Chemosensation and genetic individuality

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Numerous studies have shown that there are measurable behavioural consequences that can result from the olfactory recognition of alleles borne at the major histocompatibility complex (MHC). These consequences include simple individual recognition, disassortative mate preference, discrimination of kin from non-kin and whether a pregnancy is carried to term. Such a system, which can influence the reproductive behaviour of a species, will have profound effects on its genetic constitution and survival. The likely mechanism responsible for the production of MHC-related odours involves soluble MHC molecules that carry allele-specific odoriferous molecules from the blood via the kidneys into the urine, from where they are released into the environment. The ability of soluble MHC molecules to signal genetic individuality in this way may have evolved before the appearance of an acquired immune system in our immediate ancestors, the protochordates.

Immunobiology of classical MHC class I antigens

First, some basic genetic points. The MHCs of mice and rats are called H-2 and RT1, respectively, and they comprise many linked genes that can be divided into several regions (Fig. 1). The specific loci are called H-2K and H-2D/L in mice (Klein, 1979) and they encode the classical MHC class I antigens. The homologous loci in rats are less well defined but have been named RT1-A and RT1-U (Leong et al., 1999; Walter and Gunther, 2000). The particular allele at a given classical class I locus is conventionally denoted by a superscript letter or letters, such as H-2Kb or RT1-Aa. Many decades of study have revealed that, in each species, there is a vast number of alleles at the classical MHC class I loci. Although the full extent of the polymorphism is not clearly defined, it has been estimated that, in mice, there are up to 100 alleles at the K and D loci, whereas the L locus is less polymorphic. Similar allele frequencies are estimated for homologous loci in other mammals (Klein, 1986). Thus, in outbreeding mammals, the degree of polymorphism ensures that in each species there are > 10^9 unique class I antigenic phenotypes segregating in the population. The function of forced polymorphism on this scale is not understood.

Classical MHC class I antigens are glycoproteins inserted integrally into the limiting membrane of nearly all cells (Fig. 1). They are best known from studies on tissue transplantation because incompatibility at the MHC causes extreme rejection of grafts. The polymorphism of the MHC therefore represents a barrier to crossmatching of tissues from unrelated donors for organ grafting and also contributes to the variability at the cell surface and to what Medawar (1996) called ‘the uniqueness of the individual’. By the same token, only close relatives share similarity at the MHC and thus an individual requiring transplantation must look...
to family members to obtain closely matched tissue. Therefore, knowledge of the alleles an individual harbours at the MHC can be used as an indicator of relatedness.

Classical MHC class I antigens consist of two chains: (i) a heavy (α) chain (encoded by the H-2K and H-2D/L loci and analogous loci in mammals), of about 45 kDa, which is called β2-microglobulin (Fig. 1). A single copy gene elsewhere in the genome encodes β2-microglobulin (Kvist and Peterson, 1978). The α and β chains associate non-covalently at the plasma membrane and together they are involved in a crucial process during the induction of immune responses, namely in the presentation of foreign antigens to T lymphocytes (Zinkernagel and Doherty, 1979).

Elegant studies on the atomic structure of class I molecules have revealed how these molecules present antigen to the immune system (Fig. 2b). Key structural determinants are the α1 and α2 domains of the α heavy chain, each of which consists of an α helix and a β pleated sheet (Fig. 2b). The two β sheets join together to make a platform, which supports the two α helices and thereby defines the so-called antigen-binding cleft. Importantly, the allelic differences (as manifested by amino acid changes) that specify the MHC antigenic type are concentrated within the floor and walls of this cleft. Thus the polymorphism of the MHC is reflected by the generation of many different types of binding cleft with unique patterns of hydrophobic or charged residues. The binding clefts are normally occupied by self-peptides that are generated by proteolytic degradation of endogenous polypeptides. The spectrum of peptides present in an individual is unique. The peptides enter the cleft during synthesis of the α chain and are present in the cleft before association of β2-microglobulin with the α3 domain (Fig. 2c). Association of the β chain distorts the α chain and locks the peptides in place between the α helices and thereby...
ensures the retention of the peptide within the cleft (Kvist and Hamann, 1990; Fig. 2d,e). During infection, exogenous foreign peptides derived from the pathogen are incorporated into the cleft and it is towards this novel complex of MHC–foreign peptide that the immune response is raised.

