Chapter 12
MHC-Associated Chemosignals and Individual Identity

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Abstract The ability of animals to recognise and discriminate individual conspecifics is a vital feature of mammalian social systems. Genes of the major histocompatibility complex (MHC) have long been recognised to play an important role in influencing chemosensory cues of individual identity. In particular, the profile of urinary volatiles of mice has been related to MHC type, although a mechanism to explain this link has remained obscure. This article aims to review recent developments, which have revealed a new class of MHC-associated chemosignals. These are nine-amino acid peptide ligands bound by MHC class I molecules, which are presented at the cell surface for immune surveillance. In addition to this immune function, these peptides have been found to elicit highly sensitive and specific responses in sensory neurons of both the main olfactory and vomeronasal systems. They have also been shown to convey information about strain identity in biologically relevant contexts. Hence it now appears that there are multiple systems for signalling MHC identity, with distinct features that are likely to be adapted for use in different behavioural contexts.

12.1 The Importance of Individual and Kin Recognition

The recognition of individual identity and the relatedness of individuals play vital roles in mammalian social behaviour. They enable nepotistic behaviour towards kin, including mother-offspring interactions; the recognition of group membership and the maintenance of dominance hierarchies and territories; as well as influencing choice of mate in order to maintain immunological diversity and avoid inbreeding. Many species rely on visual or auditory cues to recognise individuals, but for most vertebrates, individual and kin recognition depend on being able to detect and discriminate differences in genetically determined chemosensory signals. In identifying these chemosensory signals of individual identity, most attention has been focused on families of polymorphic genes that differ in their expression among

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individuals. The best known of these are the genes of the major histocompatibility complex (MHC), which determine the recognition of self from non-self by the immune system, as a defence against pathogens.

One context in which individual recognition is influenced by MHC type is mate recognition, which is essential for preventing pregnancy block (the Bruce effect) in mice (Bruce 1959). The pregnancy block effect occurs when a recently mated female mouse has direct contact with the urinary chemosignals of an unfamiliar male. These chemosignals activate a neuroendocrine reflex, resulting in a fall in progesterone levels and failure of embryo implantation. Although the mating male also produces pregnancy-blocking chemosignals in his urine, they do not block his mate's pregnancy, as the female learns to recognise them during a sensitive period for memory formation at mating (Brennan, Kaba and Keverne 1990). Yamazaki and co-workers (Yamazaki, Beauchamp, Wysocki, Bard, Thomas and Boyse 1983) found that congenic mice, differing from the mating male only at the H2 region of the MHC, were not recognised by the female and were effective in blocking her pregnancy.

Mate choice in mice has also been found to be influenced by MHC genotype, as first reported by Boyse, and then investigated in a series of further studies by Yamazaki and Beauchamp (Boyse, Beauchamp and Yamazaki 1987). They studied mating preferences of male mice housed with a female of the same inbred strain and a congenic female that only differed only in their MHC genotype. They found a disassortative pattern of mating, with the male preferring to mate with the female of dissimilar MHC type, thus avoiding inbreeding. The difficulty in studying mate choice in the laboratory environment is perhaps evident from the confused picture to emerge from subsequent studies by other investigators (Jordan and Bruford 1998). Nevertheless, evidence for disassortative mate preference has been observed in semi-natural enclosures, in which colonies of mice produced fewer MHC homozygous offspring than expected from random matings (Potts, Manning and Wakeland 1991). The influence of MHC type on mate choice appears to depend on learning of kin odours in the nest environment, as it can be largely reversed by cross-fostering mouse pups onto MHC-dissimilar mothers (Yamazaki, Beauchamp, Kupniewski, Bard, Thomas and Boyse 1988; Penn and Potts 1998a).

MHC genotype has also been found to influence kin recognition, in the context of maternal behaviour in mice. Female mice are more likely to form communal nests with kin of MHC-similar genotype, minimising the delivery of maternal resources to genetically unrelated individuals (Manning, Wakeland and Potts 1992). Furthermore, if mouse pups have become scattered from the nest, females preferentially retrieve pups of similar MHC type to themselves (Yamazaki, Beauchamp, Curran and Boyse 2000). The pups themselves appear to be able to use MHC-related cues to learn the odour of their mother and siblings, as revealed by a preference for odours of maternal MHC-type in a choice test (Yamazaki et al. 2000).

