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Sensory neurons with MHC-like peptide binding properties: disease consequences

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The recent discovery of specialized sensory neurons that bind peptides in an MHC-like fashion has revealed the long-sought odorants used to recognize the MHC genotype and phenotype of other individuals. The odorants are the same MHC peptides used during immune recognition, which provides the molecular logic linking selection acting on MHC-mediated behaviors with selection acting on immune recognition; both processes influence the evolving peptide binding properties of MHC molecules. The primary function of these chemosensory mechanisms for detecting MHC-mediated odors appears to be mating preferences (observed in humans and many vertebrates) that preferentially produce offspring more resistant to both infectious and genetic disease. Recent experiments are beginning to discriminate the relative importance of these different disease-reducing mechanisms.

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Introduction

MHC-mediated mating preferences were discovered 30 years ago in mice [1]. Since then, experiments have demonstrated that MHC-associated odors can be detected by mice, rats, salmon, sticklebacks and humans. MHC-mediated mating preferences have also been documented in 11 additional species (including humans), spanning most vertebrate taxa (mammals, birds, fish and reptiles). In addition, it is known that mating preferences can be reversed by cross-fostering, which makes familial imprinting the behavioral counterpart to thymic education (see glossary). A variety of other MHC-influenced behaviors have been documented, including kin recognition during cooperative behavior and pregnancy block induced after male territory takeovers (Bruce effect) [2•]. These data suggest that MHC-mediated mating preferences (and related behaviors) are a general trait found in vertebrates [3•], despite the failure to find such behavior in a few studies [2•].

The apparent function of MHC-mediated mating preferences is to reduce disease in progeny by preferentially producing pathogen-resistant MHC genotypes and/or by using the MHC as a marker of relatedness to avoid inbreeding. This is a remarkable biological story about immune recognition genes that also influence complex behaviors in order to reduce disease in progeny; why then is this story often missing in immunology textbooks? One reason is that the mechanism of how individuals detect the MHC genotype in themselves and in others had remained elusive. However, the recent demonstration that MHC peptides (see glossary) are the neuron-activating chemosignals has removed a major barrier to linking MHC genes with their associated behaviors.

In this article, we review the experiments that led to the discovery of these sensory neurons, our current mechanistic understanding of how the MHC genotype and phenotype of an individual is detected by the olfactory system, and how these mechanisms function to reduce disease in progeny through MHC-mediated mating preferences.

Specialized sensory neurons bind peptides in an MHC-like fashion

Vomeronasal organ detection of peptides

The seminal discovery of sensory neurons that detect MHC-presented peptides was made in the vomeronasal organ (VNO; see glossary) [4]. In contrast to the main olfactory epithelium (MOE; see glossary), the VNO specializes in detecting small molecules and proteins (e.g. pheromones) that provide information about the sexual and social status of conspecifics. Stimulation of vomeronasal sensory neurons (VSNs) often initiates a behavioral or endocrine response.

Leinders-Zufall *et al.* [4] tested the hypothesis that dissociated MHC class I peptides (rather than MHC–peptide complexes, MHC molecules or their volatile metabolites) could be detected in the VNO. They synthesized two peptides known to be presented by either the H-2D^b haplotype (AAPDNRETF) or the H-2K^d haplotype (SYFPEITHI). (The peptide anchor residues are underlined.) Extracellular field potential recordings and fluorescence imaging revealed that peptides activated V2R-positive neurons in the basal zone of the VNO. VSNs responded in an MHC allele-specific

Glossary

Cross-fostering: A breeding design in which offspring are removed from their family at birth and are raised with a surrogate (foster) family.

Familial imprinting: This is sometimes called sexual imprinting. It is the process by which offspring imprint on phenotypic traits of their parents in order to inform behavioral decisions (such as mate choice) later in life.

Heterozygote advantage: A population genetics term to describe a heterozygote genotype that has a fitness advantage over the two corresponding homozygous genotypes at the same locus.

Main olfactory epithelium (MOE): Specialized tissue in the nasal cavity that contains olfactory sensory neurons. These neurons signal to the olfactory cortex information primarily gained from volatile odorants (but see [55]).

MHC peptides: Short (9–20 amino acid) peptides bound and displayed on the cell surface by MHC molecules for T-cell surveillance. Whereas an MHC molecule might have broad specificity in the diversity of peptides it binds, each peptide will have the same (or a limited set of) anchor residues. Thus, peptide anchor residues reflect their respective MHC genotype.

Non-synonymous substitutions: DNA mutations that change the protein sequence, in contrast to synonymous substitutions (mutations that do not change the protein sequence).

Odorants: Any molecule detected by the olfactory system.

Odortype: An individual-specific odor reflecting (in large part) the genotype of the individual.

Pathogen escape: Pathogens can escape MHC-dependent immune recognition by a variety of mechanisms, including mutations of anchor position residues that abolish MHC presentation of that peptide.

Thymic education: Elimination of T cells based on their affinity to bind MHC–peptide complexes during early development in the thymus. Positive selection removes T cells with weak affinity and negative selection removes T cells with strong affinity, which together provide self tolerance. The T-cell repertoire is thus restricted by the diversity of MHC–peptide complexes.

Vomeronasal organ: Auxiliary olfactory organ containing sensory neurons that can be differentiated from those in the MOE by their signal transduction mechanisms. VNO sensory neurons project to the accessory olfactory bulb and relay information primarily gained from non-volatile odorants (but see [55]).

manner with high sensitivity (to concentrations of 10^{-12} M). Whereas substitution of peptide anchor residues with alanine (AAPDARETA and SAFPEITHA) resulted in the failure to stimulate these neurons, substitutions at non-anchor positions (SYIPSAEKI) generally stimulated the same neurons (Figure 1).

