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Does the major histocompatibility complex influence choice of mate in humans and other mammals? - a review

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Reproduction is one of the basic biological functions in animals and humans. Due to the high biological relevance of reproduction and energy investment in their rearing offspring need to be of the best genetic quality and fitness to ensure preservation of the species. Both males and females employ mating strategies that would promote reproduction success and survival of their offspring. Choosing a high-quality mating partner is considered to be the main strategy in the reproduction process. One of the factors influencing the partner's attractiveness is Major Histocompatibility Complex class I (MHC I). The influence of MHC I on mate choice is well established in animals, whereas it is still questioned in humans, where the social status of a partner may strongly influence the mate choice. In this review the role of the MHC1 on mate choice in animals and humans is discussed. The studies published so far show that all investigated mammalian species can detect fractions of the MHC I molecules in urine and other body fluids. The response to the signal carried by MHC I is context-dependent and varies not only between species, but also between genders and may be modulated by various socioecological factors in every phase of the reproduction process, until zygote formation. These results suggest that MHC plays an important role in the choice of a reproductive partner in all mammal species, including humans.

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Mammals, including humans, choose their mates based on their quality. The healthiest partners are preferred, with best fitness and resistance against pathogens. Such partners most likely carry "good genes", which they can pass on to their offspring. One of the mechanisms facilitating recognition of the best male candidate for mating is based on Major Histocompatibility Complex molecules (MHC), in particular Class I (MHC I) [Potts *et al*. 1991, Wedekind *et al.* 1995, Penn and Potts 1997, Ober 1997, Edwards and Hedrick 1998, Penn and Potts 1999, Ziegler *et al.* 2005, Milinski 2006, Chaix *et al.* 2008, Havlicek and Roberts 2009, Trowsdale 2011].

MHC I are molecules present on the surface of every nucleated cell in all vertebrate species. They help to distinguish "self" cells from "non-self". Their role is to present fragments of digested intracellular proteins on the cell surface. T lymphocytes recognize such complexes (MHC I with the complementary peptide) and either tolerate the cell if it is recognised as the "self", or destroy it if the cell is recognised as a "non-self".

Genes encoding MHC are the most polymorphic genes within vertebrate genomes [Edwards and Hedrick 1998, Restrepo et al. 2006]. Such a vast number of genes ensures presence of many MHC I molecules and results in a maximum protection against pathogens. Some sets of MHC I genes (MHC I haplotypes) provide better protection than the others, depending on the type of the pathogen. For example certain MHC haplotypes provide protection against severe malaria; others protect more effectively against HIV or tuberculosis infection [Florese *et al*. 2008, Lopez *et al*. 2010, Price *et al.* 2001, Trowsdale 2011, Weatherall 2008]. Another advantage of the high polymorphism of MHC genes is connected with the fact that the set of MHC molecules is unique for every individual and may be considered as a genetic fingerprint [Slev *et al*. 2006]. This makes MHC molecules one of the best chemical signals informing on the genetic quality of the future reproductive partner. MHC molecules strongly influence the odourtype – the unique odour of every individual [Boehm and Zufall 2006].

To collect evidence that MHC influences the choice of mate in mammals, a broad range of literature was reviewed.

The mechanism of MHC I detection

The role of MHC I molecules is to bind peptides from degraded proteins inside the cell and present them on the cell surface. Peptides are bound by MHC I by specific interactions between the amino acid side chain and the binding site of the MHC molecule. It depends on the MHC I molecule structure related to MHC I genes, which peptides from the inside of the cell will be bound to and presented on the cell surface [Rammensee et al. 1995]. Moreover, the structure of MHC I molecules mirrors MHC I haplotypes of a given individual [Leinders-Zufall *et al*. 2004, Boehm and Zufall 2006, Spehr *et al*. 2006 a, Restrepo *et al*. 2006]. Complexes of MHC I molecules bound with peptides (called the MHC I peptide ligand) are constantly shed from cell surfaces and

are present in body excretions such as urine and sweat [Leinders-Zufall *et al*. 2004]. These complexes create a characteristic and unique odour of an individual, which is called odourtype. Due to a high diversity of MHC I encoding genes, the existence of two identical odourtypes is highly unlikely. The way of detecting MHC was conserved during the evolution and is present in all mammalian species [Boehm and Zufall 2006, Kwak *et al*. 2009, Penn and Potts 1997, Restrepo *et al*. 2006]. The schematic method of MHC I peptide ligand detection is shown in Figure 1.