MHC influences on behaviour are not restricted to mice. Female sticklebacks show a preference for the odour of males that is consistent with them attaining an optimum level of MHC diversity in their offspring (Reusch, Häberli, Aeschlimann and Milinski 2001). There is also good evidence that humans can discriminate

and recognise the odours from individuals on the basis of MHC type. On average, humans perceive the odours of other individuals as being more pleasant if they share fewer MHC alleles with the perceiver than either no matches or a high degree of similarity (Wedekind and Furi 1997; Jacob, McClintock, Zelano and Ober 2002). Whether such MHC-related odour preferences play a role in the complexities of modern human society is an open question. However, it is notable that fathers, grandmothers and aunts are able to identify the odour of a related infant independently of prior experience, which could point to a role in parental or nepotistic behaviour (Porter, Balogh, Cernoch and Franchi 1986).

12.2 Volatile MHC-Associated Chemosignals

The first evidence that MHC genotype could influence odour identity came from the Y-maze tests of Yamazaki and Beauchamp (Yamazaki, Yamaguchi, Baranoski, Bard, Boyse and Thomas 1979; Yamazaki, Beauchamp, Imai, Bard, Phelan, Thomas and Boyse 1990). They were able to train mice to discriminate the urine odours of congenic mice that differed genetically only at the H2 region of their MHC. Similarly, untrained mice have also been found to be capable of discriminating the MHC type of urine odours in a habituation/dishabituation test (Penn and Potts 1998b). In both of these experimental designs, mice were able to discriminate between urine odours without direct contact, on the basis of their volatile components. Analysis of the volatile constituents of urine by gas chromatography has revealed that urine from MHC-congenic mice differ in the relative proportions of volatile carboxylic acids (Singer, Beauchamp and Yamazaki 1997). Moreover, these differences are sufficient to distinguish between MHC types and elicit significantly different patterns of neural activity in the main olfactory system (Schaefer, Yamazaki, Osada, Restrepo and Beauchamp 2002). It is not surprising that the main olfactory system should be capable of distinguishing MHC-related differences in the profile of urinary volatiles. After all, the main olfactory system is adapted to learn to recognise complex mixtures of odorants that make up odours. However, the role of the individual profile of urinary volatiles in conveying individuality in biologically-relevant contexts remains to be firmly established.

12.2.1 How Does MHC Genotype Influence Urine Odour?

The H2 region of mouse chromosome 17 codes for MHC proteins of classical class I type, which are expressed on the cell membrane of nearly all nucleated cells in the body. Their immunological role is to bind peptides resulting from the proteosomal degradation of endogenous and foreign proteins (Paulsson 2004). They then present the peptides at the cell surface for immune surveillance, providing a constantly updated indication of intracellular protein composition. This enables the immune system to recognise cells that have been invaded by pathogens, which triggers cell

destruction. MHC class I proteins belong to a highly polymorphic gene family, with structurally diverse peptide binding grooves. Unrelated individuals within a population are highly unlikely to share the same MHC genotype.

Several hypotheses have been put forward to explain how MHC class I molecules could affect the profile of urinary volatiles (Penn and Potts 1998c). One of the most popular of these is the carrier hypothesis (Singh 2001). According to this hypothesis, the cleavage of MHC class I molecules from the cell membrane releases the peptide from the binding groove, which would then become available for binding small volatile molecules. Fragments of MHC class I proteins have been found in rat urine, at low concentrations (Singh, Brown and Roser 1987). And although there is no direct evidence that MHC class I proteins can bind urinary volatiles, the ability of mice to discriminate urine odours of MHC-congenic strains does appear to be related to polymorphism in their peptide-binding groove (Carroll, Penn and Potts 2002).