These results point to the structural importance of peptide anchor residues in binding V2R receptors and, given the similar binding properties of MHC molecules, reveal the convergent ligand-binding properties of these unrelated molecules. More importantly, because peptides are 'molds' of the antigen-binding site of MHC molecules, sensory receptors that detect peptides in an MHC-like fashion could, in effect, be an MHC genotyping system [5•] (Figure 1).

Main olfactory epithelium detection of peptides

Leinders-Zufall and co-workers [6••] applied the same hypotheses to the MOE sensory neurons, traditionally viewed as generalist receptors of volatile chemosignals. Surprisingly, they found that non-volatile MHC peptides gain access to the MOE and, like in the VNO, activate neurons at subnanomolar concentrations in an allele-specific fashion. There were, however, some important physiological differences in peptide detection between the two olfactory organs. First, the MOE uses a distinct transduction mechanism in the recognition of peptides [6••,7]. Second, olfactory sensory neurons detect peptides that have anchor residues substituted with alanine (AAPDARETA and SAFPEITHA), although only at higher concentrations. Third, MOE-dependent peptide recognition did not influence pregnancy block [8], but did influence odor (mating) preferences.

Taken together, these two experiments show that both the VNO and the MOE can detect class I peptides in an MHC-like fashion, but that they are associated with separate neurological, physiological and behavioral response pathways (see Update).

Experimental manipulation of peptides modifies MHC-mediated behaviors

The following studies demonstrate that MHC peptides alone are sufficient to convert the MHC odortype (see glossary) of an individual to that of a genetically dissimilar individual. These data experimentally confirm that MHC-presented peptides are odorants that control MHC-mediated behaviors (see glossary). (The following mouse experiments used class I peptides whereas the stickleback experiments used both class I and II peptides.).

Pregnancy block in mice

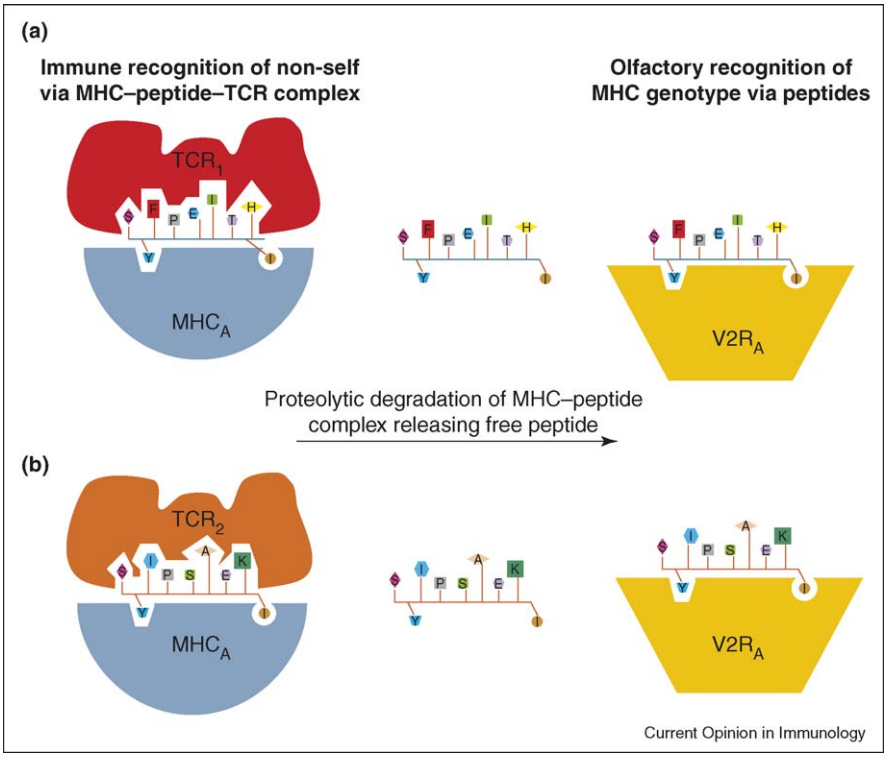
When a new male replaces the original mate of a recently mated female mouse, there is a high probability that the pregnancy will be aborted (blocked). Named after its discoverer [9], the Bruce effect works even if the original male is replaced by just the scent (e.g. urine) of a new male, and the likelihood of abortion is maximized if the new male is MHC-disparate to the original male [10].

Leinders-Zufall *et al.* [4] took advantage of this trait to show that MHC peptides could act alone as a signal of MHC genetic identity. Remarkably, addition of just three novel peptides to the stud male's urine transformed low levels of pregnancy block into high levels. In other words, a few peptides provide a strong enough signal to convert an MHC-similar signal to an MHC-dissimilar one, resulting in a profound biological act — the destruction of one's own embryos.

Odor and mating preferences

When peptides from an MHC dissimilar individual are added to odor sources that are MHC-similar to the responding individual, it increases the odor's attractiveness in mice [6••] and in sticklebacks [11••]. These results indicate that peptides are sufficient to alter odor preferences in a fashion consistent with MHC-based mating preferences.

