reflect preferences for actual body odors. Still, the T-shirt methodology is more likely to underestimate or miss actual preferences rather than to create spurious correlations. Third, Hedrick and Loeschcke (1996) worry that the subjects used nose spray to open their nasal passages and read a book about human odors. Although unnatural, it is difficult to see how such treatments could have created a spurious MHC-dependent odor preference. Finally, Wedekind et al. (1995) assumed that women prefer the odor of men whose MHC is dissimilar to themselves (self-inspection) rather than to their family. However, if humans use familial imprinting, then this assumption would underestimate preferences. The T-shirt study is sometimes misunderstood as claiming to show that human mating preferences are based mainly on MHC sharing; however, the study was not designed to determine the relative importance of MHC or odor in human mate choice (Wedekind and Seebeck 1996). Interestingly, subsequent studies have found that women pay more attention to odor cues from males than is often assumed (Herz and Cahill 1997; Gangestad and Thornhill 1998).

A second T-shirt study provides further evidence for MHC-dependent odor preferences in humans (Wedekind and Füri 1997). Wedekind and Füri (1997) asked 121 men and women to rate the odors of shirts worn by MHC-similar and dissimilar individuals (unfortunately, some were the same subjects from the first T-shirt study). Their aim was to determine if people prefer the odor of potential mates who are MHC dissimilar or if they are seeking to create particular combinations of MHC alleles. Both men and women (not using oral contraceptives) preferred the odor of MHC-dissimilar individuals. In 28 cases, the MHC-dissimilar T-shirt odors reminded both men and women of their own mate's or former mate's odor. The preferences of women using contraceptives were reversed, although the effect was not statistically significant. There was no evidence that individuals were seeking particular MHC genotypic combinations; the subjects simply preferred MHC dissimilarity. However, Wedekind and Füri (1997) did not test whether there are odor preferences for particular combinations of alleles at different MHC loci. Such mating preferences could explain the excess of particular MHC combinations found in some human populations (gametic disequilibrium; e.g., the high association of A1 and B8 alleles in Northern Europeans; Hedrick 1994).

Ober and her colleagues (1997) have found evidence for MHC-dependent mating preferences in a population of Hutterites. Hutterites are a small, isolated religious sect that has maintained genealogical records since the approximately 400 members originally migrated from Europe to North America in the 1870s (this bottleneck explains why this population has relatively low MHC diversity). Interestingly, Hutterites show a deficit of MHC homozygotes at birth (Kostyu et al. 1993), implicating abortional selection or mating preferences. Ober (1995) found that couples sharing MHC haplotypes have unusually long interbirth intervals, which may be due to abortional selection or lower copulation rates among MHC-similar couples. Ober and her colleagues (1997) tested for nonrandom mating among 411 Hutterite couples using population genotype frequencies and computer simulations. They found that couples were less likely to share MHC haplotypes than by chance, even after statistically controlling for nonrandom mating patterns among colony lineages and close inbreeding taboos. There was some evidence that Hutterites avoid mating with individuals carrying maternal MHC haplotypes (familial imprinting); however, this effect was due largely to one haplotype.

Another study attempted to determine if the MHC homozygote deficiency observed in South American Amerindians was due to disassortative mating preferences (Hedrick and Black 1997). Hedrick and Black used serotypes to examine MHC sharing (two class I loci) among 194 couples from 11 tribes and found no evidence that the MHC-homozygote deficiency was due to mating preferences. There are several reasons why this study was inadequate and unlikely to detect MHC-dependent mating preferences. First, Hedrick and Black's sample size was too small to detect selection below $s = 0.45$ (the selection coefficients on human MHC loci have been estimated to be between 0.0007 and 0.042; Satta et al. 1994). Second, Hedrick and Black's study only considered sharing between

married couples, ignoring all extrapair copulations. Extrapair matings are especially important to consider since women appear to look mainly for "good genes" during extrapair matings but primarily look for economic resources when choosing marriage partners (Buss 1989). Third, Hedrick and Black assumed self-inspection, but to adequately reject MHC-dependent mating preferences, familial imprinting must be tested. Fourth, Hedrick and Black did not control for socially enforced cross-cousin marriage proscriptions that are prevalent among these Amerindian tribes. Like imprinting, cross-cousin marriage customs change the pool of available mates and can potentially mask any MHC-dependent mating preferences among cousins. Finally, Hedrick and Black did not examine MHC class II genes, but no study demonstrating MHC-dependent mating and odor preferences has ignored class II loci.

While there is much evidence for MHC-dependent mating preferences in house mice and some evidence in humans, further work is needed to test whether MHC genes influence odor and mating preferences in other species. Although no evidence for strong mating preferences were found in feral sheep (Paterson and Pemberton 1997), the evidence for MHC-dependent mating preferences is sufficiently compelling in mice and humans to consider the potential benefits of this behavior. In the next section, we consider how MHC genes control immune recognition of parasites to evaluate the hypothesis that MHC-dependent mating preferences function to enhance the resistance of an individual's progeny to parasites.

MHC Genes: Immunological Mechanisms

The Development of Immunological Self/Nonself Recognition

The MHC genes encode class I and II MHC molecules, cell-surface glycoproteins, that present peptide antigens to T-lymphocytes (Matsumura et al. 1992). Through antigen presentation, MHC genes play a central role in controlling the development and the activation of the immune system, including both cellular and antibody-mediated defenses.