12.3 MHC Peptide Ligands as Individuality Chemosignals

Although most of the early work focused on the ability of mice to discriminate MHC-dependent urine odours, it does not mean that all individuality chemosignals are volatile. Indeed, lesions of the main olfactory epithelium do not prevent the pregnancy block effect, or affect the ability of female mice to recognise their mate (Lloyd-Thomas and Keverne 1982; Ma, Allen, Van Bergen, Jones, Baum, Keverne and Brennan 2002). Both pregnancy block and mate recognition are mediated by the vomeronasal system (Bellringer, Pratt and Keverne 1980), which has traditionally been associated with the detection of non-volatile stimuli following physical contact. This ability of the vomeronasal system to detect individuality is reinforced by the finding that neurons in the accessory olfactory bulb, respond highly selectively to the strain identity of an anaesthetized stimulus animal (Luo, Fee and Katz 2003). This puzzling situation was resolved by Boehm's hypothesis that the peptides bound by MHC class I molecules could convey information about MHC type, and represent a novel class of non-volatile chemosignal that could be detected by the vomeronasal system (Boehm and Zufall 2006).

Peptides bound by mouse MHC class I proteins are typically nine amino acids in length, a size determined by proteosomal processing. The major factor determining the specificity of their binding is the presence of large hydrophobic side chains known as anchor residues, which occupy pockets in the MHC binding groove. The position and shape of these anchor pockets varies among different MHC class I proteins. Therefore individuals with different MHC genotypes will possess a different combinations of peptides bound by their MHC class I proteins. For example, the H-2D^{b} haplotype, found in C57BL/6 mice, codes for the MHC class I D^{b} protein. This preferentially binds peptides that have asparagine (N) at position 5, such as AAPD**N**RETF. Whereas the H-2K^{d} haplotype, found in BALB/c mice, codes for the MHC class I K^{d} protein, which binds to peptides with tyrosine (Y) at posi-

tion 2, such as S**Y**FPEITHI. The position and nature of the anchor residues along the peptide chain reflects the binding characteristics of the MHC class I molecule, and therefore conveys information about MHC type. A chemosensory receptor with binding characteristics similar to a particular MHC class I protein will therefore be sensitive to peptides associated with that MHC type (Boehm and Zufall 2006).

12.3.1 Vomeronasal Responses to MHC Peptide Ligands

Sensory responses to synthetic peptides possessing the characteristic features of MHC peptide ligands have been recorded from slices of vomeronasal epithelium at concentrations down to 10^{-13} M (Leinders-Zufall, Brennan, Widmayer, Chandramani, Maul-Pavicic, Jäger, Li, Breer, Zufall and Boehm 2004). Moreover, the response characteristics showed a dependence on the presence of anchor residues similar to that determining binding to MHC class I proteins. Synthetic peptides of BALB/c-type (SYFPEITHI) or C57BL/6-type (AAPDNRETF) elicited selective responses from largely separate sub-populations of vomeronasal sensory neurons (VSNs). These responses were abolished when the anchor residues were substituted by alanines, which lack a side chain, or when the amino acid sequence was scrambled to change the position of the anchor residues. Moreover, responses were unaffected by changes in the amino acid residues between the anchor residues, implying that the position of the anchor residues determine the specificity of the VSN response.

MHC peptide ligands convey information about strain identity that influences mate recognition in the pregnancy block effect. The addition of synthetic peptides of C57BL/6 type to BALB/c urine was effective in blocking pregnancy of females that had mated with a BALB/c male, whereas the addition of peptides of BALB/c type was ineffective. Conversely, the addition of BALB/c type peptides to C57BL/6 urine altered its strain identity and caused it to block the pregnancy of a female that had mated with a C57BL/6 male (Leinders-Zufall et al. 2004). Both the responses of peptide-sensitive VSNs and their effectiveness in conveying individuality in the pregnancy block effect, were unaffected in knockout mice lacking functional TRPC2 channels (Kelliher, Spehr, Li, Zufall and Leinders-Zufall 2006). This implies that the peptide-sensitive VSNs utilise a different transduction mechanism from the TRPC2-dependent vomeronasal transduction mechanism operating in other VSNs.

Calcium imaging of peptide-sensitive VSNs revealed them to be located in the basal layer of the vomeronasal epithelium, and co-localised with V2R2 immunostaining (Leinders-Zufall et al. 2004). Although most of them responded selectively to synthetic peptides of either BALB/c-type or C57/BL6-type, a significant proportion of VSNs responded to both peptides (Leinders-Zufall et al. 2004). This could be explained by the co-expression of more than one V2R type per VSN (Martini, Silvotti, Shirazi, Ryba and Tirindelli 2001). However, it remains to be seen whether individual VSNs respond to particular combinations of MHC peptides, and the

extent to which they could respond to peptides associated with specific combinations of MHC alleles.