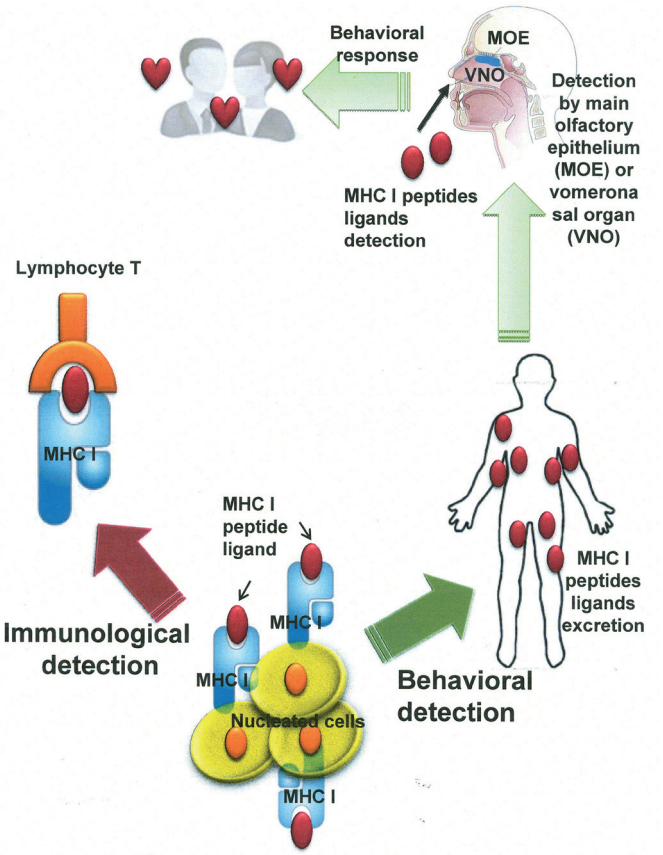

Fig1. Schematic manner of MHC I peptide ligand detection. Peptides from inside a cell are presented by MHC I molecules on the surface of every nucleated cell. Such complexes (MHC I with a bound peptide = MHC I peptide ligands) are detected by T lymphocytes in order to ensure immunological protection. The peptide presentation on the cell surface is continuous, which means that MHC I peptide ligands are constantly shed from the cell surface. After shedding a new intracellular peptide is bound by a new MHC I molecule and presented again on the cell surface. Shed MHC I peptide ligands are excreted with body fluids such as sweat and urine. During normal social interactions (both in animals and humans) MHC I peptide ligands gain access to the nasal cavity where they may be detected either by the main olfactory epithelium (MOE) or the vomeronasal organ (VNO). If detected ligands come from either a MHC heterozygous or MHC dissimilar partner it evokes a behavioral response, such as physical attraction.

Odourtypes are recognised by the olfactory system by detection of MHC I peptide ligands [Boehm and Zufall 2006, Restrepo *et al*. 2006]. A characteristic trait of animal olfaction is the existence of two distinct, but complementary systems, i.e. the main olfactory system that mainly reacts to volatile compounds, and the accessory olfactory system represented by the vomeronasal organ that processes non-volatile compounds [Petrulis 2013, Valkenburgh *et al*. 2014]. Recently it has been argued that the main and the accessory olfactory systems may function synergistically [Kelliher 2007].