Development of Self/Nonself Recognition (*Thymic Selection*). An individual's immune system must be able to distinguish between self and foreign antigens to mount a response to invading parasites. The vertebrate immune system develops the ability to discriminate self/nonself (before birth) by randomly generating a wide diversity of T-cells with highly specific antigenic receptors and then eliminating and suppressing those that recognize self-antigens presented by MHC molecules. T-cells originate in the bone marrow, with each T-cell generating its own unique receptors through rearrangements of T-cell receptor genes (Kronenberg et al. 1986; Schatz 1992). An individual generates around 10^{10} unique T-cell receptors by these somatic rearrangements. Immature T-cells migrate to the thymus to mature in a two-step selection process. During positive selection, only T-cells that bind to an individual's particular MHC molecules (and self-peptides) are preserved (von Boehmer 1994; Fink and Bevan 1995). During negative selection, the T-cells that bind with a high enough affinity to activate T-cells are eliminated, leaving primarily T-cells that bind to nonself antigens (Nossal 1994). During this process of thymic selection, as much as 99% of the original T-cell repertoire is eliminated or inactivated ("anergized"; Nossal 1994). Positive selection eliminates T-cells with low or no MHC-antigen affinity while negative selection eliminates those with high affinity, leaving only T-cells with an optimal affinity (Lo et al. 1986; Ashton-Rickardt and Tonegawa 1994). Thus, most T-cells that recognize self antigens are eliminated or inactivated before they are released into the periphery. Thus, the resulting T-cell repertoire is controlled by MHC during both positive selection and negative selection ("MHC restriction"; Pullen et al. 1989; Bevan et al. 1994).

The Activation of Immune Effectors. The MHC genes play a central role in controlling the activation of all immunological effectors, including cytotoxic T-lymphocytes (CTLs), helper T-cells, macrophages, natural killer cells, and antibody-secreting B-cells (Janeway 1993; Janeway and Travers 1994). Intracellular parasites are detected by CTLs when class I MHC molecules present foreign peptides on the surface of infected cells (fig. 2*A*). Any CTL that binds to the MHC-antigen complex is activated, which results in the proliferation of the CTL clone and destruction of similarly infected cells. Extracellular parasites and fragments are phagocytized by macrophages or bound by B-cell-surface antibodies (fig. 2*B*, *C*). Before either of these effector cells can respond to an antigen, they must present the antigen to helper T-cells via class II MHC molecules to test if the antigen is foreign. If an MHC-presented antigen is recognized by helper T-cells, these helper T-cells proliferate, activate macrophages, and trigger B-cell proliferation and antibody secretion.

Thus, MHC genes play a central role in the immune system by shaping the development of the T-cell repertoire during thymic selection (von Boehmer et al. 1988; Schaffer et al. 1989; Pullen et al. 1989), determining which foreign antigens are presented to T-cells (Falk et al. 1991), and controlling the activation of antibody-secreting B-cells (Janeway 1993). Next, we consider how parasites impose selection on MHC genes to determine how MHC-dependent mating preferences may increase the resistance of progeny to parasites.

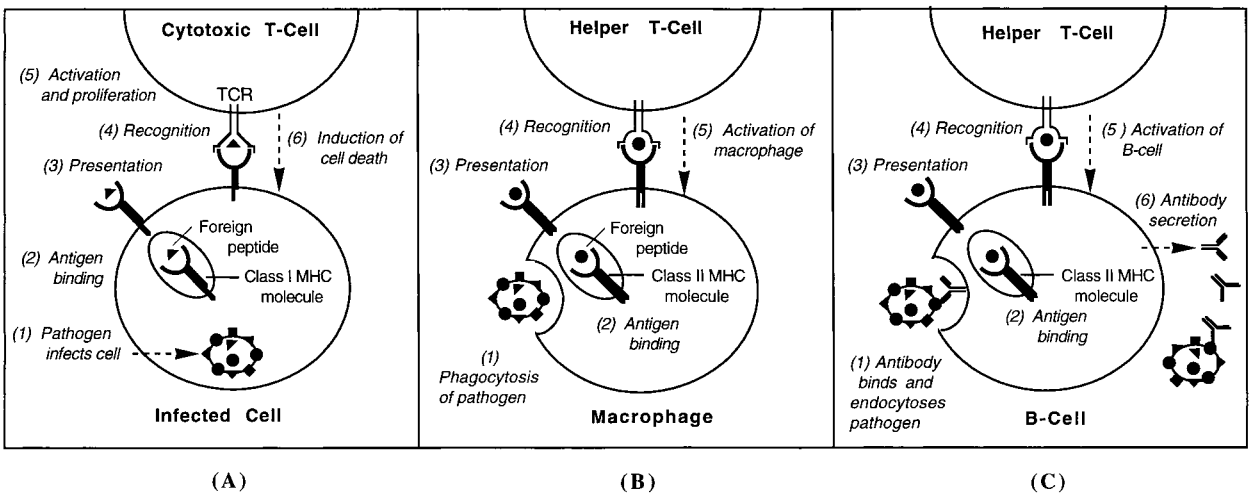

Figure 2: The MHC controls the activation of all specific immunological effectors. *A*, Infected cells use class I MHC molecules to present intracellular-derived peptides, both self and nonself, to cytotoxic T-cells. Each T-cell has its own unique receptor (TCR) that binds to MHC-antigen complexes. T-cells can recognize foreign peptides because those that bind self-antigens are normally eliminated during thymic selection. If a cytotoxic T-cell recognizes an antigen presented by an infected cell, it proliferates, and its clones kill similarly infected cells. *B*, Macrophages phagocytize extracellular pathogens and parasites and use class II molecules to present exogenous antigens to helper T-cells. If an antigen is recognized by a helper T-cell, it activates the macrophage to secrete complement proteins that destroy microbes and attract other phagocytes to the site of infection. The activated helper T-cell proliferates and stimulates the proliferation of other activated lymphocytes, such as B-cells. *C*, B-cells express cell-surface antibodies that bind to extracellular antigens. Before responding to an antigen, peptide fragments of the endocytosed antigens are presented to helper T-cells via class II molecules. If a presented antigen is recognized by a helper T-cell, it activates the B-cell to proliferate, and its clones secrete antibodies that label the foreign antigen for complement and macrophages.