Peptide-sensitive VSNs express receptors of the V2R class, which possess a large extracellular N-terminal domain, possibly involved in binding MHC peptide ligands. But intriguingly, V2Rs are co-expressed with non-classical MHC Ib proteins, which are not known to be expressed in any tissue other than the VNO (Ishii, Hirota and Mombaerts 2003; Loconto, Papes, Chang, Stowers, Jones, Takada, Kumanovics, Fischer-Lindahl and Dulac 2003), suggesting that they might have a specific chemosensory function. Moreover, V2Rs bind to MHC Ib proteins and β-microglobulin, suggesting that they might form a receptor complex (Loconto et al. 2003). Structural considerations suggest that the peptide-binding groove of the MHC Ib is empty and unlikely to bind peptides (Olson, Huey-Tubman, Dulac and Bjorkman 2005). Nevertheless, sequence variability among the nine members of the non-classical MHC Ib family is located in the peptide binding groove, and certain combinations of MHC Ib proteins are co-expressed with particular V2Rs (Ishii et al. 2003). It is possible that the combinatorial co-expression of MHC Ib proteins with V2Rs affects the peptide specificity of VSN responses, but their role remains enigmatic.

12.3.2 Main Olfactory Responses to MHC Peptide Ligands

According to the traditional view, the main olfactory system detects airborne volatile molecules, while the vomeronasal system detects non-volatile chemosignals following physical contact. However, it is becoming increasingly apparent that there is considerable overlap between the systems (Brennan and Zufall 2006). For example, both the main olfactory and vomeronasal systems respond to putative male mouse pheromones at high sensitivity. More surprisingly, olfactory sensory neurons (OSNs) from the main olfactory system also respond to MHC peptide ligands (Spehr, Kelliher, Li, Boehm, Leinders-Zufall and Zufall 2006). It may seem unlikely that the main olfactory system would respond to non-volatile stimuli such as MHC peptide ligands. However, when male mice investigated females whose anogenital region had been painted with rhodamine, which is a non-volatile fluorescent dye, fluorescence was found across all the nasal endoturbinates (Spehr et al. 2006). This suggests that non-volatile molecules are able to gain access to the main olfactory epithelium of mice following direct investigation of a stimulus.

OSN responses to peptides were found to be highly sensitive, with thresholds down to 10^{-11} M, although they were around two orders of magnitude less sensitive than VSN responses (Spehr et al. 2006). OSN responses to MHC peptide ligands also displayed a different dependence on anchor residues. Whereas replacement of anchor residues with alanines abolished the responses of VSNs, it shifted the stimulus response curve of around two thirds of the OSNs, making them less sensitive by approximately two orders of magnitude. However, OSNs still failed to respond to the scrambled version of the peptide or a mixture of its constituent amino acids (Spehr

et al. 2006). This suggests that the response of OSNs to MHC peptide ligands may be more dependent on the overall sequence of amino acids in the peptide chain, rather being solely dependent on the position of anchor residues. This is highly interesting, as the ability of OSNs to recognise specific MHC peptide ligands could theoretically confer the ability to detect peptides of pathogenic origin, and therefore convey information about the health status of a conspecific.

Peptide-sensitive OSNs have a ciliated morphology, which is characteristic of sensory neurons in the main olfactory epithelium. They also appear to use a similar transduction mechanism based on cAMP and the canonical olfactory cyclic nucleotide gated ion channel (Spehr et al. 2006). This contrasts with peptide-sensitive VSNs, in which transduction appears to involve diacylglycerol gated ion channels (Leinders-Zufall et al. 2004). Calcium imaging of the main olfactory epithelium revealed that the responses of peptide-sensitive OSNs were highly specific. OSNs were never found to respond to both C57/BL6 and BALB/c MHC peptide ligands, as was the case in VSNs (Spehr et al. 2006), suggesting that they may use a different coding strategy.

Consistent with effectiveness as stimuli for OSNs, MHC peptide ligands have been shown to have behavioural effects that are mediated by the main olfactory system. Male mice normally spend more time investigating urine from females of a dissimilar strain to themselves, and the addition of dissimilar MHC peptide ligands to urine from females of the same strain as the mating male resulted in a similar increase in investigation (Spehr et al. 2006). This behavioural response required direct contact with the stimulus and was unaffected by removal of the VNO. Moreover, the increased investigation time in response to dissimilar MHC peptide ligands was abolished in CNGA2 knockout mice that lacked the classical main olfactory transduction mechanism.