The demonstration that classical class I molecules are used by T lymphocytes of the immune system as associative recognition molecules has directed attention toward immunological explanations for their polymorphism. The prevalent explanation is that MHC polymorphism in a population ensures that lethal pathogens such as viruses cannot extinguish a species by epidemic infection (Bodmer, 1972). In the absence of polymorphism, mutation of virus proteins to mimic those of the host would result in the presentation of essentially self-peptides to the immune system.
MHC-associated odours and individual recognition

The discovery that MHC-associated odour signals are present in mice came from the use of genetically defined inbred strains (Yamazaki et al., 1976). Inbred strains consist of animals that are genetically uniform and homozygous for all their genes, that is, each chromosome pair is identical. Two strains that are identical except for allelic differences at a particular locus are called congenic strains, and any measurable characteristic that differs between the two congenic strains must be ascribed to the genes at that locus. Congenic strains of mice and rats that differ only in alleles at the MHC have been used in several different experimental paradigms to examine whether the MHC is associated with specific odour signatures. The most informative experimental approach is the Y-maze paradigm (Fig. 3a) developed by Yamazaki et al. (1979), which has been crucial in defining the general features of MHC-associated odours and in measuring the olfactory acuity of mice.

The Y-maze paradigm

The basic set-up of the Y-maze is presented (Fig. 3a). Mice are trained to enter alternative chambers scented by an airflow through odour boxes occupied, in the original experiments, by MHC-congenic mice. Mice were trained by water deprivation and reward. In this scheme, a trainee mouse is deprived of water before the experiment (for about 24 h) and then given a drop of water when it enters one of the arms of the Y-maze. The mouse first learns to discriminate the differences between two strong odours, normally juniper and cinnamon: it is rewarded, for example, when it enters the cinnamon arm. It is deemed to have learnt the ability to discriminate between the two odours when it chooses the correct arm at least 80% of the time (degree of concordance). The tasks then become more difficult and the mice are gradually trained to discriminate between two inbred strains and then to distinguish congenic strains that differ only in the alleles at the MHC. In an important development, a generalized (transfer of training) procedure was adopted to ensure that no artefact of the test procedure or unknown variation in odour constitution was responsible for the discrimination (Yamaguchi et al., 1981). Accordingly, previously unused samples of the same odour sources were tested without reward. If the test mice respond correctly to these new samples (concordant response to the learned scent) it can be concluded that incidental or unrelated cues are not involved in the discrimination, it is down to the MHC alone.

Use of the Y-maze paradigm showed that:

- No sensory perception other than olfaction was required to distinguish between MHC types (Yamazaki et al., 1979).
- Urine was as good a source of MHC-specific odours as the whole animal (Yamaguchi et al., 1981).
- Both males and females had equal ability to distinguish between MHC types (Yamaguchi et al., 1981).
• Olfactory acuity of mice could enable the discrimination of MHC class I molecules that differ only in three amino acids. This was a key observation because it confirmed that MHC-related odours map directly to the class I genes rather than to a related locus (Yamazaki et al., 1983a). Moreover, no amount of training could enable a mouse to distinguish between individuals of the same inbred strain (Yamaguchi et al., 1981).

• Mice could also discriminate between allelic differences in the class II and Qa:Tla (now known as the Q/T/M region; Fig. 1) regions, indicating that all three genetic loci of the MHC can contribute to individual odours (Yamazaki et al., 1982, 1984).

• Use of radiation chimaeras showed that the haematopoietic system is a source of MHC-associated odours (Yamazaki et al., 1985).

• The ease of training indicated that the MHC is as potent a source of individual odours as the rest of the genome taken together (Boyse et al., 1987). X and Y chromosomes can also be discriminated between, but are much less potent in scent marking than the MHC (Yamazaki et al., 1986a).

The Y-maze paradigm enabled researchers to investigate the ability of trained mice to discriminate between MHC-related odours in the absence of any other variables (stimuli). In contrast, the recognition of MHC-related odours in nature is likely to be both spontaneous and in the context of a variety of other (competing) stimuli. In a possibly more natural paradigm, in which the ‘habituation–dishabituation’ test was used, it could be shown that rodents can indeed discriminate between MHC types without prior training. The ‘habituation–dishabituation’ test is a simple and powerful technique for determining whether the subject can detect a difference between two odours (Sundberg et al., 1982).