Parasites and MHC Polymorphisms

MHC alleles differ in their resistance to parasites and susceptibility to autoimmune diseases (reviewed in Apanius et al. 1997), so why does natural selection not eliminate all but the most resistant allele? Several lines of evidence indicate that the antigen-binding site of MHC molecules is under balancing selection for long periods of evolutionary time (reviewed in Hughes and Hughes 1995; Apanius et al. 1997). Because the MHC plays such a pivotal role in the immune system, the diversity of MHC alleles is generally assumed to be maintained by parasites (Haldane 1949; Clarke 1976; Potts and Wakeland 1990; Hedrick 1994; Hughes and Hughes 1995; Parham and Ohta 1996). It often assumed that MHC diversity is maintained because it "provides broad immunological protection for the species as a whole" (Roy et al. 1989, p. 574) as "a strategy to keep parasites from spreading through the entire population" (Klein and O'Huigin 1994, p. 355). This argument implies that MHC polymorphisms are maintained because populations with high MHC diversity have a better chance of survival than populations with low diversity. Such group selection may be favoring MHC diversity (Apanius et al. 1997); however, the problem is that if directional selection and drift are eliminating MHC diversity within populations in the short term, then there will be no diversity for selection to act on among populations in the long term. Therefore, there must be some other explanation besides group selection for the maintenance of MHC diversity.

There are two nonmutually exclusive hypotheses for how parasites can maintain MHC diversity within host populations. Selection can maintain MHC polymorphisms if MHC heterozygotes are more resistant to parasites than homozygotes (heterozygote advantage; Hughes 1992; Takahata et al. 1992) or MHC alleles are under negative frequency-dependent selection from parasites (rare-allele advantage; Haldane 1949; Clarke 1976; Potts and Wakeland 1990; Slade and McCallum 1992). In the next section, we show that if MHC diversity is maintained by selection from parasites—through either heterozygote or rare-allele advantage—then MHC-disassortative mating preferences will also be favored by selection.

The Heterozygote Advantage Hypothesis

If MHC heterozygotes are more resistant to parasites than homozygotes, then MHC-disassortative mating preferences will subsequently be favored as a mechanism to produce MHC-heterozygous offspring (table 2). MHC het-

Table 2: Predictions of the adaptive hypotheses for MHC-dependent mating preferences

Proposed functions	Type of selection maintaining MHC diversity	MHZ-heterozygotes disease resistant	In species at risk of inbreeding	MHC used for kin recognition	Familial imprinting	Fluctuating MHC disease associations
Immunological resistance: Heterozygote advantage	Overdominant and sexual selection	Yes	No	No	No	No
Red Queen	Frequency-dependent and sexual selection	No	No	No	Perhaps	Yes
Inbreeding avoidance	Sexual selection	No	Yes	Yes	Yes	No

Note: Because these are not mutually exclusive hypotheses, "yes" indicates a strong prediction, but "no" does not indicate a rejection of the hypothesis; for example, heterozygote advantage may be a component of inbreeding depression, but it is not a necessary prediction of the inbreeding avoidance hypothesis.

erozygotes present a wider diversity of antigens to the immune system than homozygotes (Doherty and Zinkernagel 1975); however, there is surprisingly little evidence from population surveys and experimental infections to support the heterozygote advantage hypothesis. A recent study on feral sheep found no MHC-heterozygote advantage against a nematode parasite (Paterson et al. 1998), and a large survey study on malaria in humans found that MHC heterozygotes had a disadvantage (Hill et al. 1991). Despite numerous experiments in the laboratory with mice and chickens, which used a wide range of infectious agents, MHC heterozygotes do not show any general resistance compared with homozygotes (reviewed in Apanius et al. 1997).

There are several reasons why the MHC-heterozygote advantage hypothesis has not been adequately tested. First, the protective effect of MHC heterozygosity may only occur when individuals are infected with multiple parasites (strains or species) as occur in the wild (Apanius et al. 1997). Hughes and Nei (1992) suggest that MHC heterozygotes are protected against multiple parasites because they recognize a wider array of antigens than homozygotes. However, if this argument were correct, then MHC heterozygotes should also be resistant to single parasites. A stronger reason to expect that MHC heterozygotes are protected against multiple infections is that MHC alleles conferring resistance to one parasite increase susceptibility to others (Apanius et al. 1997). Contrary to Hughes and Nei (1992), such trade-offs in resistance are common among MHC alleles (Apanius et al. 1997; table 3). Thus, if resistance to infection is generally dominant or semidominant to susceptibility, then MHC heterozygotes should have an advantage over homozygotes (fig. 3). A recent survey of humans in West Africa found that individuals heterozygous at a class II MHC locus are resistant to hepatitis B (Thrusz et al. 1997). The authors attributed this effect to the polymorphism of the hepatitis virus; however, experimental tests are still needed to test the multiple infection hypothesis.

Second, MHC heterozygotes may be protected against rapidly evolving parasites, such as HIV, that evade the immune system by diverging into multiple strains within individual hosts. Since MHC heterozygotes can potentially recognize a given parasite in more ways than homozygotes, successful evasion of immune recognition may be more difficult. This hypothesis is supported by the observation that viral escape variants emerged more easily in MHC homozygous compared with heterozygous mice (Weidt et al. 1995).

Third, MHC-heterozygote advantage may have been overlooked if functional MHC homozygotes have been misclassified as heterozygotes. Most human MHC alleles belong to only a few supertypes based on similarities in their peptide-binding properties (Sidney et al. 1996). If MHC-heterozygote advantage only occurs when individuals are heterozygous for MHC functional supertypes, then classifying individuals as "heterozygotes" based on allelic differences may fail to detect a true heterozygote advantage. Some evidence suggests that the allelic distribution of MHC supertypes is more uniform than allelic differences indicating that selection is operating on supertypes. This suggests that some other form of selection is operating on MHC subtypes besides their ability to bind to foreign antigens. Thus, the discovery of MHC supertypes may have important implications for understanding how MHC genes influence odor and mating preferences (Penn and Potts 1998*a*).