Figure 1



Olfactory recognition of MHC genotype via MHC-presented peptides. MHC peptides involved in immune recognition can be translated into the sensory detection of MHC genotype because these peptides are also bound by the V2R receptors on VSNs. **(a)** The upper panel shows a class I peptide from the H-2K^{d} haplotype of BALB/c mice (SYFPEITHI) (anchor residues underlined) interacting with a T cell, being released as a free peptide, and binding a sensory neuron (V2R). **(b)** The bottom panel shows the same MHC molecule presenting a peptide that has altered non-anchor residues (SYIPSAEKI). This second peptide engages a different T cell, but still binds the same sensory neuron. The anchor residues of the peptide act as a surrogate marker for olfactory determination of MHC genotype because specific VNO sensory neurons and specific MHC molecules appear to express similar peptide binding properties.

It is important to note, however, that MHC-associated volatile compounds appear to also be used in mate choice [12,13], suggesting that odorants in addition to peptides might provide signals conveying MHC genotype information. Furthermore, when choosing mates females assess male traits indicative of both genetic quality and genetic compatibility [14]. This helps explain why MHC-mediated mating preferences are never observed to be absolute.

The evolution of chemosensory detection of peptides

The primordial function of MHC

It is generally assumed that MHC-mediated adaptive immunity is primordial and that other features and functions of MHC are derived. The opposite possibility that inbreeding avoidance was the primordial function of MHC, with immune recognition being a derived trait, was first suggested by Brown [15]. Boehm [16•] recently provided a mechanistic framework for this hypothesis (see also Update). Mechanisms for discriminating relatives, many of which are consistent with a peptide detection system, are pervasive across animal species and could certainly be co-opted for recognizing self versus non-self peptides in immunity. These two alternative hypotheses should be discriminated when we discover the function of MHC genes in jawless fish — the only vertebrates to not have MHC-based adaptive immunity [17•,18–20].

Coevolution of MHC and chemosensory receptor genes

More than 1% of the mammalian genome is devoted to chemosensory receptor genes [21]. What type of selection should be operating on receptors specialized for MHC-presented peptides? If these receptors have to track evolving MHC genes, then they too should show high rates of non-synonymous changes (see glossary). Interestingly, in the human–chimp genome comparisons, some of the highest rates of non-synonymous substitutions are found in chemosensory receptor genes [22], which often show high rates of evolutionary change [23–25]. Alternatively, they might form a conserved set of receptors that cover the universe of MHC-presented

peptides. Just as MHC molecules can be grouped into about 10 supermotifs per locus based on overlapping peptide repertoires [26], the number of chemosensory receptors required to cover MHC-presented peptides has been estimated to be <50 [5•].

Familial imprinting is the behavioral counterpart to thymic education

When female mice are cross-fostered on the day of their birth into a family that has a different MHC, their MHC mating preferences are reversed; they now avoid mating with males that express the foster family MHC [27,28]. This is referred to as familial imprinting. They have learned which MHC-mediated (peptide) odors belong to relatives (family) and they cooperate with strangers expressing these familial odors (such as preferring to communally nest with MHC-similar individuals [29]), but avoid mating with such individuals [3•,30]. In an analogous fashion, during thymic education the body 'learns' which T cells are self-reactive and eliminates them, which leaves a T-cell repertoire that attacks (recognizes) non-self. Thus, thymic education teaches the body to discriminate between self and non-self molecules and familial imprinting teaches the body to discriminate between kin and non-kin. The ultimate functionality is the same: cooperation among self or near-self (relatives) and defense against incursions from non-self or non-relatives, except during mating (Figure 2) [16•].

What is the functional significance of MHC-mediated mating preferences?

MHC-disassortative mating preferences could function to: first, produce MHC-heterozygous offspring; second, create a moving target against rapidly evolving pathogens; and/or third, avoid inbreeding [2•,31]. In all cases, the result is production of offspring who have reduced levels of either infectious or genetic disease (Figure 2). The evolution of MHC-disassortative mating preferences is predicted by both pathogen-driven mechanisms (first two functions) thought to diversify MHC genes, and is thus consistent with all of the conventional immunological thinking about MHC functions.

Heterozygote advantage

The idea that MHC heterozygotes have an advantage because they present a wider variety of (peptide) antigens than homozygotes, and consequently respond more effectively to a particular infection, was first proposed by Doherty and Zinkernagel (see glossary) [32]; this theory persists in the literature, despite being generally disproved [33]. For any pair of MHC resistant and susceptible alleles against any pathogen, the heterozygote is generally intermediate in resistance compared with the homozygotes, not better (Figures 3a and b). These data disprove the original hypothesis because MHC heterozygotes must be superior to both relevant homozygotes to achieve heterozygote advantage with its associated diversity-maintaining properties.