The ‘habituation–dishabituation’ paradigm

This paradigm is based on the simple premise that most mammals are like us: they are usually inquisitive when presented with a novel stimulus, but the novelty can wear off upon extended exposure to the stimulus. The test is very simple and involves placing an experimental animal in a test arena consisting of a plastic box with a removable wire lid. The animal is left in the test arena for a short time so that it has an opportunity to explore and become familiar with it. It is then presented with the first urine odour on a piece of filter paper which is attached to the wire lid. This odour represents a novel stimulus and almost invariably the subject animal responds by orienting to the odour, rearing on its hind legs and sniffing it (Fig. 3b). The animal is presented with the first urine sample three times. By the third exposure, it no longer rears to investigate – it has habituated to the odour. The key test comes in the next trial. When the lid is next changed, a novel urine sample is presented to the animal subject. If it perceives the odour of this new sample to be different from the first sample there is a rapid dishabituation. The rat lifts its head, sniffs the air, and moves toward the new odour and rears to investigate it (Fig. 3b). If the second urine odour is not perceived as different, the animal remains habituated.

MHC-associated odours and reproduction

Spontaneous recognition of the MHC was first observed in the original experiments on mating preference, in which a male mouse was presented with congeneric females that differ at the MHC (Yamazaki et al., 1976). The male, who is the recipient of the alternative MHC signals, is thought to have the active role and usually, though not always, chooses a female that is different from him at the MHC. A more recent experiment indicates that females can also have an active role in choosing mates. A study on seminatural populations of mice, which nest communally and can mate freely, showed that females choose mates and prefer to mate with males of different MHC (Potts et al., 1991). This observation is in agreement with theoretical considerations which predict that it is more important for females than males to choose mates since their genetic investment is greater (Trivers, 1972): after formation of the zygote the female has the sole responsibility for development of the embryo and care of the young.

The effect of the MHC on murine reproduction is by no means limited to mate preference. Experiments designed around the well-known ‘Bruce effect’ showed that recognition of the MHC could have clear neuroendocrine effects that influenced the ability of mothers to carry a pregnancy to term. The Bruce effect is the abortion of pregnancy during the preimplantation stage of development brought about by exposure of the pregnant female to a strange male (Bruce, 1959). This effect can be seen when the only differences between the stud and strange males are in the alleles of the MHC (Yamazaki et al., 1983b). Indeed, it was shown that abortion could be elicited when the only genetic differences between the stud and the foreign male were three point mutations in the H-2Kb molecule (H-2Kb for the stud versus H-2Kbm1 for the strange male and vice versa; Yamazaki et al., 1986b). Abortion can be prevented by administration of prolactin or progesterone (Dominic, 1966a), indicating that the effect is likely to be due to neuroendocrine disturbance. Moreover, it was demonstrated that the urine of the foreign male contains the pheromone that elicits the effect, since bedding or urine from the foreign
male is as good a source of the odours as the whole animal (Parkes and Bruce, 1962; Dominic, 1966b).

MHC-based mating preferences and pregnancy blocking may provide additional selective pressures that act to maintain MHC polymorphism. This will be discussed later when the evolutionary implications of MHC recognition are considered. The following section is concerned with mechanisms that might underpin the elaboration of MHC-associated odours.