Fourth, MHC-heterozygote advantage may be overlooked if the benefit of heterozygosity lies in reduced immunopathology rather then increased immune respon-

Table 3: MHC alleles show disease resistance trade-offs

	Effect of host MHC on different infectious agents	
Mouse MHC haplotype	Resistant	Susceptible
k	*Taenia, Giardia*	*Trichurus*, MAIDS, Theiler's virus
d	MAIDS, Theiler's virus, *Plasmodium, Giardia*	*Taenia*
b	Theiler's virus, Ectromelia, *Taenia, Trichurus, Heterakis*	*Heterakis polygyrus*, *Giardia*, *Plasmodium*
q	*H. polygyrus*	Theiler's virus, MAIDS

Note: References in Apanius et al. 1997. MAIDS = Murine acquired immune deficiency syndrome.

siveness (Carter et al. 1992). Immune responses can be too strong as well as too weak; however, experimental studies have generally ignored immunopathology even though it is probably the most important cost of immunological defenses (Wakelin 1997; Gemmill and Read 1998; Penn and Potts 1998*d*). One problem with this "optimal immunity" hypothesis is that experimental evidence from mice indicates that MHC heterozygotes respond more aggressively to infection and consequently suffer more immunopathology than homozygotes (Doherty and Zinkernagel 1975).

Fifth, MHC-heterozygote advantage may be overlooked if the optimal number of MHC molecules expressed in an individual's immune system is less than complete heterozygosity. Individuals with more heterozygous MHC loci present more antigens to the immune system; however, they probably have smaller T-cell repertoires (because of thymic selection), that is, there is a pleiotropic trade-off between maximizing the number of different antigens presented by MHC and the number recognized by T-cells (fig. 4). The finding that tetraploid *Xenopus* frogs have silenced half of their MHC genes (Du Pasquier et al. 1989) suggests that there is a cost to having too many MHC genes expressed. This optimal MHC-heterozygosity hypothesis is consistent with evidence that MHC heterozygotes sometimes have an advantage but other times have no advantage or a disadvantage (Apanius et al. 1997). If there is an optimal level of MHC heterozygosity for combating infections, then females should prefer to mate with males having intermediate levels of MHC dissimilarity. Such a mating preference would not necessarily require a complicated olfactory recognition mechanism; degrees of MHC disparity might be detected by quantitative differences in odor (Singer et al. 1997).

If MHC heterozygosity per se offers no immunological benefits, then there is still a way that MHC-disassortative mating preferences may increase the resistance of an individual's progeny to parasites. This mechanism has not been previously described; therefore, we develop the hypothesis in the next section.

The Red Queen Hypothesis

Another way that parasites can maintain MHC diversity is through a frequency-dependent, coevolutionary arms race between hosts and parasites. If MHC alleles have different susceptibilities to a particular parasite, then the most resistant allele will be favored and spread through the population (Hill et al. 1991, 1992*a*, 1992*b*). However, a resistant MHC allele will not necessarily go to fixation because, when the resistant allele becomes common, this increases selection on parasites to evade recognition by this common allele. Any parasite that escapes recognition will spread and impose selection against the common host MHC allele. This coevolutionary arms race is suspected to create cycles of frequency-dependent selection that maintain MHC polymorphisms indefinitely (Clarke and Kirby 1966; Slade and McCallum 1992).

We suggest that, if MHC diversity is maintained by rapidly evolving parasites, then MHC-disassortative mating preferences will provide a moving target to parasites that evade immune recognition (the moving target or Red Queen hypothesis) (table 2). The most important parasites driving MHC diversity are suspected to be vertically transmitted (Klein and O'Huigin 1994). As parasites adapt to their host's MHC genotype, then MHC-disassortative mating preferences will enable hosts to render parasite adaptations obsolete in their progeny. The MHC-disassortative mating preferences may function to produce progeny that are MHC dissimilar from their parents rather than heterozygous per se. This hypothesis is a corollary of both the Red Queen hypothesis of sexual reproduction, which suggests that sex provides a moving target against rapidly evolving parasites (Hamilton et al. 1990; Ridley 1993; Ebert and Hamilton 1996), and the Hamilton-Zuk hypothesis, which suggests that mating preferences can

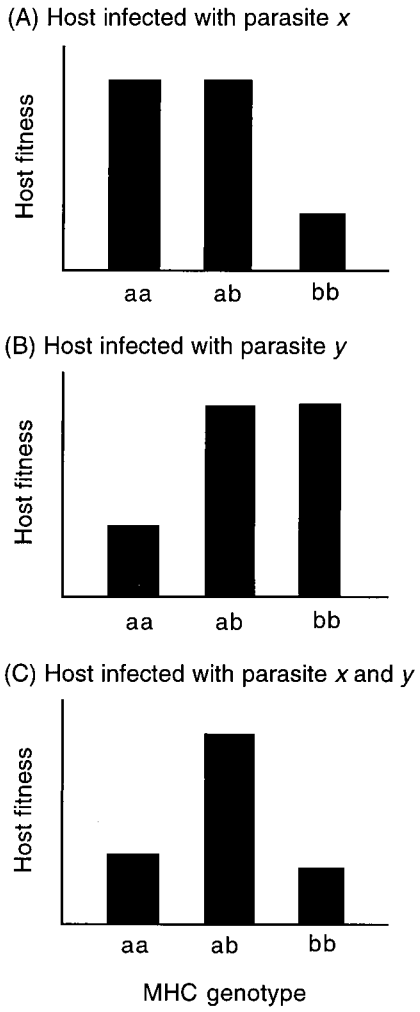

Figure 3: MHC heterozygosity may confer resistance to multiple infections, even if there is no advantage to any single pathogen or parasite species. *A*, If the *a* allele is resistant to parasite *x* and (*B*) the *b* allele is resistant to parasite *y*, then (*C*) *ab* individuals will be resistant to both *x* and *y* parasites (if resistance is dominant to susceptibility). Since each MHC allele confers resistance to some but susceptibility to other parasites, MHC heterozygotes should have an advantage to multiple parasites (from Apanius et al. 1997).

further enhance the resistance of an individual's progeny to parasites (Hamilton and Zuk 1982). Next we show that there are two ways that MHC-dependent mating preferences can create a moving target against parasites by altering the antigens presented by MHC molecules and shifting the T-cell repertoire.