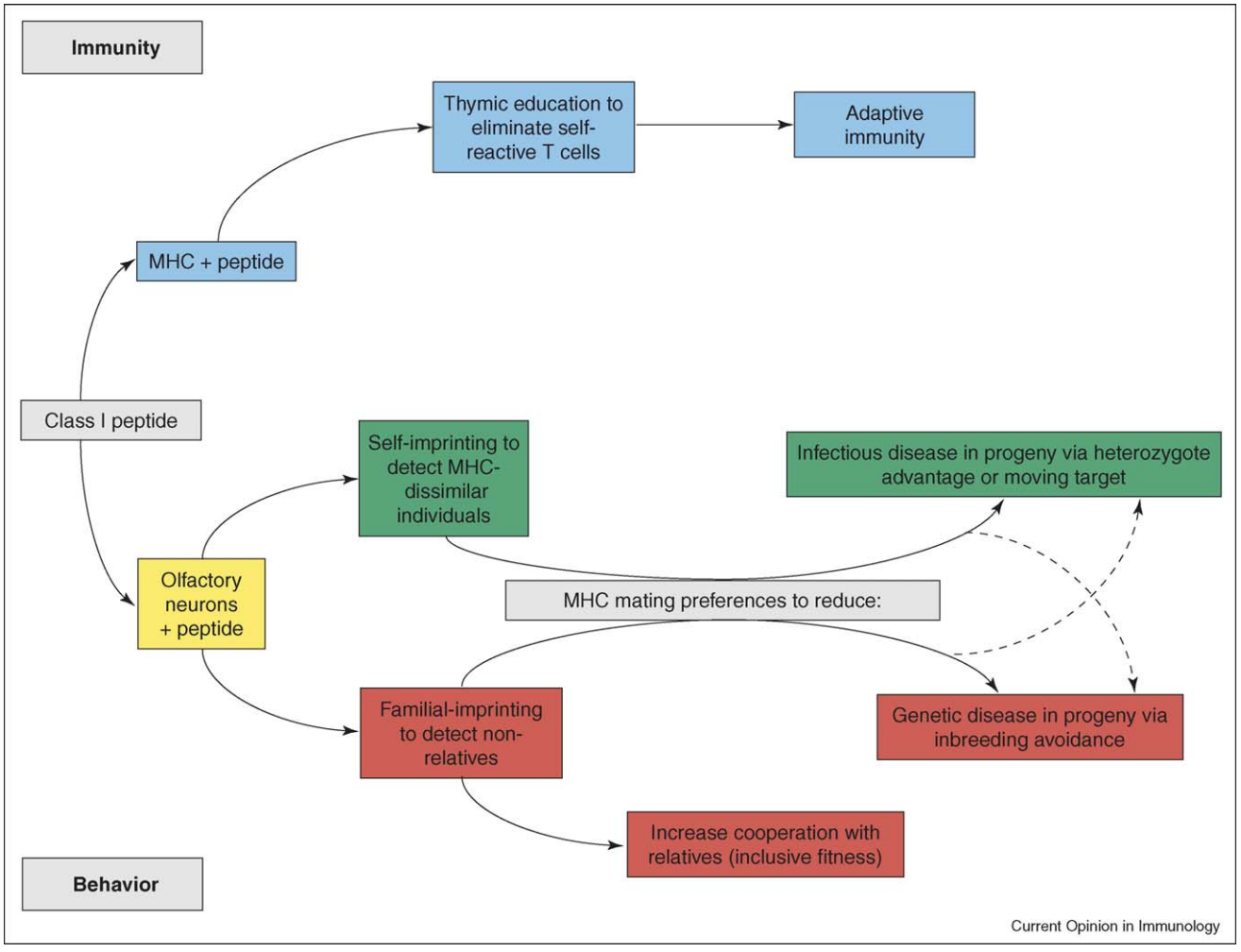
Alternatively, heterozygotes should have an advantage after multiple infections if resistance is dominant to susceptibility, which is the case for 70–80% of infectious agents [24]. Thus, heterozygotes will express resistance profiles of each homozygote, which would mask some susceptibilities. This hypothesis, illustrated in Figure 3, was tested recently by comparing co-infections with pathogens (*Salmonella* and Theiler's virus) that express opposite susceptibility profiles (Figures 3a and 3b) in MHC homozygous and heterozygous mice. The results were as predicted in Figure 3c: MHC heterozygotes were not superior to homozygotes during either single infection (infection with pathogen X or pathogen Y), but during co-infection (infections with pathogen X + Y) the combined pathogen load was significantly (41%) lower than both homozygotes. These data demonstrate the emergence of heterozygote advantage during the infection of two or more pathogens [34], providing one function for MHC-mediated mating preferences — preferential production of disease-resistant offspring (i.e. MHC heterozygous offspring).

Moving target against pathogen escape of MHC-dependent immune recognition

Pathogen escape of MHC-dependent immune recognition (see glossary) is well-established in a restricted set of chronic pathogens: HIV [35], hepatitis C [36] and human T-cell leukemia virus type 1 in humans [37], and simian immunodeficiency virus (SIV) in primates [35]. In general, the relative importance of these escape events to host fitness has been difficult to evaluate, but the effects clearly range from those that are minor to those that are more costly [35]. The technique of serial passages (or single passages of chronic pathogens) in experimental animals promises to be an important experimental tool for exploring pathogen escape of MHC-dependent immune recognition. Escape of MHC immune recognition is common in SIV and can have dramatic fitness consequences for hosts [38•]. In contrast, serial passage of the pathogenic fungus *Cryptococcus neoformans* results in dramatic increases in virulence, but MHC affects were only a minor component of the overall virulence increase [39]. (Most of the non-MHC components represented previously unknown virulence mechanisms [40], the identification of which becomes an additional benefit of this approach.)