Although MHC I peptide ligands are non-volatile, they are detected by both the main and the accessory olfactory systems. They gain access to the main olfactory epithelium during normal social interactions such as sniffing, licking and touching. The vomeronasal organ is able to actively transport (via an active pumping mechanism) droplets of body excretions, such as urine, with dissolved MHC I peptide ligands, to the vomeronasal sensory neurons in order to detect them [Spehr *et al.* 2006a, Spehr *et al*. 2006b, Bauma and Cherry 2014]. Similarly to the immune system, the main olfactory epithelium and the vomeronasal sensory neurons recognize the amino acid side chains of MHC I peptide ligands [Spehr *et al.* 2006b]. The main difference to the immune system is that the MHC I peptide ligands do not carry the information concerning a potential pathogen; potentially, they carry the information on the genotype of an individual [Kwak *et al*. 2009, Slev *et al*. 2006]. Since the main olfactory epithelium and the vomeronasal organ are anatomically separate and have different ways of conducting a signal [Spehr *et al*. 2006 a Spehr *et al*. 2006b], it has been suggested that the signal from one MHC I peptide ligand can evoke different responses. A behavioral reaction depends on which system (the main olfactory epithelium or vomeronasal organ) detects the MHC I peptide ligand [Boehm and Zufall 2006, Spehr *et al.* 2006a, Spehr *et al*. 2006b, Bauma and Cherry 2014]. An example of such a behavioral response that depends on the manner of detection is the Bruce Effect (termination of early pregnancy in mice). The behavioral response is present only if the signal from MHC I peptide ligands is conducted via vomeronasal sensory neurons [Kelliher *et al.* 2005]. More research is required to determine which neural pathways are responsible for certain behavioral responses and how/if both detection systems (the main olfactory epithelium and the vomeronasal organ) cooperate.

The physiology of reproduction differs between males and females and thus reproductive strategies differ in the two genders. Females have a lower rate of reproduction than males. A female has to evaluate the cost of mating against the quality of the offspring and their prospects of survival [Ramm and Stockley 2014, Fitzpatrick *et al.* 2015]. To ensure that the effort she puts in maintaining a pregnancy and rearing the offspring will be worthwhile, a female has to choose the best partner possible [Milinski 2006, Ziegler et al. 2005]. Natural selection favors MHC I heterozygotes. Heterozygotes carry more variants of MHC I and therefore they are more protected against a wider range of pathogens, and thus have a better chance to cope with diseases.

The experimental data showing that females prefer to mate with MHC dissimilar males are, however, inconsistent [Penn and Potts 1998]. Some studies indicate that

female mice tend to mate with MHC dissimilar males to produce heterozygous offspring [Milinski 2006], whereas no conclusive evidence could be found to show that females would prefer the urinary odours of MHC-disparate males as an indication of mate choice, meaning that females did not show a significant preference for the MHC-dissimilar males [Ehman and Scott 2001].

MHC heterozygous offspring may be conceived in two ways. The female can choose a partner with respect to her own genome, which means her breeding partner will be MHC I dissimilar. Such a match will ensure that the offspring will be heterozygous [Milinski 2006]. This is also a well-known mechanism to avoid inbreeding, especially in closely related populations.

Another possibility for the female is to choose a male heterozygous in MHC I, regardless of her own MHC I. As it was mentioned before, heterozygotes are usually healthier and fitter and a heterozygous partner also increases the chance for having heterozygous offspring [Drury 2010].

Males evaluate the quality of available females based on females' MHC. Early studies of Yamazaki et al. (1976; 1978) showed that in four out of six congenic mice strains males preferred to mate with MHC dissimilar females. Males invest more energy in mating with genetically suitable females, thus increasing the probability of reproductive success [Kelly and Jennions 2011, Lemaitre *et al*. 2012, Ramm and Stockley 2014, Burger *et al*. 2015].

It could be hypothesised that choosing the partner, either with dissimilar MHC I or heterozygous at the MHC I, is not a conscious choice or conscious decision. If the MHC I peptide ligand comes from an appropriate partner, besides the behavioral response it probably evokes some kind of pleasure. This could be related to the release of endorphins. Thus, choosing a MHC I dissimilar or heterozygous partner, not only increases chances for healthy offspring, but for the female it also has some rewarding value.

In this review three different groups of animals: mice, horses and non-human primates, as well as humans were compared as to the MHC dependent mate choice.

Mice

Data regarding the potential influence of MHC I on mate choice have mainly been collected from studies on rodents. First experiments testing that hypothesis were conducted by Yamazaki et al. [1976, 1978]. Unlike most researchers, they assumed that it is the male, not the female, who chooses a partner and they designed their experiment in a way that was supposed to test male mate choice. They used mice differing only in the MHC region on a chromosome being MHC homo- or heterozygotes. A male was presented with two females in estrus and the female he mounted first was considered to be the male's choice. Results of the experiments indicated that the male mice prefer to mate with females MHC I dissimilar to the male.