Shifting MHC Presentation Holes

The MHC-disassortative matings will produce progeny that can present a different set of antigens than their parent's and should therefore recognize parasites that have evaded their parent's MHC presentation (fig. 5). MHC molecules bind to small peptides (nine to 20 amino acids in length) at only two to three critical amino-acid anchor positions; therefore, substitutions at these positions should enable parasites to evade presentation (Koup 1994; Potts and Slev 1995). For example, a strain of Epstein-Barr virus that infects people in New Guinea has an amino acid substitution that prevents presentation of peptides normally recognized by a class I allele (De Campos et al. 1993). This particular MHC allele is uncommon except in New Guinea, suggesting that the common allele has favored the viral escape variant.

Shifting T-Cell Recognition Holes

Another way that parasites can evade MHC-dependent immunity is by escaping T-cell recognition. Since the MHC shapes an individual's T-cell repertoire during thymic selection (Schaffer et al. 1989; Vukusic et al. 1995), MHC-dependent mating preferences will alter the T-cell repertoire of an individual's progeny and their ability to recognize foreign antigens. Parasites can evade T-cell recognition through several mechanisms: by single amino-acid substitutions in antigens recognized by T-cells (Pircher et al. 1990; Lewicki et al. 1995; Moskophidis and Zinkernagel 1995; Price et al. 1997), by punching a "hole" in their host's T-cell repertoire by inactivating antigen-specific T-cell clones ("anergy"; Bertoletti et al. 1994; Kle-

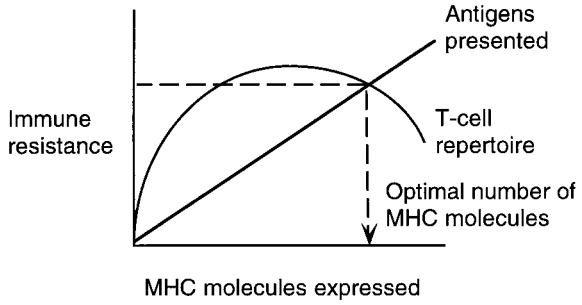

Figure 4: Increasing the number of MHC molecules expressed during ontogeny will initially increase immunological resistance by increasing both the diversity of antigens presented and increasing the number of T-cells preserved during thymic selection (Takahata 1995). However, at some point, increasing the number of MHC molecules expressed should cause a net loss of T-cells as negative thymic selection exceeds positive selection (Lawlor et al. 1990). This trade-off between increasing antigens presented and T-cell depletion is thought to maintain multiple MHC loci and prevent the further duplication of MHC loci. It also suggests that selection might favor individuals with an optimal number of loci and an optimal level of MHC heterozygosity (Nowak et al. 1992; De Boar and Perelson 1993; Percus et al. 1993).

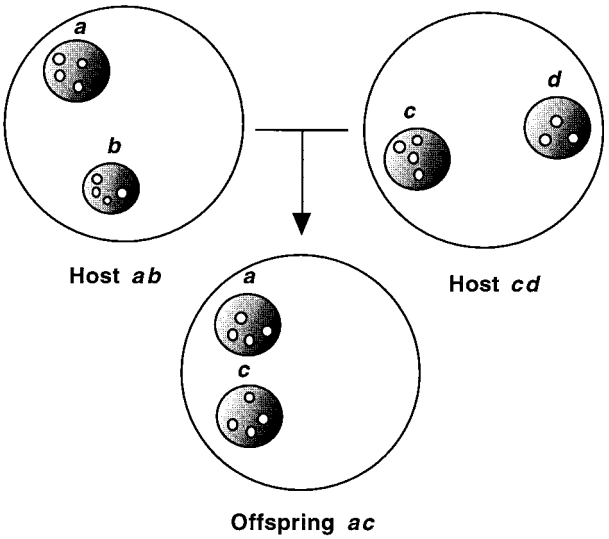

Figure 5: Shifting MHC-presentation holes. Individual hosts present only a small fraction of all of the possible peptides of the antigenic universe (represented by small dark spaces within the larger open circles). Among the peptides presented by any MHC allele, some are unrecognized by T-cells because of self-tolerance holes in the T-cell repertoire (represented by small open circles within the dark circles). We suggest that MHC-disassortative mating preferences will provide a moving target to rapidly evolving parasites that evade presentation by MHC molecules. Such parasite adaptations will be diminished in offspring with disparate MHC genotypes from their parent's because novel MHC molecules allow offspring to recognize parasites in new ways.

nerman et al. 1994), and by resembling host antigens (molecular mimicry) parasites take advantage of the holes in their host's T-cell repertoire (Hall 1994). Molecular mimicry creates a particularly important challenge to the immune system if cross-reactivity triggers autoimmunity (Baum et al. 1996; Benoist and Mathis 1998)—the disease most commonly associated with the MHC in humans (Tiwari and Terasaki 1985). Common MHC alleles will tend to accumulate an autoimmune load as a result of molecular mimicry, and this autoimmune load may create negative frequency-dependent selection on MHC genes (Apanius et al. 1997). Thus, MHC-disassortative mating preferences will alter the T-cell repertoire of an individual's progeny, potentially enhancing their resistance to parasites and decreasing their risk of autoimmunity (fig. 6).

The moving target hypothesis assumes that parasites are able to adapt to their host's MHC genotypes and that MHC-disassortative mating preferences will alter the immune system of an individual's progeny. These assumptions could be tested using a serial passage experiment (Ebert 1998). The hypothesis predicts that MHC-disassortative mating preferences will slow the rate at which parasites adapt to host MHC genotypes. This prediction could be tested by comparing the virulence of these passaged viruses to viruses passaged through mice in which different MHC-congenic strains of mice are infected at each passage, thereby altering MHC but holding background genes constant. If MHC-disassortative mating provides a moving target, then altering MHC at each generation should retard the rate of viral adaptation to a host's MHC.

