

# Wisdom through immunogenetics

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Genes of the Major Histocompatibility Complex (MHC) are extraordinarily diverse. MHC variants influence many important biological traits, including immune recognition, susceptibility to infectious and autoimmune diseases, individual odors, mating preferences, kin recognition, cooperation and pregnancy outcome. The MHC story now becomes even more complex with the demonstration that human females prefer odors from males carrying allelic matches to their own paternally inherited MHC genes.

In a wry comment on one of the vagaries of love and kinship, Shakespeare remarked in *The Merchant of Venice*, "It is a wise father who knows his own child". It would be an even wiser child who knows her own father. An unexpected source of such wisdom is revealed on page 175 of this issue, where Suma Jacob and colleagues<sup>1</sup> show that females can identify and prefer male body odors mediated by MHC alleles matching those inherited from their father. Many studies in humans and a variety of animals have demonstrated the ability to detect MHC-mediated odors. The major new finding of this study is the discrimination of, and preference for, paternally inherited alleles. This curious twist in an already remarkable tale is not easy to interpret, but before trying, let's set the scene.

## MHC-mediated behaviors

MHC molecules have a critical role in immune recognition. Two classes of MHC genotypes seem to have an advantage against infectious agents. First, MHC heterozygotes have an advantage because more antigenic peptides are presented to T-lymphocytes, increasing the probability of a successful immune response. For example, HIV-infected MHC heterozygotes progress to AIDS more slowly than homozygotes<sup>2</sup>. Second, rare MHC genotypes generally have an advantage in the molecular arms race with pathogens that are constantly evolving to evade host immunity (HIV, for example<sup>3</sup>). Rarity is an

advantage because most pathogen evolution will be directed against common host MHC genotypes. Both mechanisms select for MHC diversity and both also favor the evolution of mating preferences for MHC-dissimilar or heterozygous mates, as has been demonstrated in humans<sup>4</sup>, mice<sup>5,6</sup>, salmon<sup>7</sup> and sticklebacks<sup>8</sup>. These mating preferences function by preferentially producing disease-resistant progeny—MHC heterozygotes, rare MHC genotypes, and genotypes that merely change from the previous generation, creating a moving target for pathogen adaptation<sup>9</sup>.

These disassortative mating preferences would further increase MHC genetic diversity, making these loci increasingly useful as kin recognition markers. MHC-based kin recognition can function either to direct cooperation toward kin<sup>10</sup> (increasing inclusive fitness) and/or to avoid matings with kin (to avoid inbreeding<sup>6</sup>). Inbreeding has recently been shown to produce dramatic declines in vertebrate fitness<sup>11</sup>. These MHC-mediated behaviors represent the first and still the most compelling case of genes controlling complex behaviors that serve important functions (see table). Which functions evolved first and which are historically and currently most important is uncertain for any species.

## Odors and preferences

Although the actual odorants involved in MHC-mediated odors are still uncertain, there is little doubt they exist. MHC-asso-

ciated odors are detectable in several species, including rats, mice<sup>5</sup>, humans<sup>12</sup>, salmon<sup>7</sup> and sticklebacks<sup>8</sup>. Most of these studies use entire MHC haplotype differences, leaving open the possibility that linked genes might control these odors. This concern is mitigated, however, by the demonstrations that MHC single-gene differences influence odors detectable by both mice<sup>5,13</sup> and 'electronic noses'<sup>14</sup>.

To evaluate MHC-mediated odor preferences, Jacob *et al.*<sup>1</sup> asked females of an isolated community to rank odors from men outside of the community. For two days, body odors were absorbed on T-shirts worn by each of the male subjects while other confounding sources of odor were minimized. The first major finding was that odors of men most MHC-similar to each female were preferred. Although most previous studies have reported preferences for MHC dissimilarity, two studies provide a precedent for MHC-similar preferences. Human females practicing oral contraception prefer MHC-similar men<sup>12</sup>, as do mice choosing other females as communal nesting and nursing partners<sup>10</sup>. As the authors point out, the differing results from comparable human studies<sup>12,15</sup> could also be explained by the contrasting ways in which questions were phrased to female subjects. Finally, these inconsistencies in odor preferences are perhaps not too surprising given our poor understanding of olfaction, particularly when functions change depending on context and species. For example, mice prefer

Relationships among MHC-mediated behaviors, their functions, imprinting and paternity

	Functional categories			
	MHC heterozygous offspring	Offspring with rare/changing MHC genotypes	Inbreeding avoidance	Cooperation with kin
Functions	disease-resistant offspring		outbred offspring	↑ inclusive fitness
Behaviors	mate with MHC dissimilar individuals			cooperate with MHC similar individuals
Requisite information	identify self MHC		identify kin	
Optimal mechanisms if paternity is	Certain	imprint on self MHC odors/genes		imprint on parental or familial MHC odors
	Uncertain	imprint on self MHC odors/genes		imprint on paternally inherited and all maternal MHC odors

Note: If both major functional classes operate, then kin identification mechanisms should be used, because they will also produce disease-resistant offspring.



