

Artigo de Revisão

The role of the Major Histocompatibility Complex in the Immunobiology of Self-Aromas

O papel do Principal Complexo de Histocompatibilidade (MHC) na imunobiologia dos aromas

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RESUMO

Os autores apresentam uma revisão sobre os mecanismos imunobiológicos no processo da olfação, reunindo informações atuais e relevantes sobre os odores liberados pelo organismo de vertebrados e sua associação com o sistema imune. Algumas teorias sobre características estruturais de odores ou aromas têm sido propostas, sendo as mais importantes: a teoria estereoquímica e da vibração do odor. Diversas técnicas baseadas nas atividades cerebrais associadas a processos sensoriais, têm sido particularmente importantes na avaliação dos efeitos fisiológicos dos odores. Moléculas do Principal Complexo de Histocompatibilidade (MHC) foram identificadas nos odores próprios (odortipos), e componentes voláteis do MCH, detectados na urina de camundongos. Os estudos mais importantes que relacionam os receptores olfatórios com o MHC foram obtidos em modelo experimental murino. Esses estudos demonstram que os odores próprios desempenham um importante papel na escolha do companheiro(a), e na relação entre mãe e prole. Um sistema de sensor de gases chamado "nariz eletrônico" foi usado como instrumento capaz de detectar moléculas do MHC nos odortipos. Concluindo, a diversidade de odores próprios ou odortipos parece ser consequência do elevado polimorfismo do MHC, que é próprio de cada indivíduo. Apesar das controvérsias entre cientistas em relação a imunobiologia dos aromas principalmente em seres humanos, pode-se supor que odores próprios influenciam a escolha de parceiros em humanos. Mais estudos são necessários para esclarecer e confirmar esta hipótese.

Unitermos: MHC, Odores, Olfato.

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SUMMARY

The authors present a review of the immunobiological mechanism of olfaction considering current and relevant information about the odors released by vertebrate organisms, and its association with the immune system. Many theories concerning to the type and the quality of the molecular structures of odors or aromas have been proposed, but the most important are the steric theory of odor and the vibration theory of odor. Several techniques based on brain activities have been studied in association with sensorial processes, and they were particularly important to

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evaluate the physiological effects of odors. Molecules of the Major Histocompatibility Complex (MHC) have been identified in individual body odors (odortype), and volatile compounds of the MHC were easily detected in the urine of mice. The major relevant studies related to the Olfactory Receptors (ORs) and the MHC were conducted in mice models, and these studies demonstrated that the odortype has an important role in the partner choice, as well as in the relationship between mothers and their offsprings. A sensorial gas apparatus called "eletronic nose" has been used as an instrument capable of detecting molecules of the MHC in the odortypes. In conclusion, the diversity of self-aromas or odortypes seems to be generated in the context of the MHC, and consequently varies according to the genetic background of the individual. In spite of several controversies among scientists concerning to the immunobiology of the aromas, mostly in human beings, we could hypothesize that similar types of odors could influence the human choice. Future studies are necessary to clarify and confirm these findings in human beings.

Keywords: MHC, Odors, Smell.

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AROMA

Aroma is a Greek word that means fragrance, but is also called odor. Odors are perceived by the Olfactory System¹, and many theories relating to the type and quality of the molecular structures of the odors have been proposed. The most important are the steric theory of odor and the vibration theory of odor^{2,3}.

During the fifties, an English scientist named John Amoore proposed the steric theory of odor. He speculated that the nose receptors responsible for sending each aroma signal to the brain, work as a system of the type "key-lock". The combination of the odor molecules of different structural forms (keys) with their specific receptors (locks) generate signals, which in turn are sent to the brain, and culminate with the perception of different aromas^{2,3}.

The vibration theory of odor initially proposed by Dyson, and later on by Wright, defends that such recognition and the similarities among the molecules of the aromas are related to their intramolecular vibration, rather than to their molecular shapes^{2,3}. Keller & Vosshall using psychophysical methods in humans to test the vibration theory showed no evidence to support this theory, so the steric theory is the most accepted at present⁴.

In order to appreciate the physiological effects of odors, several techniques based on the brain activity associated to sensorial information processes have been evaluated⁵.