The results concerning MHC-dependent mating preferences in laboratory mice are contradictory [Penn and Potts 1998]. Laboratory conditions differ from the natural environment of the mouse in many aspects, the mice being exposed to pathogens and being able to exhibit freely all kinds of social behaviors. However, the influence of MHC on mate choice was confirmed later by other researches [Potts *et al*. 1991, Eklund 1997a]. Potts *et al*. [1991] tested mate preferences of mice in semi-natural conditions. Mice were derived from wild caught individuals and were kept in enclosures big enough and with a complexity that ensured normal social and breeding behavior. Results showed that these mice from semi-natural conditions chose their mates based on the MHC haplotype in order to ensure an optimal level of heterozygosity in the offspring. Behavioral observations confirmed that the females were actively looking and choosing the mate partners (females travelled through territories of different males in order to find the best partner, whereas males never followed estrous females outside their territories).

Mate choice preferences are modulated by socioecological factors such as the rearing environment. Such a hypothesis was tested by Beauchamp *et al*. [1988] and Yamazaki *et al*. [1988]. Their studies revealed a phenomenon called familial imprinting. Homozygous mice which differed only in the MHC haplotype were used as parents for pups to be used as testing subjects. Neonate mice (the whole litter) were separated from their parents within 16 hours after birth and moved to foster parents, whose own litter was removed at the same time. At the age of 21 days mice were weaned and sexed. Male mating preferences and females' acceptance to be mated by males were tested when mice reached sexual maturity. The experimental setup was similar to earlier studies of Yamazaki *et al*. [1976, 1978]. Males preferred to mate with females whose MHC genotype was different from the genotype of their foster family, even if in fact the females were MHC similar to them. Further studies by Eklund [1997b] confirmed the influence of family imprinting on mate choice in mice. The main differences between experiments of Yamazaki *et al*. [1988] and Beauchamp *et al*. [1988] when compared to that of Eklund [1997b] were that only one pup from the litter was fostered and that mate choice was investigated in both sexes. A majority of females chose males with MHC dissimilar to that of their foster family, whereas males showed no preferences during most of the experiment. This influence of family imprinting was confirmed in semi-natural conditions in enclosures large enough to allow normal reproductive behaviour [Penn and Potts 1998]

Radwan *et al*. [2008] using a Y-maze when testing bank voles (*Clethrionomys glareolus)* demonstrated that females spent more time near the scent of MHC dissimilar males than near those of a similar MHC. The authors suggested that it provided evidence that bank voles use MHC-related cues to choose compatible mates.

Generally the results of the research carried on rodents support the hypothesis that mate choice is MHC-depended, as well as the fact that in most cases it is the female that chooses a mate [Penn and Potts 1997, Penn and Potts 1999].

Horses

Horses exhibit much sniffing and the so-called *flehmen* behavior during social interactions [Hothersall et al. 2010]. During flehmen the animal inhales with the nostrils, curls back its upper lip to facilitate the transfer of semiochemical substances into the vomeronasal organ [Saslow 2002]. Observations carried out on feral horses showed that unlike domesticated horses, it is often the mare that actively looks for a stallion. It is also the mare that starts most of sexual interactions [McDonnel 2000, Heitor and Vicente 2011]. Burger *et al*. [2010] conducted an experiment, in which they were looking for a mechanism that determines how horses choose a mate. Nineteen mares of different breeds and ages were moving freely in a specially designed stable in order to choose their favorite stallion. Each mare was tested during 2 consecutive cycles, 2 times in estrus (approximately 9-22 hours prior to ovulation). Afterwards the Equine Leukocyte Antigen I (Equine MHC I) was determined serologically. Unfortunately, the contact between mares and stallions was restricted (a small opening in the door) and time limited (several hours) and thus the experimental conditions did not allow for normal reproductive behaviour of tested horses. However, mares in estrus, therefore with the highest possibility of conception, chose MHC I dissimilar stallions, which supports the hypothesis on the MHC I influence on mate choice.