MHC-dissimilar mates, but prefer MHC-similar communal nesting partners. Ober and coworkers<sup>4</sup> have already demonstrated MHC-dissimilar marriage patterns in this same population; it is probably more reliable to draw conclusions about function from marriage patterns than from odor preference tests where boxes with unknown, odiferous contents are briefly sniffed!

### Imprinting on MHC

The second major, and most surprising, result was that odor preferences were based on paternally inherited alleles. What might cause special discrimination of paternally inherited MHC alleles? A likely candidate is the problem identified by Shakespeare—that paternity is always more uncertain than maternity. This creates the possibility that different mechanisms might be used to identify maternal and paternal MHC alleles. Maternal MHC alleles can be reliably determined by behavioral imprinting on maternal MHC-mediated odors. Such behavioral imprinting on familial MHC-mediated odors has been experimentally demonstrated in mice and has been shown to dominate over self-imprinting<sup>16,17</sup>. As the social father may not be the genetic father, behavioral imprinting on social fathers can impart inaccurate paternity information. Consequently, a different mechanism should be used to identify paternal MHC alleles (see table). This could occur through genomic imprinting or by inferring paternally inherited MHC alleles by knowing maternal and self MHC alleles. Jacob *et al.*<sup>1</sup> could not discriminate between these alternatives.

Parent-of-origin effects have been demonstrated in two previous odor/mating preference studies. Ober and colleagues<sup>4</sup> demonstrated MHC dissimilar mating preferences in humans that were significantly stronger when maternally inherited alleles were involved. Genomic imprinting has recently been shown to influence odor preferences in female mice, where maternal strain odors were avoided over all other strain odors<sup>18</sup>. These females were transferred as embryos into third strain foster mothers, thereby excluding any possibility of behavioral imprinting.

It is too early to infer function from the striking pattern of paternally inherited MHC-based odor preferences observed by Jacob *et al.*<sup>1</sup>. We can, however, present a plausible theoretical framework (see table). If the only function of MHC-mediated behaviors is to produce disease-resistant offspring, then imprinting on self MHC would be the optimal solution. But if kin recognition functions are also important, imprinting on non-inherited parental MHC alleles comes into play because they carry as much kin information as inherited alleles. The observation that behavioral imprinting on MHC includes non-inherited parental alleles<sup>16,17</sup> suggests that functions requiring kin recognition are operating. When paternity is uncertain, then imprinting on paternally inherited MHC becomes the best and only source of paternal information.

Regardless of the details and current difficulties in making solid interpretations,

there is little doubt that MHC genes influence odors and that these odors influence behaviors. The MHC story is spectacular in its complexity and importance; perhaps the two most complicated (biological) systems on earth, the vertebrate nervous and immune systems, have united to help solve two of the greatest challenges to living systems—mutational deterioration and attack by pathogens. MHC-mediated behaviors function to produce disease-resistant offspring, avoid inbreeding and enhance kin cooperation. Consequently, MHC-mediated behaviors start to rival MHC-mediated immunity in importance. □

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## The human body as microbial observatory

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The human body is grossly contaminated with microbes and, for the most part, this is beneficial. Consequently, the finding of microbial and viral transcripts within human EST databases should not come as a big surprise. However, the extent of human-associated microbial diversity and the possible role of infectious agents in common human diseases remains relatively unknown. An increasingly detailed understanding of the human genome will allow us to distinguish between endogenous human transcripts and those expressed by microbial residents.

The human species lives in a dynamic state of co-existence with a myriad of microbial life forms. Nearly all of these host-microbe relationships are mutually beneficial. On occasion, however, mutu-

alism gives way to parasitism, and damage to the human host ensues. Given the fundamental importance of our ongoing relationships with the microbial world (including viruses, bacteria and

unicellular eukaryotes), our level of ignorance concerning the variability of microbial diversity within the human body and the role of microbes in disease is striking.