Pathogen escape of MHC-dependent immune recognition would favor MHC-dissimilar mating preferences because this provides progeny with new ways to recognize pathogens that might have adapted to either parental genotype. Progeny become a moving target for pathogens. There is no doubt that pathogen escape operates, but its importance and pervasiveness across pathogens is

Figure 2



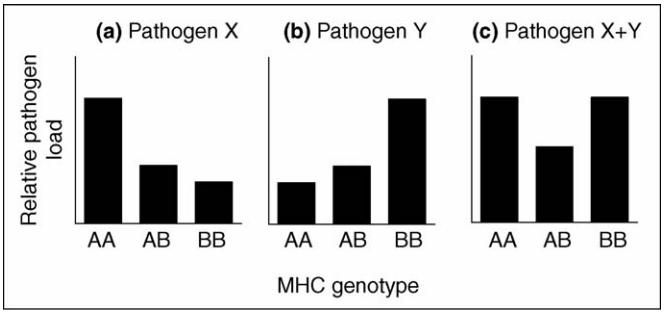
Using peptides as a common currency, familial imprinting and thymic education have been shown to have analogous functions. In the immune system (blue), self peptides bound to MHC molecules determine T-cell fate during thymic education producing the self/non-self recognition mechanism of adaptive immunity. The ultimate function is the reduction of disease. In the sensory system (yellow), the same peptides bound to olfactory neurons mediate imprinting that will determine social behavior, depending on the origin of the peptide (self, relative, etc.). Self-imprinting (green) allows for the detection of MHC-dissimilar mates to produce heterozygous offspring or to create a moving target against evolving pathogens. Familial-imprinting (red) allows for discrimination among kin and non-kin to avoid inbreeding and to increase inclusive fitness (cooperation among kin). In the only two experiments to evaluate the mechanistic basis of imprinting, familial imprinting was found rather than self imprinting [27,28]. An ultimate function of both self and familial imprinting is the reduction of disease in progeny. Dashed lines indicate less-efficient functional pathways. Notice that only the inbreeding avoidance function of MHC mating preferences predicts familial imprinting. The pathogen-driven functions are more efficient under self imprinting [28] (see text).

still unclear. An important recent development is the discovery that many escape variants suffer substantial fitness costs, as indicated by rapid reversion to wild-type [41,42] or development of compensatory mutations [43] when transmitted to a host who has a different MHC. If escape mutations were not costly then pathogens could completely escape host immune recognition until MHC alleles were driven to fixation. This possibility has been a central criticism against the importance of pathogen escape in favoring MHC diversity [44]. These new data minimize this criticism.

Inbreeding avoidance

Meagher *et al.* [45] used seminatural populations of mice to demonstrate that one generation of full sib inbreeding reduces fitness of offspring by 57%; this effect is largely expressed through males, in which fitness is reduced by 80%. These estimates are conservative because fitness measures were only taken across the first half of the lifespan of these mice (40 weeks), and by this time 90% of inbred territorial males were dead compared with 24% of outbred males. One generation of full sib mating was effectively lethal for sons, a dramatic affect that had

Figure 3



Heterozygote advantage can emerge during multiple infections, despite being absent for all single infections. MHC homozygotes are frequently susceptible to one pathogen (X) but resistant to a different pathogen (Y) (e.g. MHC AA in panels **[a]** and **[b]**), but other homozygotes can have the opposite susceptibility profile (e.g. MHC BB in panels [a] and [b]). Because resistance tends to be dominant to susceptibility, heterozygotes tend to be more like the most resistant homozygote (e.g. MHC AB in panels [a] and [b]). **(c)** Consequently, when individuals are infected with both pathogens X and Y, heterozygotes will have a lower overall pathogen load than both homozygotes. Because all hosts suffer infections from multiple pathogens, females are expected to favor MHC-dissimilar mates to produce heterozygous offspring that have increased resistance to multiple pathogens. See text for details (adapted from [34]).

been completely missed by previous studies [45,46]! We have recently demonstrated that overall fitness is reduced by 43% in offspring of first-cousin matings (WKP *et al.*, unpublished). These and other field studies suggest that levels of inbreeding expected to occur commonly in nature can affect fitness dramatically [46], thus providing an important third function for MHC-disassortative mating preferences. The only other genetic systems that have all of the unique diversity features of MHC (extreme polymorphism, relatively uniform allelic frequencies, ancient allelic lineages and high rates of non-synonymous substitutions) are plant self incompatibility loci, which function as disassortative mating preferences to avoid inbreeding [47]. These comparative data demonstrate the plausibility that MHC-based mating preferences could function to avoid inbreeding, which by itself appears sufficient to explain most of the relatively unique features of MHC diversity.

Previous inbreeding studies under laboratory conditions greatly underestimated the fitness effects found under ecological conditions [45,46]. Moreover, the true consequences of genotype, mutations, breeding strategies or any other treatment is almost always greater under the stressful and competitive conditions of nature, and often dramatically so [48,49]. Consequently, fitness effects must be measured in natural conditions if their true importance is to be ascertained.

Which disease-reducing functions are most important for favoring MHC mating preferences?

To answer this question one needs to know the fitness consequences of the three possible functions of MHC-based mating preferences. This has been done in part for inbreeding where the fitness consequences were found to be substantial [45] (see above). There are considerable problems associated with determination of the fitness consequences of the two pathogen-driven mechanisms. Both hypotheses require fitness measurements over a lifetime of infections. We do not even know all the pathogens of the two best-studied vertebrates — mice and humans. Even if we did, the experiment is intractable in the laboratory. One solution is to study naturally infected animal populations in the wild. In such studies, only 3 of 6 species showed evidence for heterozygote advantage [2•,31,50,51], but the fitness differential between heterozygotes and homozygotes was large (34%) in the single study that estimated fitness [51]. It will be difficult to obtain comparable fitness measures for the pathogen escape mechanism because it predicts that selection will be operating differently for each pathogen and in variable directions over time, dependent on the timing and significance of pathogen escape events. So, although we have obtained signatures of this type of selection [2•,31,50–52], it is difficult to imagine any way to obtain overall fitness consequences.