Thus, parasite-mediated selection on MHC genes, both heterozygote advantage and frequency-dependent selection, would favor the evolution of MHC-dependent mating preferences. If parasites maintain the diversity of MHC genes, through either heterozygote or rare-allele advantage, then MHC-disassortative mating preferences can function to create heterozygous progeny or to provide a moving target against rapidly evolving parasites.

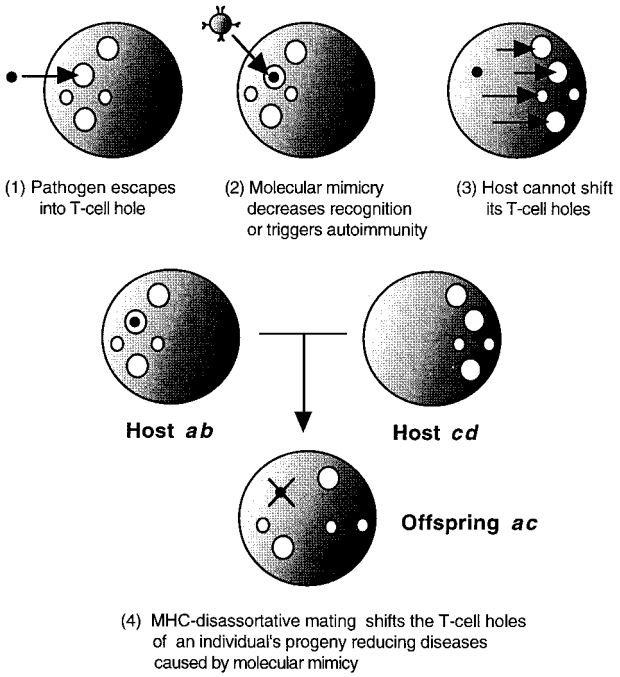

Figure 6: Shifting T-cell holes. Immunological self-tolerance requires that individuals delete 99% of their T-cells, effectively creating "holes" in their T-cell repertoire. *1*, Parasites that resemble host antigens can escape into these T-cell holes (molecular mimicry). *2*, Infections by molecular mimics trigger autoimmunity as a result of cross-reactivity. *3*, Hosts could recognize molecular mimics without incurring autoimmunity if they generated a new T-cell repertoire, but this is impossible without undergoing thymic selection with a dissimilar MHC allele or self-antigens. *4*, Hosts can generate a dissimilar T-cell repertoire in their progeny through MHC-disassortative mating preferences in two ways: by positively selecting a new T-cell repertoire and by acquiring new self-antigens (outbreeding) to present to T-cells during thymic selection.

Why Are Other Immunological Genes Not as Polymorphic as the MHC?

If parasites maintain MHC diversity, then why are other genes that influence disease resistance not as polymorphic as the MHC? The MHC is widely cited as an example of genetic diversity driven by parasites, yet the largest survey on MHC and disease resistance found evidence for directional selection (Hill et al. 1991), which reduces genetic diversity. There are several possible reasons for this inconsistency. First, disease resistance genes are generally polymorphic, but the variation is hidden and will require molecular techniques to uncover. This explanation seems unlikely because most major immune system genes, such as T-cell receptor and immunoglobulin genes, are not particularly polymorphic (Kurth et al. 1993). Second, MHC genes are unusually polymorphic because their role in the immune system is qualitatively different from other genes. If this is so, then why are transporters associated with antigen processing (TAP) genes, which have similar functions to the MHC, relatively monomorphic (Pearce et al. 1993)? The TAP genes are located within the MHC region, and like MHC molecules, they control antigen presentation (Powis et al. 1996)—therefore, parasite evasion should provide a similar selective force on TAP and MHC genes. Last, MHC genes are polymorphic because they also influence odor and disassortative mating preferences. If MHC diversity is driven primarily by sexual selection, then what is the function of MHC-dependent mating preferences?

The Inbreeding Avoidance Hypothesis

Because MHC genes are highly polymorphic, individuals sharing MHC alleles are likely to be related. Therefore, MHC-dependent mating preferences may function to avoid kin matings and deleterious consequences of inbreeding (table 2; Brown 1983; Uyenoyama 1988; Potts and Wakeland 1993). Inbreeding is deleterious because it increases overall genetic homozygosity, which increases the expression of recessive deleterious mutations and destroys any heterozygote advantages (Allendorf and Leary 1986; Charlesworth and Charlesworth 1987; Thornhill 1993).

The inbreeding avoidance hypothesis predicts that MHC-dependent mating preferences will be favored among species at risk of inbreeding. House mice live in stable social groups, and genetic differentiation has been found in several populations, which indicates that dispersal is low enough to create a potential inbreeding risk (Selander 1970; Lidicker and Patton 1987; Dallas et al. 1995). Inbreeding is detrimental for house mice in laboratory conditions (Lynch 1977; Connor and Bellucci 1979) and is probably worse under the stressful conditions of the wild (Pusey and Wolf 1996). The hypothesis that inbreeding is selected against in wild populations is supported by evidence that mice have inbreeding avoidance mechanisms (Hayashi and Kimura 1983; Winn and Vestal 1986; Krackow and Matuschak 1991). Humans also have incest avoidance mechanisms (Wolf 1995) to reduce the negative fitness consequences of inbreeding (Morton 1961, 1978; Bittles and Neel 1994). More species must be tested for MHC-dependent mating preferences to determine if this behavior is more likely to occur in species at risk of inbreeding.

