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Editorial Comment

MHC genes, body odours, and odour preferences

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Introduction

Increasing evidence indicates that the highly polymorphic genes of the major histocompatibility complex (MHC) influence odour and mating preferences in house mice and humans [1]. MHC genes encode cell-surface glycoproteins (class I and II molecules) that bind short peptides and present them to T lymphocytes. Through this mechanism, MHC genes control the immunological self/non-self discrimination, and subsequently, tissue rejection and immune recognition of infectious diseases. Thus, it is suspected that the extraordinary polymorphism of MHC loci is maintained by balancing selection from infectious diseases, though direct evidence for this hypothesis is lacking [2]. Surprisingly, the best evidence indicates that MHC polymorphisms are driven by sexual selection. Studies in house mice indicate that both males and females prefer MHC-dissimilar mates [3–5], who they apparently recognize by odour cues [6]. Studies in humans have also found MHC-associated odour [7] and mating preferences [8]. Such disassortative mating preference could explain the diversity of MHC genes, though several questions remain unanswered about how the MHC influences odour production and why MHC-dependent mating preferences evolved.

Hypotheses about the functional significance

Three non-mutually exclusive hypotheses have been proposed to explain the function of MHC-dependent mating preferences (reviewed in [1]). First, MHC-dependent mate preference may function to produce certain MHC combinations or increased heterozygosity in offspring to increase resistance to infectious diseases. Although increased MHC heterozygosity is associated with increased resistance to HIV [9] and hepatitis [10], experimental infections with single infections in mice have not supported this idea [2]. Second, MHC-dependent mate preference may enable hosts to provide a 'moving target' against rapidly evolving parasites that adapt to their host's MHC genotypes [1]. These two ideas can be called the 'parasite hypotheses'. Third, MHC- dependent mate preferences may function to avoid inbreeding (the 'inbreeding avoidance hypothesis' [11,12]. Inbreeding has extremely negative fitness effects in wild house mice [13], therefore, inbreeding avoidance through genetic kin recognition would be advantageous. Humans, like other mammals, avoid inbreeding through familiarity (the Westermark effect) [14], and there is evidence that odour cues are used for recognizing kin [15].

Odour and mating preferences in humans

Two studies found MHC-associated odour preferences, and one study found MHC-dependent mating preferences. First, Wedekind *et al.* [7] found that women prefer the odour of MHC-dissimilar men. Forty-nine female and 44 male students were typed for their HLA-A, -B and -DR. The men wore a T-shirt for two nights. On the following day, the women were asked to judge the odours of six T-shirts each, and the shirts' odours were judged as more 'pleasant' when they had been worn by men whose MHC genotype was different from that of the judging woman. In contrast, the odours were judged less pleasant when the MHC genotype of the odour-producing males and that of the judging women were similar. This difference in odour assessment was reversed when the women were taking oral contraceptives. Furthermore, the odours of MHC-dissimilar men more frequently reminded the women of their own present or former partners than did the odours of MHC-similar men. Although this is no direct evidence that odour influences mating preferences in humans (but see [16]), this study suggests that the MHC or linked genes influence human mate choice.

Second, Wedekind and Füri [17] tested whether odour preferences are aimed at producing offspring with certain MHC allele combinations (since certain combinations may offer increased resistance against pathogens) or simply increased heterozygosity. The former (but not the latter) possibility would specifically support the parasite hypotheses, since a preference for specific allele combinations that are beneficial under