In summary, there is strong evidence that all three disease-reducing functions of MHC-based disassortative mating preferences operate to produce healthier progeny. Determining the relative contributions of each function will require more data and will be difficult because of the problems associated with obtaining comparable fitness measures for the pathogen escape hypothesis.

Conclusions

Histocompatibility genotype is so important to offspring fitness directly, or as a marker for other fitness-related traits (e.g. inbreeding), that complex neural and reproductive mechanisms have evolved to preferentially produce offspring genotypes that have reduced disease. The involvement of both infectious and genetic disease increases the importance and complexity of this story. The recent discovery of the neurosensory mechanisms

that explain how MHC genotype is detected in self and in others should revitalize the efforts to characterize the specific components of this complex mechanism for reducing disease.

Update

In a recent intriguing review, Boehm [53•] expands on the possibility that the primordial function of MHC peptide binding is for discriminating kin from non-kin to avoid inbreeding during mate choice (first proposed in [15] and later developed in [16•]). This ancient discrimination system is postulated to have been co-opted during the evolution of the vertebrate immune system to play a crucial role in self/non-self discrimination [53•].

Roberts *et al.* [54] demonstrate that observed MHC-based mating preferences could function to preferentially produce MHC heterozygous offspring (compatibility) or to cause an individual to prefer MHC heterozygous (healthier) mates. Discriminating between these two functions will be hindered by the fact that genetic similarity and heterozygosity are correlated parameters [54].

Spehr *et al.* [55] review the similarities and differences of how the main and accessory olfactory systems process social signals. Much of this review is based on studies focused on MHC-mediated odors. Contrary to the conventional view that these different olfactory systems largely detect different odorants, this article shows that they appear to detect overlapping sets of odorants. They conclude that the main and accessory olfactory systems should be viewed as complimentary rather than separate processes for chemical communication.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Yamazaki K, Boyse EA, Mike V, Thaler HT, Mathieson BJ, Abbott J, Boyse J, Zayas ZA: **Control of mating preferences in mice by genes in the major histocompatibility complex**. *J Exp Med* 1976, **144**:1324-1335.

2. • Piertney SB, Oliver MK: **The evolutionary ecology of the major histocompatibility complex**. *Heredity* 2006, **96**:7-21.
This review characterizes the nature of selection that acts on MHC genes, particularly as revealed by field studies.

3. • Ziegler A, Kentenich H, Uchanska-Ziegler B: **Female choice and the MHC**. *Trends Immunol* 2005, **26**:496-502.
This review explores the diverse ways females might influence MHC-associated mating patterns (especially post-copulatory mechanisms), and frames the observations into an immunological perspective.

4. Leinders-Zufall T., Brennan P., Widmayer P, S PC, Maul-Pavicic A, Jager M, Li XH, Breer H, Zufall F, Boehm T: **MHC class I peptides as chemosensory signals in the vomeronasal organ.** *Science* 2004, **306**:1033–1037.

5. • Boehm T, Zufall F: **MHC peptides and the sensory evaluation of genotype**. *Trends Neurosci* 2006, **29**:100-107.
This review characterizes the discovery of sensory neurons that bind peptide in an MHC-like fashion and integrates these findings in an immunological and neurological framework.

6. •• Spehr M, Kelliher KR, Li XH, Boehm T, Leinders-Zufall T, Zufall F: **Essential role of the main olfactory system in social recognition of major histocompatibility complex peptide ligands**. *J Neurosci* 2006, **26**:1961-1970.
This study demonstrates that peptides are detected in an MHC-like fashion in the MOE. There are many similarities to the original and seminal discovery in the VNO [4], but there are also important differences.

7. Kelliher KR, Spehr M, Li XH, Zufall F, Leinders-Zufall T: **Pheromonal recognition memory induced by TRPC2-independent vomeronasal sensing**. *Eur J Neurosci* 2006, **23**:3385-3390.

8. Kelliher KR, Spehr M, Li XH, Zufall F, Leinders-Zufall T: **Relative roles of the main and accessory olfactory systems in behavioral responses to MHC class I peptides: Bruce effect**. *Chem Senses* 2005, **30**:A18.

9. Bruce HM: **An exteroceptive block to pregnancy in the mouse**. *Nature* 1959, **184**:105.

10. Yamazaki K, Beauchamp GK, Wysocki CJ, Bard J, Thomas L, Boyse EA: **Recognition of H-2 types in relation to the blocking of pregnancy in mice**. *Science* 1983, **221**:186-188.

11. •• Milinski M, Griffiths S, Wegner KM, Reusch TB, Haas-Assenbaum A, Boehm T: **Mate choice decisions of stickleback females predictably modified by MHC peptide ligands**. *Proc Natl Acad Sci USA* 2005, **102**:4414-4418.
This study uses class I and class II peptides to manipulate stickleback odor preferences. Sticklebacks prefer MHC-disimilar mates that produce offspring that have somewhat less than maximal allelic diversity. This study utilizes this unique feature to show that peptides added to a low MHC-diversity odor source increases attractiveness, but the same peptides added to a high MHC-diversity odor source decreases attractiveness.

12. Singer AG, Beauchamp GK, Yamazaki K: **Volatile signals of the major histocompatibility complex in male mouse urine**. *Proc Natl Acad Sci USA* 1997, **94**:2210-2214.

13. Willse A, Belcher AM, Preti G, Wahl JH, Thresher M, Yang P, Yamazaki K, Beauchamp GK: **Identification of major histocompatibility complex-regulated body odorants by statistical analysis of a comparative gas chromatography/mass spectrometry experiment**. *Anal Chem* 2005, **77**:2348-2361.