The MHC-dependent mating preferences may function to increase the resistance of an individual's progeny to parasites and to avoid inbreeding, but which is potentially more important? To address this question, Potts and his colleagues (1994) measured several fitness components of mice living in seminatural enclosures. They found no detectable fitness decline associated with MHC homozygosity, yet there was a demonstrable fitness decline associated with inbreeding. This study suggests that inbreeding avoidance is a more substantial benefit to mating preferences than simply producing MHC-homozygous offspring. This study may not have been a stringent test of the MHC-heterozygote advantage hypothesis, however, since the parasite loads in these seminatural enclosures were probably not as high or as diverse as in wild populations. The problem is that increasing parasite loads is expected to reveal an MHC-heterozygote advantage and increase the fitness costs of inbreeding (Allendorf and Leary 1986; O'Brien and Evermann 1988).

The hypothesis that MHC genes play a role in inbreeding avoidance is consistent with several lines of evidence that MHC genes play a role in kin recognition for purposes other than mate choice (reviewed in Brown and Eklund 1994). First, female house mice often rear their young cooperatively in communal nests, and they prefer to nest with sisters or MHC-similar individuals (Manning et al. 1992*b*). This suggests that mice use MHC similarity to recognize sisters for cooperatively rearing offspring. Second, female mice preferentially retrieve pups with the same MHC as their own offspring, and pups are attracted to adult females and other pups with MHC-similar odors (Yamazaki et al. 1996). Finally, juvenile Arctic charr (*Salvelinus alpinus*) grow faster when reared with their siblings, and these fish can discriminate the odors of their siblings from other individuals even when they have been reared separately since fertilization. Recent work indicates that Arctic charr can discriminate the odors of MHC-similar and dissimilar siblings, and they prefer the odor of MHC-similar siblings (Olsén et al. 1998). Taken together, these studies imply that MHC genes are used to discriminate kin from nonkin for nepotistic reasons as well as for avoiding inbreeding.

House mice recognize their kin by learning individuals with which they are reared, but they are also able to discriminate kin from nonkin among unfamiliar individuals (Winn and Vestal 1986; König 1994). Such genetic kin recognition requires that individuals have a referent, either themselves (self-inspection) or close kin (familial imprinting), with which to compare individuals (Lacy and Sherman 1983). The MHC-dependent mating preferences are often cited as an example of self-inspection (which is empirically indistinguishable from so-called recognition alleles, or green beard genes; Getz 1981). Although self-inspection has not been completely ruled out, much evidence indicates that mice use familial imprinting (Beauchamp et al. 1988; Yamazaki et al. 1988; Eklund 1997*a*; Penn and Potts 1998*c*). It is unclear why mice use familial imprinting, but this may allow individuals to avoid mating with close kin carrying dissimilar as well as similar MHC haplotypes (Penn and Potts 1998*c*; fig. 7). Another possibility is that familial imprinting may allow individuals to confer resistance to their progeny against parasites that have adapted to their close kin (i.e., the moving target hypothesis; Tooby 1982).

The only other genes known to have comparable polymorphisms to the MHC are the self-incompatibility (SI) alleles that have evolved in some flowering plants to avoid inbreeding (Haring et al. 1990; Hiscock et al. 1996; Richman and Kohn 1996). When a pollen grain attempts to fertilize a female's ovules, females selectively inhibit fertilization or abort the young of pollen carrying similar SI alleles. Self-incompatibility is controlled by two different mechanisms: compatibility requires matching between the genotype of the female and the haploid genotype of the male's pollen (gametophytic incompatibility) or, in other species, matching between the genotype of the female and the diploid genotype of pollen's parent (sporophytic incompatibility; Matton et al. 1994). The MHC and SI genes share many similarities, such as a high number of alleles, high sequence divergence among alleles, and ancient allelic lineages (Potts and Wakeland 1993). Thus, the inbreeding avoidance hypothesis is consistent with comparative evidence that plants use highly polymorphic loci to reduce inbreeding.

If MHC-dependent mating preferences function to avoid inbreeding, then how can we explain the origins of MHC diversity? MHC loci provide useful kin-recognition markers only if they are polymorphic. One possibility is that parasites provided the initial selective pressure that diversified MHC genes that were then coopted for recognizing kin (Potts and Wakland 1993). Similarly, self-incompatibility systems in plants are suspected to have been modified from pathogen defenses (Dickinson 1994). Another possibility is that MHC diversity originated as a genetic incompatibility system and was then coopted for immune recognition. Lewis Thomas (1975) suggested that MHC loci and vertebrate immunological self/nonself recognition evolved from invertebrate kin-recognition systems. Histocompatibility loci are used by a wide diversity of colonial marine invertebrates to control fusion of colonies (allorecognition). In the colonial tunicate *Botryllus,* kin recognition and fertilization of gametes is controlled by a highly polymorphic histocompatibility locus (reviewed in Brown and Eklund 1994). However, it is unclear if the histocompatibility loci of *Botryllus* or other marine invertebrates are homologous to MHC genes.

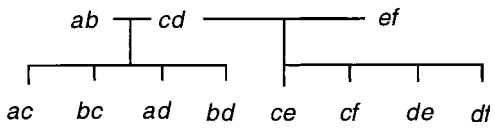

Figure 7: The MHC genotypes of closely related mice can illustrate the potential benefits of familial imprinting as a mechanism to reduce the risk of inbreeding. Individuals in the wild are usually heterozygous for the MHC because MHC genes are so polymorphic. This means that self-inspection alone will be an ineffective mechanism for reducing inbreeding. For example, if individual *ac* uses self-inspection, she will risk mating with one-fourth of her siblings (*bd*) and one-half of her half siblings (*de, df*; Potts and Wakeland 1993). In contrast, individuals using familial imprinting can avoid mating with MHC-similar and dissimilar kin. For example, if individual *ac* uses familial imprinting, she can effectively avoid mating with all full siblings (*bc, ad, bd*), all half siblings (*ce, cf, de, df*), and half of all cousins. And since house mice are often reared in communal nests containing aunts (Wilkinson and Baker 1988), familial imprinting may enable mice to avoid matings with most of their first cousins.