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given environmental conditions would not be expected by the inbreeding avoidance hypothesis. The study was also designed to test for gender effects, and to get a first estimate of the amount of variance in pleasantness scorings that is correlated to the MHC. This time, 58 women and 63 men, all typed for their HLA-A, -B and -DR, were asked to score the odours of six T-shirts, worn always by the same two women and four men. The pleasantness scorings correlated again negatively with the degree of MHC similarity between smeller and T-shirt wearer in men and in women who were not using the contraceptive pill (but not in pill users). Depending on the T-shirt wearer, the amount of variance in the scorings of odour pleasantness that was explained by the degree of MHC similarity ($=r^2$) varied between nearly 0 and 23%. The six T-shirt-wearers differed significantly from each other in the degree to which pleasantness scorings correlated to the MHC. There was no significant effect of gender in the correlation between pleasantness and MHC similarity: the highest r^2 was actually reached with one of the male odours sniffed by male smellers. Men and women who were reminded of their own mate/ex-mate when sniffing a T-shirt had significantly fewer MHC-alleles in common with this T-shirt wearer than expected by chance. This suggests again that the MHC or linked genes influence human mate choice. This study found no significant influence of the MHC on odour preferences when the degree of similarity between T-shirt wearer and smeller was statistically controlled. This negative finding suggests that body odour preferences are mainly influenced by the degree of similarity or dissimilarity at the MHC in the Swiss study population. The observed preferences would increase heterozygosity in the progeny, without producing specific combinations at the MHC. As mentioned above, a more specific choice of particular alleles would have provided strong evidence in favour of the parasite hypothesis, as opposed to the inbreeding avoidance hypothesis. However, this second study did not provide such evidence.

Third, Ober *et al.* [8] conducted a large study on American Hutterites, a reproductively isolated community of Austrian-German ancestry, and found direct evidence for MHC-disassortative mating preferences. Married couples were less likely to share MHC loci than expected by chance, even after inbreeding taboos were statistically controlled. However, Hedrick and Black [18] did not find such an effect in South Amerindians. Although the latter study had a lower statistical power (the sample size in their field study was much smaller than in the study by Ober *et al.* [8] while the heterogeneity on the MHC seemed to be larger, and fewer alleles had been analysed), the possibility remains that there might be population differences with respect to mating preferences. A study by Paterson and Pemberton [19] tested for MHC-dependent mate preferences in another mammal, the Soay sheep (*Ovis aries*). In contrast to the many studies in mice and the studies on humans mentioned above, they could not find any indication of such mate preferences in an unmanaged population on a Scottish island. Their analysis was conservative with respect to their conclusion, and their sample size was large, which strongly suggests that MHC-dependent mate choice is not universal among mammals.

Hypotheses about the mechanism of odour production

There is much evidence that MHC genes influence individual odour in laboratory mice and rats (reviewed in [20]), and several hypotheses have been proposed to explain how. First, since MHC molecules occur in the urine and sweat, they may provide the odourants [21]. This is unlikely since MHC molecules are large, involatile proteins, and furthermore, denaturation of proteins in urine does not destroy the distinguishability of MHC-mediated odours by mice [22]. Second, MHC molecules bind to allele-specific subsets of peptides, and their volatile metabolites, such as carboxylic acids, may provide the odourants. Class I MHC molecules bind peptides that are hydrophilic, highly evolutionarily conserved, universally expressed and derived from hydrophobic proteins, whereas Class II- bound peptides are more conserved than their source proteins but less conserved than class I-bound peptides [23]. Singer *et al.* [24] found that the relative concentrations of volatile carboxylic acids were characteristic of the urinary odour of different MHC-congenic inbred mouse strains. Third, MHC genes may alter odour by shaping specific populations of microbial flora, although the evidence for this idea is inconsistent [25–27]. Fourth, MHC molecules may change their conformation to bind volatiles, instead of peptides, and carry them to scent glands [28]. Finally, when taken together, the evidence suggests that MHC-bound peptides are metabolized and made volatile by microbes [20]).

Human chemical communication is not well understood and somewhat controversial. It is known that human skin has two types of glands that produce odour: (i) sebaceous glands, which are located all over the body, secrete an odourless oily liquid that is broken down by bacteria into volatile molecules, mostly fatty acids, and (ii) apocrine glands in the axillary region, which play an important role in odour production [29]. Protein carriers (lipocalins) bind and transport odourants to the axillae where they are metabolized and made volatile by bacteria [30]. Besides work on the MHC, there are other findings that indicate human odours play a role in sexual behaviour: (i) humans have a functional vomernasal organ (a chemical sensory system in mammals used to detect pheromones) [31], (ii) pheromones influence women's reproductive synchrony [32,33], and (iii) women prefer the odour of physically symmetrical men [34]. Interestingly, all of these studies on odour communication in humans, including studies on MHC genes, odour, and mating preferences, are rather controversial. Perhaps people are sceptical to the idea of chemical communication in

our species because it goes on 'right under our nose', not necessarily with any conscious processing.

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