In populations of wild horses, foals learn the genotype of their herd members and avoid mating with them in the future. Observations carried out on a group of Camargue horses [Duncan *et al*. 1984] for a period of 6 years showed that horses exhibit low levels of sexual behavior towards members of their own herd (harem stallion, mother, maternal sibling). Horses prefer to mate with partners that are not familiar to them, even though it sometimes means mating with a relative. Similar observations were conducted on the same group of Camargue horses [Monard and Duncan 1996] and on Sorraia horses [Heitor and Vicente 2011]. They showed that young mares, which separated from their juvenile herds, choose new herds with an unfamiliar stallion and familiar mares. Although relatedness between horses was not determined based on MHC I, results allow to speculate that the young mares' choice was based on MHC I of the horses from the new herd. These results also suggest that foals learn the genotype of their herd members, probably through memorizing the MHC odourtype (which depends on the MHC haplotype) and the mechanism is similar to familiar imprinting in mice (for more details see chapter "Pre-copulatory mate choice in females – mice, page 5), and avoid mating with them in the future. According to Klinger [1975], young mares of free-roaming horse breeds are expelled by their fathers from the maternal herds rather than disperse on their own initiative. Kaseda and Nozawa [1996] on the basis of genetic tests in feral Misakai-horses showed that father-daughter matings accounted for only 2% of all matings and occurred only when the father and daughter were separated before reaching sexual maturity of the daughter. This was in accordance with some earlier opinions that stallions based their avoidance of incest on familiarity rather than kin recognition [Berger 1986].

Non-human primates

Non-human primates live in various socio-ecological populations, solitary, in pairs in groups, with different levels of relatedness. They also exhibit a variety of mating patterns such as monogamy or polygamy and different levels of parental care [Setchell and Hutchard 2010]. All experiments in non-human primates were carried either in their natural environment or in a semi-natural environment, thus both reproductive behavior, mating preferences and actual mate choice could be determined [Schwensow *et al.* 2008a, 2008b, Setchell *et al*. 2010, Aarnink *et al*. 2014]. In groups where females mated with many males, females preferred to be fertilised with sperm of MHC dissimilar males [Schwensow *et al*. 2008a, Setchell *et al*. 2010], which was determined by MHC testing of the offspring. In small and closed populations, which members were highly inbred, females were also choosing MHC dissimilar males [Aarnink *et al*. 2014]. Interesting results came from observations of populations where females live with males in life-time pairs. Genetic tests showed that their offspring was sired both by the legitimate partner as well as by other males. The extra partners were chosen based on their MHC and they were either MHC heterozygous or MHC dissimilar [Schwensow *et al*. 2008b].

Humans

People live today in a highly complex environment. This complexity and a wide variety of factors influence human senses and make the choice of an appropriate partner difficult [Lee *et al.* 2014]. As in other species, women choose reproductive partners, often actively looking for them [Eaton and Rose 2011]. The female's preferences vary across the menstrual cycle. During the fertile phase of her cycle she looks for the man whose genes and overall fitness makes him the best partner for potential offspring [Thornhill and Gangestad 1999, Thornhill *et al*. 2003, Gangestad and Cousins 2001, Havlicek and Roberts 2009]. An experiment conducted by Wedekind *et al*. [1995] where women rated the smell of T-shirts worn by men started the era of research on the influence of MHC I on mate choice in humans. A group of 49 female and 44 male students were typed for their Human Leukocyte Antigen (HLA – human MHC). Men were given 100% cotton T-shirts and were asked to wear them for two consecutive nights. During that time they were asked to live, as much as possible, an odour neutral life (use only perfume-free detergents, avoid odour producing foods and behaviors such as staying in a smoking area). On the third day every woman was asked to rate the odours of six T-shirts: three worn by MHC similar men and three worn by MHC dissimilar men. Every odour was rated for its intensity, pleasantness and sexiness. Results depended on the hormonal status of women. Those women who were not using any hormonal contraception tended to rate odour of MHC I dissimilar men as the most pleasant and sexy. Women using oral contraception preferred odours of men with a similar MHC. Hence, the use of oral contraception interferes with natural

mate choice [Grammer *et al*. 2004, Roberts *et al.* 2012, Little *et al.* 2013]. A similar experiment conducted by Wedekind and Furi [1997] confirmed these results.

The influence of a number of shared MHC alleles on the attractiveness of body odour to the opposite sex was the subject of other experiments [Carvahlo Santos *et al*. 2005, Havlicek and Roberts 2009, Lie *et al*. 2010]. All of those experiments supported the hypothesis that humans, women in particular, prefer MHC dissimilar partners. Moreover, it was shown that MHC homo- or heterozygotes are seen as less or more sexually attractive, respectively. The MHC heterozygotes are usually healthier, their skin tone and complexion is brighter and their faces and bodies are more symmetrical [Thornhill *et al*. 2003, Roberts *et al*. 2005, Havlicek and Roberts 2009, Lie *et al*. 2010].