Abortional Selection: Cryptic Female Choice?

The MHC genes may also play a role in postcopulatory mate choice in which females selectively abort the sperm or offspring of certain males (cryptic mate choice; Eberhard and Cordero 1995), such as when they are genetically incompatible (Jennions 1997; Birkhead 1998). Many studies on humans and rodents indicate that females tend to "spontaneously" abort MHC-similar pregnancies (reviewed in Ober 1992; Apanius et al. 1997; Rülicke et al. 1998). Moreover, in vitro fertilizations are more likely to fail when couples share MHC alleles (Ho et al. 1994). These findings are paradoxical from a mechanistic perspective because similarity between maternal and fetal antigens should decrease rather than increase the risk of fetal rejection (Medawar 1953). Since MHC sharing appears to play a role in infertility problems, physicians have been using immunotherapy to treat recurrent spontaneous abortion (although its efficacy is questionable; Apanius et al. 1997).

Why would females abort MHC-similar sperm or fetuses? The MHC-mediated abortion may be a "back-up" postcopulatory mate-choice mechanism to reduce inbreeding or to produce MHC-heterozygous offspring (Wedekind 1994). Alternatively, abortional selection may not be due to classical MHC genes but rather to defective genes at closely linked loci that control development (inbreeding depression; Jin et al. 1995; but see Apanius et al. 1997). If the abortions are due to lethal genes, then this would provide an advantage to MHC-dependent mating preferences to reduce such deleterious effects from inbreeding.

The MHC-dependent abortional selection is generally assumed to be controlled by interactions between maternal and fetal (or sperm) antigens; however, abortion may be triggered by odor cues, that is, women have more difficulty maintaining pregnancy when they are exposed to the odor of their MHC-similar mates. There is evidence that the MHC plays a role in odor-mediated pregnancy block (Bruce effect): female mice are more likely to block pregnancy if the stud male and the introduced male are MHC dissimilar than when they are genetically identical (Yamazaki et al. 1986). However, no one has tested whether MHC-similar males are more likely to trigger pregnancy block than males who are MHC dissimilar to females. An odor-triggered mechanism predicts that in vitro fertilizations will be unaffected by the male donor's MHC among artificially fertilized women when they are single. Moreover, it suggests that aroma therapy will be more effective at treating pregnancy block than immunotherapy.

Not all studies indicate that MHC sharing between couples results in abortional selection, and the variation among studies remains the central problem (reviewed in Ober 1992). Initial experiments with rodents indicated that MHC-similar pregnancies were at risk of being aborted, but later studies failed to find such an effect. One possible reason for the disparate results is that MHC-dependent abortional mechanisms may depend on a female's infectious status. Wedekind and his colleagues (1996) observed that the proportion of MHC-heterozygous progeny produced by female mice increased during an epidemic in the colony. A subsequent experiment found that virally infected females produced more MHC-heterozygous embryos than noninfected controls (Rülicke et al. 1998). However, the excess MHC heterozygotes were not significantly greater than Mendelian expectations. The results were significant only because the sham-infected controls for some unexplained reason produced fewer than expected MHC heterozygotes (the increased heterozygosity of the progeny from infected mice was not significant compared with random expectations; C. Wedekind, personal communication). Still, these data are intriguing because they suggest that the inconsistent results among abortional studies may be due to variation in the infection status of females.

Conclusions

The extreme diversity of MHC genes is generally thought to be driven by parasite-mediated selection, but mating preferences may also play a role in some species (fig. 8). We have shown that there is much evidence for MHC-dependent mating preferences in house mice and mixed evidence in humans (table 1). Feral sheep do not appear to have strong MHC-dependent mating preferences (Paterson and Pemberton 1997), yet weak selection from mating preferences may still play a role in maintaining MHC diversity. Edwards and Hedrick (1998) complain about the "inconsistent results" of studies on MHC-dependent mating preferences and, therefore, favor the hypothesis that parasites alone drive MHC diversity. However, they fail to point out that studies on parasite-mediated selection on MHC diversity also give inconsistent results (Apanius et al. 1997).

The MHC-dependent mating preferences may not be a general pattern for vertebrates (just as self-incompatibility is not universal among angiosperms), but to account for any variation among taxa, we must determine the adaptive significance of this mating behavior. The MHC-dependent mating preferences may enhance the immunity of an individual's progeny, depending on how parasites impose selection on MHC alleles. We have shown that, if parasites drive MHC diversity, through either heterozygote or rare-

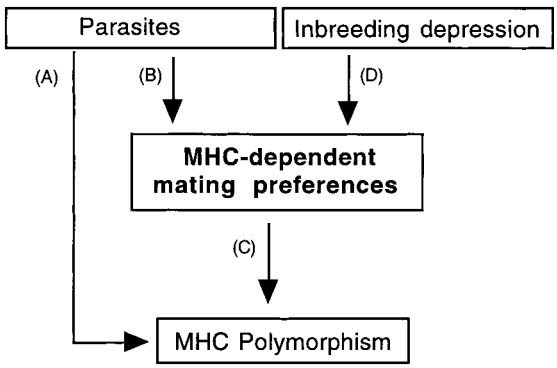

Figure 8: The potential selective factors that favor MHC-dependent mating preferences and MHC polymorphisms. *A* = selection from parasites can maintain MHC diversity through heterozygote and rare-allele advantage. *B* = if parasites drive MHC diversity, through either mechanism, then MHC-disassortative mating preferences will also be selectively favored. *C* = MHC-disassortative mating preferences will further drive MHC diversity. *D* = inbreeding can have severe consequences, and MHC-disassortative mating preferences will reduce inbreeding.

allele advantage, then selection will also favor MHC-dependent mating preferences. The MHC-dependent mating preferences may also function to avoid inbreeding, especially among species at risk of inbreeding. In either case, MHC-dependent mating preferences would represent an example of "good genes" sexual selection.

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