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Mate Choice Optimizes Offspring MHC Genetics and Drives Sexual Reproduction

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Abstract

Sexual reproduction can be maintained only in an ever-changing world of diseases generating a never-ending co-evolutionary arms race between infectious diseases and their hosts. The polymorphic Major Histocompatibility Complex (MHC) allows vertebrates including humans to track changing parasites through olfactory mate choice for the partner that offers the currently optimal complementary set of *MHC* alleles. The extremely high standing variation with more than 1000 different *MHC* alleles present also in human populations offers ample opportunity for choice. What is needed to respond to a new parasite mostly already exists and does not need to be invented through mutations. Adapting to locally different parasites can induce speciation through locally adapted sets of immunogenes.

Keywords: Polymorphic; Major histocompatibility; Sexual reproduction

Why Sex?

Sexual reproduction is inefficient: a female throws away half of her genes (during meiosis), tries to find a male who has done similarly, and fills up what she has dropped with what she gets from him. An asexual female just produces identical copies of herself. The second problem is the production of sons which neither lay eggs nor give birth although they cost as much as daughters to be produced. Sons seem to be a waste [1]. By producing only daughters the asexual female has twice has many grandchildren as the sexual one (Figure 1). Therefore sexuals will be out competed within several generations [1]. However, almost all plants and animals reproduce sexually. Thus, sexual reproduction must have a short-term evolutionary advantage compared with asexual reproduction. If sex is superior to asexual reproduction, its short-term advantage should be such that offspring with the combination of the new and the retained half of genes are more than twice as fit as if the female had either made just a copy of herself or chosen a mate randomly. Selective mate choice has to achieve at least a two-fold genetic benefit in each generation anew compared to random mating. Is this feasible?

Three demanding conditions have to be fulfilled [2]: (i) There must be a never ending dramatic change of the environment so that grandmother's optimal choice of genes for her offspring is no longer fitting the new environmental demand – the mother has to combine again half of her genes with a well-chosen different half. The daughter needs to do it again, etc. If the environment would stop changing, the last well-chosen combination of genes will stay on to be optimal and asexual reproduction would take over. (ii) The genes with which we and other animals respond to this dramatic environmental change must be polymorphic so that there are many potential partners each offering different versions of the genes to choose. (iii) The different versions of these genes must be detectible from the outside - no mouse, fish, bird or choosing human can use next-generation sequencing technology to learn about a potential partner's genes. All three conditions may be fulfilled at least in vertebrates including humans.

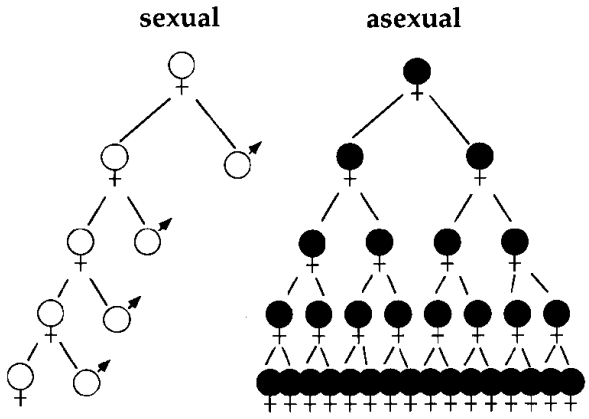

Figure 1: The disadvantage of sexual versus asexual reproduction. See text for details. Adapted from [2].

Infectious Diseases Drive Sexual Reproduction – The Parasite Red Queen

Infectious diseases occur in enormous numbers of species and individuals. They are selective forces that change strongly between generations, able to favour sexual reproduction. They may change so rapidly that for hosts "it takes all the running you can do, to keep in the same place" as the Red Queen said to Alice in Wonderland [3]. The parasite red queen hypothesis [4-10] assumes that new combinations of genes for resistance are required to cope with the currently dominating infectious diseases in every generation anew.

Polymorphic Major Histocompatibility Complex Genes

Are immunogenes sufficiently polymorphic? The genes of the major histocompatibility complex (MHC; in humans: human leukocyte antigen, HLA) contain the most polymorphic gene loci known in vertebrates [11]. As of October 2014, 11,846 different *HLA* alleles have been recognized [12]. These highly polymorphic *MHC* genes play a major role in the immune function in jawed vertebrates [13]. MHC molecules present self- as well as parasite-derived peptides to T-lymphocytes. The peptides that can bind to a given MHC molecule have the same aminoacid residues at two or three particular positions along their sequence but they can vary otherwise. The aminoacids at these positions, the anchor residues, insert into pockets of the binding groove of an appropriate MHC molecule. Every MHC molecule can present only peptides that match its peptide-binding groove. Different MHC molecules bind different sets of peptides with different anchors. Possessing different *MHC* alleles and hence different MHC molecules increases the range of pathogen-derived peptides that can be bound and displayed to T-cells at the cell surface [11,14].

If the advantage of sexual reproduction consists in adjusting the immunogenetics for offspring in every generation anew in order to survive the arms race with ever changing infectious diseases, the primary goal of mate choice should be to find mates that offer optimally complementary immunogenes, i.e. *MHC* genes.

Mate Choice for MHC Dependent Body Odor

The MHC has been demonstrated to influence also mate choice, not just in mice [15,16], voles [17], fish [18-25] and birds [26-28], non-human primates [29], but also humans are able to recognize *MHC* alleles from body odor [30-37]. Early studies done with inbred mice found that that the smell of potential partners that have *MHC* alleles that differ from those of the choosing individual is preferred [15]. Later studies with wild caught sticklebacks showed that these fish have an intermediate rather than a maximal MHC heterozygosity [18]. When both an inbred and an out bred stickleback population was mimicked in a laboratory study, within the "inbred" population fish went for different *MHC* alleles, within "out bred" populations for less different *MHC* alleles when choosing partners [19]. It seems as if individual MHC heterozygosity is optimized in out bred populations.