The effect of MHC on mate choice in humans may be best verified in the actual choice of the partner. Ober *et al*. [1997] typed 411 Hutterite couples for their MHC. The population was ethnically homogenous and the number of MHC gene alleles was limited. The number of MHC alleles shared between spouses was lower than expected from random mating [Ober *et al*. 1997]. Similar results were obtained from analyzing MHC similarity between 30 European American couples from Utah and 30 African couples from Yoruba. Spouses were matched with respect to dissimilar MHC [Chaix *et al*. 2008]. Results of the above observations confirm the hypothesis that similarly as in other species, humans prefer to choose MHC dissimilar partners.

Humans do not always match according to their MHC. However, MHC has a substantial impact on their sex life [Garver-Apgar *et al*. 2006]. Forty eight couples underwent 3 sessions of interviews related to their intimate life: one in the beginning of the study, one in the fertile phase and one during the infertile phase of the women cycle. Participants were rating their relationship satisfaction (sexual life, loyalty, faithfulness, etc.), partner's perceived satisfaction, willingness to have sex with the current partner, extra pair copulations and fantasies about having sex with somebody else. As expected, with the increasing number of shared MHC alleles between partners, women declared a lower sexual responsiveness to their partner and less satisfaction from sex, which agreed with men's perception (men declared that partners were less responsive to them and have less satisfaction from sex). The number of MHC shared alleles did not have any influence on other aspects of their relationship. During the fertile phase of the women's cycle, women were reluctant to have sex with MHC similar partners. Instead they reported extra pair sex. However, it has to be noted that MHC does not predict overall satisfaction from the relationship, but only the physical aspect of it [Garver-Apgar *et al*. 2006].

All the experiments involving humans were supposed to test the human mate choice. However, in humans mate choice preferences and the actual choice of a reproductive partner should be distinguished. Women might look for a partner either to spend a life with him or for casual sex that will result in robust offspring [Gangestad and Cousins 2001, Garver Apgar *et al*. 2006, Larson *et al*. 2012, Thornhill and Gangestad 1999]. MHC similar partners might be perceived by women as more agreeable and caring,

which is more beneficial in a long term relationship [Larson *et al*. 2012, Roberts *et al.* 2005]. MHC dissimilar men are favored as reproductive partners, because they increase chances for conceiving MHC heterozygous offspring.

Males' mate choice

Males' reproductive strategies differ from the ones employed by females. While females invest more in offspring, due to pregnancy and lactation, males tend to maximize reproductive success and to sire as many offspring as possible by taking as many mating opportunities as possible. Males, however, also have to decide how to invest reproductive energy, because sperm production is costly [Firman *et al.* 2013, Ramm and Stockley 2014, Burger *et al*. 2015, Fitzpatrick *et al.* 2015]. Ejaculate composition is modulated depending on the male's judgment of female's quality and potential fertilization success [Kelly and Jennions 2011, Lemaitre *et al*. 2012, Leivers *et al*. 2014, Ramm and Stockley 2014].

Generally MHC-dependent mating preferences in males are more difficult to detect, as such preferences are weaker than in females [Penn and Potts 1998]. Females' MHC is a signal that informs the male how much effort he should put into a particular mating. This was confirmed by studies in mice and horses [Koyama and Kamimura 2000, Firman *et al*. 2013, Burger *et al*. 2015]. Males of both species exhibit higher sperm number counts and higher testosterone levels after being exposed to MHC dissimilar females, when compared to males exposed to MHC similar females.

Conclusion

Even though the methodology of the research often varied, results of many studies imply that MHC influence mate choice in mammals.

Based on the results described in the literature, it may be stated that MHC is the main molecular basis determining an individual's identity and is a signal of that individual's quality as a reproductive partner. Preferences for certain MHC genes are modulated by the constantly changing environment (both social and ecological factors) and as a result mate choice may differ with every mating. Because of the genetic quality encoded in MHC and MHC dependent mate choice, preferences are context dependent. Furthermore, detection of MHC signals from the opposite sex not only modulates behavioral responses (choice of partner), but also physiological ones, such as modulation of genes and peptide expression within the reproductive tract of females and males. It shows that mate choice is both a behavioral and a physiological process, which is adapted by animals and humans under environmental pressure in order to achieve reproductive success to ensure preservation of the species.

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