Olfactory System

The odors are volatile chemical compounds carried to the Olfactory Region by the inhalation of the air^{2,6-8}. When the aromas are inhaled, their particles go to the olfactory membrane, which possess Olfactory Receptors (ORs) composed by bipolar nervous cells derived from the Central Nervous System (CNS)^{6,7,9}. The odor in contact with the olfactory surface spreads out in the mucus, opening the cilia. Then, each molecule of odor binds to a protein receptor present in the cilia membrane, and

finally, the olfactory nerve transmits a signal to the CNS as an action potential^{6,9}.

The olfactory signals are transmitted to the Olfactory Bulb that spreads out the distribution of the neural receptors odor innervation on the Nasal Epithelium, and supplies projections of the axons to the Olfactory Cortex, also called Skull Nerve I. The brain receives the axons and releases neurochemical substances^{6,7,9,10}.

In addition, there are glomeruli inside the Bulb. The glomeruli are discrete neuropil structures formed by the incoming axons of a subset of olfactory receptor neurons expressing the same olfactory receptor and by the dendrites of the mitral cells making synaptic connections with these incoming axons^{6,7,9,10}. Recent researches suggest that different glomeruli respond to different odors, so, it is possible that the glomeruli are the best way for the analysis of different signals transmitted to the CNS from the odors⁶.

Several studies have demonstrated that some species of vertebrates possess the Vomeronasal Organ (VNO), which is a peripheral sensorial organ, accessory to the Olfactory System. The function of the VNO seems to be exclusively the detection of chemical signals, which could be related to sexual behavior and mark of territory¹¹.

It is not known if there is some place for human communication through the odors and the pheromones. In adult human beings, the VNO does not exist, but the pheromonal actions are likely mediated by the main Olfactory Epithelium. One of the evidence of this chemical communication among humans is the notable example of a synchronization tendency of the menstrual cycles in women who live together¹¹.

Olfactory Code

The ORs are encoded by a large family of genes that including approximately 900 genes in humans and 1,500 in mice. The polymorphism in the sequences of the OR genes have already been described, and shows the oc-

currence of individual differences in the odors detection. Each neuron of the Olfactory Epithelium expresses only one allele of *OR* gene¹². In addition, 70% of the human *OR* genes had become not functional pseudogenes¹³.

The studies of the diversity, polymorphism and evolution of the *OR* genes, will provide a better comprehension of the biology of the olfactory process^{12,14}, important to understand the specific bind of the odors to their receptors, including the MHC⁸.

Major Histocompatibility Complex

The Major Histocompatibility Complex (MHC) belongs to a group of surface molecules encoded by a family of approximately 50 genes. The great diversity of these genes suggests that their mechanisms have had an enormous evolutionary evolution¹⁵.

The MHC is responsible for the molecular recognition of antigens presented in the cells surface, and acts always in addition to CD4 and CD8 molecules. The MHC has also a biological function of restriction of the self/nonself system^{16,17}.

Odortype

Individuals of different species, including human beings, have individual body odors (odortypes), and by the Olfactory System it is possible to distinguish one individual from another^(15,18-21). The odortype transmits important information concerning to the identity, the reproductive status, and the health of the individual. It also promotes recognition between generations^{20,22}.

Even though the human MHC is more difficult to detect compared to the mice MHC²³⁻²⁶, a preference for odortypes has also been demonstrated in humans, mainly in the context of Class I molecules²⁴. The knowledge of the human odortype expressed in urine is still restricted¹⁹.

It is known that the combinatorial potential of the MHC genes is quite vast, therefore, a small change of one nucleotide can modify the odortype¹⁵.

Neural Activation of the Olfactory Bulb

Odortypes from mice differing in the MHC elicit distinct, but overlapping spatial activity map in the glomerular layer of the Olfactory Bulb. This shows that the spatial activity map in the Olfactory Bulb carries enough information to allow the mice to discriminate MHC odortypes.

In order to understand the neural activation of the Olfactory Bulb, mice are killed soon after odortype exposition, and the sensor stimulation of Olfactory Bulb are explored²⁰. The space standards obtained of the odortype activity are used as a fingerprint of each mice

MHC. This kind of approach permits to describe the odortypes^{20,21}.