12.4 Conclusions and Future Directions

In addition to their immunological role, MHC peptide ligands have recently been discovered to function as chemosignals, linking individuality at the immunological and behavioural levels. The discovery of peptide-sensitive OSNs in the main olfactory system extends their possible influence to species that lack a VNO, such as humans. Given the ubiquity of class I MHC proteins amongst vertebrates, the role of MHC peptide ligands in signalling individual identity is likely to be widespread, and not just limited to mice. Indeed, the addition of synthetic MHC peptide ligands has been shown to bias the mate preference of female sticklebacks, in a way consistent with attaining optimum MHC diversity in their offspring (Milinski, Griffiths, Wegner, Reusch, Haas-Assenbaum and Boehm 2005). Furthermore, there is a plausible argument that the role of peptides in signalling individuality actually preceded their role in immune recognition (Boehm 2006).

There is clear evidence that highly sensitive receptors for MHC peptide ligands can be found in both the main olfactory and vomeronasal systems of mice.

Furthermore these peptide ligands can elicit behavioural and physiological effects, when presented in biologically relevant contexts. And yet there remains a prominent gap in this picture, as MHC peptide ligands have not been identified in biological secretions. This is somewhat unusual in the field of pheromonal research in which research normally proceeds from finding a biological effect; via identification of a potential chemosignal released by an animal; to its synthesis and testing in a bioassay. Filling this gap in our understanding will not be a trivial, as the concentrations of the MHC peptide ligands are likely to be low, and difficult to identify among a forest of other small peptides. However, it at least serves as a reminder that there is more than one route to the identification of potential pheromones. Studies on MHC peptide ligands have so far concentrated on using urine as a stimulus. However, strain-specific responses of neurons in the accessory olfactory bulb were recorded during investigation of an anaesthetised animal, and were elicited equally effectively by investigation of the head and the anogenital area (Luo et al. 2003). Future investigations need to test for the presence of MHC peptide ligands in a wider range of biological secretions, from a variety of species, including saliva, skin and vaginal secretions, and numerous poorly characterised secretions from specialised scent glands.

Many interesting questions remain in the study of the receptor and transduction mechanisms involved in the detection of MHC peptide ligands. The role of the MHC Ib molecules in ligand binding, and in determining the specificity of the potential receptor complex with V2Rs, will be of particular interest. As will a comparison of the receptor proteins between peptide sensing OSNs and VSNs. Further investigations into the co-expression of V2Rs, and the receptor coding strategy of the peptide-sensing VSNs compared to OSNs, will be of great importance in elucidating how the information is handled by the neural systems that mediate the physiological and behavioural effects. There is also much to be gained from a greater understanding of the different transduction mechanisms used by the ever-expanding variety of chemosensory sub-systems (Brennan and Zufall 2006). This will enable them to be targeted more selectively using genetic technology, which will in turn allow a greater understanding of the role of MHC peptide-ligands in natural behavioural contexts.

Our understanding of the chemosensory role of the MHC has been revolutionised by the discovery of responses to MHC peptide ligands. However, it should not be forgotten that a wealth of evidence has accumulated over the last 20 years, linking MHC type with the profile of volatile constituents of mouse urine. Moreover, other genetic differences between individuals can also signal individuality, such as the major urinary proteins of mice (Hurst and Beynon 2004). Therefore a picture emerges of a variety of chemosensory signals of individuality that can be sensed by both the main olfactory and vomeronasal systems. Different chemosignals and chemosensory systems are likely to be used in different behavioural contexts. In particular, the main olfactory system's capacity to learn and recognise complex mixtures of airborne volatiles, provides a way of linking volatile and non-volatile signals into a multimodal sensory representation of an individual or social group. It additionally provides a signal that can be sensed at a distance, avoiding the

potential dangers inherent in investigating non-volatile stimuli directly (Hurst and Beynon 2004). Teasing apart the relative contributions of innate and learnt responses to the different cues, in different species and behavioural contexts, will provide continuing interest to this field for some time to come.

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