**MHC-associated odours: the ‘carrier hypothesis’**

Three mechanisms have been proposed to explain how the MHC might produce an odour of individuality. First, on the basis of evidence that MHC polymorphism can determine variation in the development of organs and cell populations, it has been suggested that MHC-based developmental variations give rise to distinctive odour profiles (Boyse et al., 1987). This hypothesis is difficult to test and it will not be discussed further. A second hypothesis was based upon the known functions of the MHC as encoding molecules involved in the restrictive recognition of foreign antigen (Howard, 1977). It was argued that the intimate linkage of MHC class I genotype with urinary odour was indirect and reflected the immune response against commensal bacterial flora of the skin, urinary tract and gut. Individual MHC types would be associated with unique flora. The volatile odorants in the excretions were thought to be secondary metabolites derived from these organisms. A priori this hypothesis seemed unconvincing since it requires that the types and relative numbers of commensal bacteria are constant over time, which is known not to be the case (Savage, 1977). More importantly, three experiments using the Y-maze paradigm have shown that immune regulation of commensal flora is not necessary for the determination of MHC-associated odours. Firstly, it is possible to discriminate between urine samples taken from germ-free MHC congenic mice, which lack commensal flora (Yamazaki et al., 1990). Secondly, radiation chimaeras reconstituted with F1 bone marrow smell like the MHC of the bone marrow donors, rather than the recipients (Yamazaki et al., 1985). Thus, the MHC-associated odours in these chimeras are not determined by MHC restriction of the immune response, which is heavily skewed towards that of the recipient (Katz et al., 1978), but reflects the genotype of the bone marrow donor. This finding is consistent with the idea that the genotype of haematopoietic lymphoid cells is the crucial determinant of MHC-related odours (Yamazaki et al., 1985; Singh et al., 1988). Finally, it has been observed that fetal MHC-associated odours are evident in the urine of mothers as early as day 9 of gestation (Beauchamp et al., 1994), before the fetus has a functioning immune system (Owen and Ritter, 1969). Clearly, neither bacterial flora nor immune responses are necessary for the elaboration of MHC-associated odours.

We have presented a third mechanism for the elaboration of MHC-associated odours, the ‘carrier hypothesis’ (Singh,
which can accommodate all the evidence to date. The idea for this hypothesis came from work in rats which showed that classical MHC class I antigens are not only found as membrane-bound molecules but also in true solution, in the lymph, blood and urine (Singh, 1986; Singh et al., 1987). The serum molecule is a heterodimer with a heavy chain of 39 kDa associated non-covalently with \( \beta_2 \)-microglobulin (Fig. 4). Proven sources of the molecules are macrophages and dendritic cells of haematopoetic/lymphoid lineage (Singh et al., 1988). They are present in the serum at a concentration between 350 and 390 ng ml\(^{-1}\), have a short half-life of 2.7 h and are excreted into the environment via the kidneys (Singh et al., 1988). In the urine, the molecules undergo degradation, giving rise to a major molecular mass species of 27 kDa (Fig. 4), corresponding to cleavage at the junction between the \( \alpha_2 \) and \( \alpha_3 \) domains of the heavy chain (Fig. 5c). Thus, classical class I molecules, which in their membrane-bound form act as markers of tissue individuality, are excreted in the urine and might serve as individuality markers in the environment, which can be detected by olfaction (Singh, 1986).

Class I molecules are unlikely candidates for the odoriferous components in the urine as they are large and consequently lack a vapour pressure. However, drawing on their role as associative molecules in the immune system, it was suggested that classical class I molecules might associate with smaller molecules, in an allele-specific way, and transport them from the blood into the urine (Singh, 1986; Singh et al., 1987, 1988). Thus a unique mixture of volatiles would be selected from a common pool of metabolites, to which commensal flora could contribute (Singh et al., 1990), and would be transported to the urine to impart a unique MHC-specific odour. The advantages of such carrier proteins as mediators of olfactory signals are well known (Albone, 1984): the slow steady release of small volatiles from the carrier; control of excretion of the volatile molecules; and protection of these volatiles from decomposition.