Partner Choice in Mice

The ORs first studies were performed in mice in 1991 by Buck and Axel, and until now, the major studies that correlate the ORs with the MHC have been carried in murine models². Of note, Linda Buck and Richard Axel were awarded with the 2004 Nobel Prize in Physiology or Medicine, because of their inestimable contribution on the study of aromas. They discovered in 1991, a large gene family that give rise to an equivalent number of Olfactory Receptor types²⁷.

According to gender, some researches demonstrated that males exclude females who have identical MHC. These data stand that the identification among mice occurs by the odortype detection, and has a profound effect in social interactions. These observations distressed immunobiologists and neurobiologists in a recent past, but nowadays they show great progress in relation to the study and understanding of this effect^{20,21}.

Involvement of the MHC since the Birth

Female mice have the ability and the tendency to recognize their offspring through the MHC. In a few days the newly born mice are able to recognize their mothers by the odortype^{15,20,21}. This type of study has demonstrated that the MHC is the mainly determinant of the relationship between the mother and the newly born mice, followed by secondary factors¹⁵.

One study carried with women after the birth of their babies showed that whether mother's urine were mixed with urine from their own baby and from other baby, a trained mouse was capable to recognize the sample which present urines of the same genomic origin, which means, recognition of the similar odortypes²⁸.

Partner Choice in Humans

Different from mice, a few numbers of studies have been conducted in humans. In one of them, 49 women and 44 men were identified in relation to their own MHC. The men had worn a t-shirt for two nights. On the following day, the women had been asked to judge the most pleasant t-shirts odors. Interestingly, they chose the t-shirts that had been worn by the men with the MHC genotype different from their own genotype. In contrast, when the women had to decide on the least pleasant odor, they chose the t-shirts used by men with the MHC genotype more similar to theirs (similar odortypes)²⁹. Curiously, women who were in the fertile period of the menstrual cycle did not show clear preference²⁹. A very similar study showed that men also prefer t-shirts worn by women whose odortype is different from theirs²⁹.

Some hypotheses have been proposed to explain the MHC involvement in partner choice²⁸. These hypotheses emphasize the MHC miscellaneous in the population and consequently the enhancement of the resistance against infectious diseases and parasitic diseases, and prevention of blood relative marriages²⁸.

“Eletronic Nose”

“Eletronic nose” (“e-nose”) is an apparatus of a sensorial gas that detects particles of the MHC in odors. The “e-nose” consists of a set of chemistry-physicists detectors, made of microscales of quartz crystal and oxidated metal to semiconduction. This sensor changes the frequency and the conduction of some molecules present in the gas. The changes are characterized by particular odors²⁶.

An experiment with the “e-nose” performed in a total of 153 urine samples from six females and six male mice, indicated that the MHC molecules are detectable by the “e-nose” as the major urine odor component. In addition, the “e-nose” showed differences in urine compounds among the same male species; the Class II MHC are not detected in several cases, while the Class I MHC products are always detected²⁶. These findings proved that the MHC is directly related to the odortype^{15,20,22,26}.

Odor compounds present in serum of mice are also clearly distinguished by the “e-nose” apparatus²⁶. It is believed that the human sweat contains the MHC odor. Through the “e-nose” it was possible to distinguish primary and secondary components in human odortype, which indicates MHC influences²⁶.

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Odortype and the Diagnosis of Diseases

It is well known that genetic changes as well as metabolic changes, modify the human body odors, and some human diseases can be diagnosed by the odortype. Recently, it was observed in mice presenting the virus responsible for the Mouse Mammary Tumor Virus (MMTV), that their odor changed in males and females, regardless the presence or the absence of the tumor. This finding stimulated studies of odortype in humans infected with virus that causes diseases, and stands the possibility of treating with success these infected patients, before developing a tumor³⁰.

CONCLUSIONS

The studies presented in this review show the importance of the odortype in the social relationship, mostly in animal models. Indeed, confirm the presence of the volatile compounds of the MHC in urine of mice. Studies in human beings are rare, but the data collected until now induce doubts and curiosities, and stimulate new studies concerning the real influence of the odortype in human choice.

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