14. Roberts SC, Gosling LM: **Genetic similarity and quality interact in mate choice decisions by female mice**. *Nat Genet* 2003, **35**:103-106.

15. Brown JL: **Some paradoxical goals of cells and organisms: the role of the MHC**. In *Ethical Questions in Brain and Behavior.* Edited by Pfaff DW. Springer Verlag; 1983:111-124.

16. • Boehm T: **Co-evolution of a primordial peptide-presentation system and cellular immunity**. *Nat Rev Immunol* 2006, **6**:79-84.
This review develops the intriguing hypothesis that adaptive immunity is not the primordial function of the MHC. Mechanisms to discriminate relatives (or self) from non-relatives are present throughout all living systems, including the MHC-mediated mechanisms found in vertebrates. The simplest explanation for the evolutionary development of the immune system is that this existing discrimination system was co-opted to achieve self/non-self immune discrimination. This contrasts with conventional wisdom, which assumes that the involvement of the MHC in self/non-self discrimination originated during the development of the vertebrate immune system. This review develops the unorthodox hypothesis, including plausible mechanistic scenarios.

17. • Alder MN, Rogozin IB, Iyer LM, Glazko GV, Cooper MD, Pancer Z: **Diversity and function of adaptive immune receptors in a jawless vertebrate**. *Science* 2005, **310**:1970-1973.
This study documents the unique mechanisms by which jawless fish generate a lymphocyte receptor repertoire estimated at 10^{14} using rearrangement mechanisms that are totally different from those used

by other vertebrates. This and other recent findings have spawned a group of reviews [18–20] exploring the remarkable discovery of the independent evolution of two different adaptive immune systems within the vertebrates.

18. Pancer Z, Cooper MD: **The evolution of adaptive immunity**. *Annu Rev Immunol* 2006, **24**:497-518.

19. Cooper MD, Alder MN: **The evolution of adaptive immune systems**. *Cell* 2006, **124**:815-822.

20. Litman GW, Cannon JP, Dishaw LJ: **Reconstructing immune phylogeny: new perspectives**. *Nat Rev Immunol* 2005, **5**:866-879.

21. Mombaerts P: **Genes and ligands for odorant, vomeronasal and taste receptors**. *Nat Rev Neurosci* 2004, **5**:263-278.

22. Nielsen R, Bustamante C, Clark AG, Glanowski S, Sackton TB, Hubisz MJ, Fledel-Alon A, Tanenbaum DM, Civello D, White TJ *et al.*: **A scan for positively selected genes in the genomes of humans and chimpanzees**. *PLoS Biol* 2005, **3**:e170.

23. Shi P, Bielawski JP, Yang H, Zhang YP: **Adaptive diversification of vomeronasal receptor 1 genes in rodents**. *J Mol Evol* 2005, **60**:566-576.

24. Grus WE, Shi P, Zhang YP, Zhang J: **Dramatic variation of the vomeronasal pheromone receptor gene repertoire among five orders of placental and marsupial mammals**. *Proc Natl Acad Sci USA* 2005, **102**:5767-5772.

25. Clark AG, Glanowski S, Nielsen R, Thomas PD, Kejariwal A, Todd MA, Tanenbaum DM, Civello D, Lu F, Murphy B *et al.*: **Inferring nonneutral evolution from human–chimp–mouse orthologous gene trios**. *Science* 2003, **302**:1960-1963.

26. Lund O, Nielsen M, Kesmir C, Petersen AG, Lundegaard C, Worning P, Sylvester-Hvid C, Lamberth K, Roder G, Justesen S *et al.*: **Definition of supertypes for HLA molecules using clustering of specificity matrices**. *Immunogenetics* 2004, **55**:797-810.

27. Yamazaki K, Beauchamp GK, Kupniewski J, Bard J, Thomas L, Boyse EA: **Familial imprinting determines H-2 selective mating preferences**. *Science* 1988, **240**:1331-1332.

28. Penn D, Potts W: **MHC-disassortative mating preferences reversed by cross-fostering**. *Proc Biol Sci* 1998, **265**:1299-1306.

29. Manning CJ, Wakeland EK, Potts WK: **Communal nesting patterns in mice implicate MHC genes in kin recognition**. *Nature* 1992, **360**:581-583.

30. Ihara Y, Feldman MW: **Evolution of disassortative and assortative mating preferences based on imprinting**. *Theor Popul Biol* 2003, **64**:193-200.

31. Sommer S: **The importance of immune gene variability (MHC) in evolutionary ecology and conservation**. *Front Zool* 2005, **2**:16.

32. Doherty PC, Zinkernagel RM: **Enhanced immunological surveillance in mice heterozygous at the H-2 gene complex**. *Nature* 1975, **256**:50-52.

33. Lipsitch M, Bergstrom CT, Antia R: **Effect of human leukocyte antigen heterozygosity on infectious disease outcome: the need for allele-specific measures**. *BMC Med Genet* 2003, **4**:2.

34. McClelland EE, Penn DJ, Potts WK: **Major histocompatibility complex heterozygote superiority during coinfection**. *Infect Immun* 2003, **71**:2079-2086.

35. Goulder PJ, Watkins DI: **HIV and SIV CTL escape: implications for vaccine design**. *Nat Rev Immunol* 2004, **4**:630-640.