The proposed hypothesis was tested by Pearse-Pratt et al. (1999). Purified class I molecules of the RT1-A\(^a\) type were injected into normal PVG.RT1\(^u\) animals which possess the RT1\(^u\) haplotype. The effect of this procedure was measured in a habituation–dishabituation assay and it was shown that the smell of the urine taken from the injected animals had been affected. Specifically, the urine samples taken from the animals was found to be indistinguishable from urine taken from PVG.RT1\(^u\) animals, which belong to a recombinant inbred strain that possesses the A\(^a\) allele at the RT1-A locus and are otherwise identical to the PVG.RT1\(^u\) animals. The clear explanation for this result is that injection of the RT1-A\(^a\) molecule transferred the authentic RT1-A\(^a\) odour to the PVG.RT1\(^u\) urine. This explanation is entirely consistent with the ‘carrier hypothesis’. Given these data, it is possible to sketch a molecular mechanism by which class I molecules pick up unique mixtures of volatile odorants via their binding cleft and transport them into the urine to be used in individuality marking (Fig. 5). Accordingly, soluble class I molecules are generated by proteolytic cleavage from cells at a juxta-membranous cleavage site (Fig. 5a). The soluble molecules with their associated peptides are thereby released into the circulation (Fig. 5b). They undergo further fragmentation by...
proteases in the body fluids, giving rise to the major proteolytic 27 kDa fragment in the urine, which represents cleavage of the binding cleft (the joined proteases in the body fluids, giving rise to the major proteolytic 27 kDa fragment in the urine). The effect of this degradative pathway is relaxation of the binding platform, opening of the cleft and release of any bound peptides. The now empty platform can bind a unique cocktail of odorants, which is transported into the urine where further degradation leads to release of the molecules and production of an MHC-specific odour. There is good evidence that proteolysis is necessary for production of MHC-associated odours (Yamazaki et al., 1999). Serum has an odour but cannot be used to discriminate between MHC types (Brown et al., 1987; Yamazaki et al., 1999). However, when sera from MHC-congenic mice are treated with proteases, MHC-specific odorants are released and discrimination between MHC types is possible (Yamazaki et al., 1999). This finding indicates that the MHC-specific odorants are present prerenally in serum and that their liberation requires proteolysis. The nature of the specific odorant molecules that are bound to soluble class I molecules is unknown, although carboxylic acids may be one source (Singer et al., 1997).

Fig. 6. The selective pressures that drive major histocompatibility complex (MHC) polymorphism in mice. The direction of the arrows indicates the selective forces that favour MHC polymorphism. These include the two types of pathogen-driven selection, namely frequency-dependent selection and heterozygous advantage (over-dominance) (Bodmer, 1972). More indirectly, disassortative mating preferences based on the MHC will also increase MHC polymorphism. It is thought that pre-mating mechanisms of this type are more efficient at generating polymorphism that those involving pregnancy blocking, since pre-mating mechanisms do not involve the costs associated with mating and aborted embryos. For further details see Potts and Wakeland (1993).

MHC-associated odours: evolutionary considerations

It has been argued that the unprecedented diversity of MHC classical class I genes is due to pathogen-driven selection that favours rare MHC alleles (Bodmer, 1972). Under both laboratory conditions (Yamazaki et al., 1976) and in semi-wild populations (Potts et al., 1991) mice prefer to mate with individuals that are different from them at the MHC. The combination of these two selective pressures, pathogen-driven and reproductive selection, allowed Potts and Wakeland (1993) to propose a simple model to explain the evolution of MHC polymorphism (Fig. 6). Potts and Wakeland (1993) proposed that the generation of MHC polymorphism is primarily driven by pathogens (for example frequency-dependent selection). This selection in turn allows the evolution of MHC-dependent disassortative mating preferences because these matings produce progeny that are heterozygous at the MHC and thus possess a greater fitness (for example they have better defence against highly mutable pathogens). Pregnancy blocking (the Bruce effect) can also be incorporated into this scheme; as discussed earlier, an established pregnancy can be aborted if a female is presented with the opportunity to mate with a male that is different at the MHC, which may function to avoid inbreeding (Yamazaki et al., 1983b). Another effect of increasing MHC polymorphism by pathogen-driven and reproductive selection is that it also increases the usefulness of the MHC as a marker of genetic relationships (Potts and Wakeland, 1993). This is because the more polymorphic the MHC in a population, the less likely non-kin will share alleles at this locus. This feature has long been recognized in medicine in the fact that the best donors for tissue grafting are kin of the recipient.