36. Bowen DG, Walker CM: **Mutational escape from CD8$^+$ T cell immunity: HCV evolution, from chimpanzees to man**. *J Exp Med* 2005, **201**:1709-1714.

37. Furukawa Y, Tara M, Izumo S, Arimura K, Osame M: **HTLV-I viral escape and host genetic changes in the development of adult T cell leukemia**. *Int J Cancer* 2006, **118**:381-387.

38. Fernandez CS, Stratov I, De Rose R, Walsh K, Dale CJ, Smith MZ, • Agy MB, Hu SL, Krebs K, Watkins DI *et al.*: **Rapid viral escape at an immunodominant simian–human immunodeficiency virus cytotoxic T-lymphocyte epitope exacts a dramatic fitness cost**. *J Virol* 2005, **79**:5721-5731.
This study documents rapid cytotoxic T lymphocyte escape by SIV, but the equally rapid reversion in the absence of the specific cytotoxic T lymphocyte response. This suggests that the escape mutant has a significant overall advantage, despite a substantial cost.

39. McClelland EE, Adler FR, Granger DL, Potts WK: **Major histocompatibility complex controls the trajectory but not host-specific adaptation during virulence evolution of the pathogenic fungus *Cryptococcus neoformans***. *Proc Biol Sci* 2004, **271**:1557-1564.

40. McClelland EE, Perrine WT, Potts WK, Casadevall A: **Relationship of virulence factor expression to evolved virulence in mouse-passaged *Cryptococcus neoformans* lines**. *Infect Immun* 2005, **73**:7047-7050.

41. Kent SJ, Fernandez CS, Dale CJ, Davenport MP: **Reversion of immune escape HIV variants upon transmission: insights into effective viral immunity**. *Trends Microbiol* 2005, **13**:243-246.

42. Friedrich TC, Dodds EJ, Yant LJ, Vojnov L, Rudersdorf R, Cullen C, Evans DT, Desrosiers RC, Mothe BR, Sidney J *et al.*: **Reversion of CTL escape-variant immunodeficiency viruses *in vivo***. *Nat Med* 2004, **10**:275-281.

43. Friedrich TC, Frye CA, Yant LJ, O'Connor DH, Kriewaldt NA, Benson M, Vojnov L, Dodds EJ, Cullen C, Rudersdorf R *et al.*: **Extraepitopic compensatory substitutions partially restore fitness to simian immunodeficiency virus variants that escape from an immunodominant cytotoxic-T-lymphocyte response**. *J Virol* 2004, **78**:2581-2585.

44. Takahata N, Nei M: **Allelic genealogy under overdominant and frequency-dependent selection and polymorphism of major histocompatibility complex loci**. *Genetics* 1990, **124**:967-978.

45. Meagher S, Penn DJ, Potts WK: **Male–male competition magnifies inbreeding depression in wild house mice**. *Proc Natl Acad Sci USA* 2000, **97**:3324-3329.

46. Keller LF, Waller DM: **Inbreeding effects in wild populations**. *Trends Ecol Evol* 2002, **17**:230-241.

47. Charlesworth D, Vekemans X, Castric V, Glemin S: **Plant self-incompatibility systems: a molecular evolutionary perspective**. *New Phytol* 2005, **168**:61-69.

48. Frankham R: **Stress and adaptation in conservation genetics**. *J Evol Biol* 2005, **18**:750-755.

49. Carroll LS, Potts WK: **Functional genomics requires ecology.** *Adv Study Behavior* 2006, in press.

50. Bernatchez L, Landry C: **MHC studies in nonmodel vertebrates: what have we learned about natural selection in 15 years?** *J Evol Biol* 2003, **16**:363-377.

51. Sauermann U, Nurnberg P, Bercovitch FB, Berard JD, Trefilov A, Widdig A, Kessler M, Schmidtke J, Krawczak M: **Increased reproductive success of MHC class II heterozygous males among free-ranging rhesus macaques**. *Hum Genet* 2001, **108**:249-254.

52. Charbonnel N, Pemberton J: **A long-term genetic survey of an ungulate population reveals balancing selection acting on MHC through spatial and temporal fluctuations in selection**. *Heredity* 2005, **95**:377-388.

53. Boehm T: **Quality control in self/nonself discrimination**. • *Cell* 2006, **125**:845-858.
Precise discrimination between self and non-self during immune recognition is a difficult problem, which has never been, and probably never will be, completely solved. In his article, Boehm takes us back to the most difficult of times, during the invention of a somatic-generated receptor repertoire, the unpredictability of which creates many self-reactive receptors. He provides a plausible mechanistic scenario of how existing mechanisms for discriminating kin from non-kin (to promote outcrossing) were used to achieve self/non-self discrimination in immunity through the elimination of self-reactive receptors. This hypothesis predicts that the primordial function of MHC molecules was for discriminating kin from non-kin through a polymorphic peptide-carrier mechanism with sensory receptors for detecting the peptide signature, perhaps similar to the

sensory receptors present in vertebrates today [4]. This ancient discrimination system was co-opted to achieve self/non-self discrimination in a revolutionary new type of immune recognition, which we today call vertebrate adaptive immunity.

54. Roberts SC, Hale ML, Petrie M: **Correlations between heterozygosity and measures of genetic similarity: implications for understanding mate choice**. *J Evol Biol* 2006, **19**:558-569.

55. Spehr M, Spehr J, Ukhanov K, Kelliher KR, Leinders-Zufall T, Zufall F: **Parallel processing of social signals by the mammalian main and accessory olfactory systems.** *Cell Mol Life Sci* 2006*,* in press.