Much theoretical work has been done on the evolution of altruism and how kin recognition mechanisms might be used to enhance the inclusive fitness of genes (Hamilton, 1964; Dawkins, 1976). The MHC is particularly salient to this work because its polymorphism enables a measure of the genome-wide relatedness: only related individuals are likely to share alleles at the MHC. Its role in kin recognition was addressed in a series of experiments in which it was shown that female mice usually choose nest mates that are similar at the MHC (Manning et al., 1992). These studies were conducted using semi-wild populations in which the animals had freedom of choice with regard to mating and nesting. Under these conditions, female mice nested communally, gave birth at about the same time and suckled each other’s pups indiscriminately. Unexpectedly, the choice of nest mate appeared to be made on the basis of the MHC: nest mates normally shared alleles at the MHC. Moreover, in an important control using congenic strains of mice, it was shown that the choice of kin could not be explained by shared alleles at other genetic loci. Thus recognition of kin was synonymous with recognition of the alleles at the MHC and it was similarity at the MHC that mattered.

The use of MHC or MHC-like antigens as a system to...
discriminate kin from non-kin is likely to extend beyond vertebrates. Unlike the situation in vertebrates, natural tissue rejection is well documented in our immediate ancestors, the protochordates (Burnet, 1971; Magor et al., 1999). More importantly, rejection is due to the recognition of highly polymorphic histocompatibility antigens (Scofield et al., 1982), which can also be used to discriminate between kin and non-kin (Grosberg and Quinn, 1986). In the colonial tunicate, Botyllus schlosseri, two colonies that share alleles at the histocompatibility loci are able to fuse together, whereas disparity leads to necrosis at the interface between colonies, rejection and often the death of the smaller colony (Fig. 7). It is not known whether the histocompatibility loci encode true structural homologues of their vertebrate counterparts. (Whether modern-day MHC molecules are structurally related to the histocompatibility antigens found in protochordates is not germane to the argument. For an individuality system based on histocompatibility antigens to work, the antigens should be polymorphic and it should be possible for the members of the species to detect this variation.) Nevertheless, there is evidence that soluble forms of these histocompatibility antigens might be involved in a recognition system that enables discrimination between histocompatibility types. Larvae of B. schlosseri live as free-swimming plankton, which eventually settle and form a colony. Genotyping nearest neighbours of settled larvae has shown that there is a significant preference to settle close to larvae that share identity at the histocompatibility loci (Grosberg and Quinn, 1986). This recognition does not involve direct physical contact and thus requires a vector by which the larvae can recognize each other’s histocompatibility type. The most likely candidates for the vector are soluble forms of the histocompatibility antigens. This example has been considered a primitive form of kin recognition in which relatedness is measured solely by recognition of histocompatibility alleles. It may also represent the ultimate in altruistic behaviour because the larvae that settle close to each other and share histocompatibility alleles have greater opportunity to fuse and form a single colony. By sharing resources in this way, a bigger (fitter) colony is formed.

**MHC-associated odours: conclusions**

It is well known that polymorphism at the MHC enables this genetic locus to act as a tissue individuality marker. Less well known is the fact that there are measurable behavioural consequences when mice and rats perceive this genetic individuality by olfaction. In the appropriate context, recognition of the MHC can lead to simple individual recognition, disassortative mate preference, discrimination of kin from non-kin and can determine whether a pregnancy is carried to term. Thus, as originally envisaged by Thomas (1974), MHC-based recognition systems extend beyond immune surveillance to influencing the behaviour of animals. There is evidence that humans produce an MHC-specific odour (Ferstl et al., 1990; Eggert et al., 1999), which correlates with the presence of soluble MHC molecules (Wobst et al., 1999). The olfactory acuity in humans also extends to the ability to discriminate between MHC types (Gilbert et al., 1986). However, it is unclear whether, in the welter of other social and biological factors, the MHC influences human behaviours such as mating preference and maintenance of pregnancy (see Wedekind et al., 1995; Beauchamp and Yamazaki, 1997; Penn and Potts, 1998). This area requires further study.

Our work on the mechanisms by which MHC-associated odours might be produced indicates that MHC molecules...
could act as vectors that transport volatile metabolites into the environment. These volatiles, which are peculiar to each MHC type, represent the odoriferous component that can be used to discriminate between individuals. Such evidence indicates that individual recognition in many animals could involve soluble highly polymorphic histocompatibility-like antigens.

The author would like to thank Peter Sharp for his interest in this work and the opportunity to write this review. He would also like to thank Geoffrey Butcher for information on the rat MHC and Norrie Russell and Ian Cowell for help with artwork.

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