The Chemical Nature of the MHC-Dependent Odor Signal

Two studies [20,38] tested the so-called MHC ligand peptide hypothesis. The range of peptides displayed by an individual's MHC molecules mirrors the diversity of its *MHC* alleles in a key-lock-like manor. Thus, the peptides themselves that are bound to MHC molecules may be the polymorphic signal. MHC ligand peptides function as stimuli for a subset of olfactory neurons in the vomeronasal organ of mice [38]. Individual neurons responded to only one specific MHC ligand peptide each, this specificity depending on the anchor residues of the peptide with which it binds to "its" MHC molecule. A neuron did not distinguish between peptides with the same anchors but different residues in other positions. However, it did not respond when only the anchors were mutated to alanine, which never serves as an anchor. These olfactory neurons respond exactly to those residues of the peptide, which mirror the binding specificity of the MHC molecule. Do MHC peptides function also during social recognition? Bruce [39] found that pregnancy failed when a recently mated female mouse was, after removing the stud male, housed with a new male from a different strain (or presented only with its odour). Yamazaki et al. [40] showed that females block pregnancy when the odours of new and stud males are from MHC congenic strains that differ only by one *MHC* class I allele. The "Bruce-effect" could be induced when, e.g., a BALB/c female that had mated with a C57BL/6 male was presented with a BALB/c specific MHC peptide, but did not block pregnancy when presented with a C57BL/6 specific MHC peptide [38]. This shows that MHC ligand peptides function as individuality signals in mice, see also [41].

Are MHC ligand peptides used in actual mate choice decisions? If peptides are the natural odour signal that reveals a male's *MHC* alleles, it should be possible to manipulate this information by supplementing further peptides. Because a female stickleback prefers the scent of a male that offers the optimal complementation of her own alleles [19,42], supplementing its odour with a mix of four different synthetic MHC peptides should increase the attractiveness of a suboptimal male but should render an optimal or super-optimal male unattractive. When gravid females chose between spiked and un-spiked water from the tank of one male per female, they preferred the peptide side when the combined MHC diversity of the pair was below the optimum, but they avoided the spiked side when it was at or above the optimum (Figure 2). Hence, MHC ligand peptides are likely to be the natural odour cues with which individual mice and sticklebacks signal their own mix of *MHC* alleles.

Mate choice is predicted to have two steps. (a) Females (in some species also males) approach a partner that offers by olfactory signalling the optimally complementary mix of *MHC* alleles. (b) The female decides by taking into account the male's expression of secondary sexual ornamentation, e.g. its brightness of coloration, whether it is healthy [43] and thus likely to offer the specific *MHC* allele, among his complementary set, that provides resistance against the currently prevailing infectious disease [44]. If the male is dull, the female continues her sequential search until she finds a male that fulfils both expectations to a reasonable extend [45].

The Chemical Nature of the MHC-Dependent Odour Signal in Humans

After having determined the nature of the *HLA* (*MHC*) immune gene alleles in female test subjects, MHC ligand peptides that would be bound by an MHC molecule of a subject were synthesized for each subject and tested as potential components of the subject's body odour [46]. To this end, the test subjects were asked to mix the artificial peptide ligands with their own armpit perspiration, one side with their own peptide and the other side with another subject's peptide, and to decide which variant appealed to them most. It emerged that the test subjects identified the underarm perspiration as particularly pleasant and their preferred scent when it had been mixed with the peptide ligand corresponding to their own MHC genotype.

It was further examined whether the olfactory perceptions could be detected in the brain, and if so where in the brain. To this end, synthetic peptide ligands of either the test subjects' own or another type were forwarded to the subject's nose, and studied their perception in the brain using functional magnetic resonance imaging. Astonishingly, a small area located in the right middle frontal cortex always responded when the test subjects smelled one of their own peptides, irrespective of the chemical nature of that self-peptide. These results show that the peptide ligands transported by the MHC molecules actually determine the natural body odour not only in

animals, but also in humans. These findings offer new possibilities for the production of innovative perfumes that can provide a better signal of an individual's immune gene repertoire to a potential partner through the intensification of his or her body odour [46].

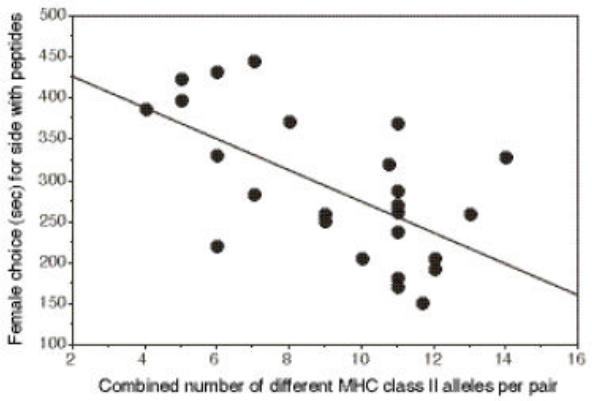

Figure 2: Synthetic MHC ligand peptides added to male water are counted as signals of additional *MHC* alleles of the male. In a two-choice flow channel, single gravid female three-spined sticklebacks chose between the water from the tank of a single male supplemented with solvent only or four peptides in solvent. The time (of a total of 600 s) females spent in the side of the flow channel to which peptides were supplemented is shown as a function of the combined number of different *MHC* class II alleles of the pair. Offspring of a pair with a combined diversity of 10 alleles would have about 5 alleles because each parent has haploid gametes [20].

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An Optimal Number of Different MHC Alleles per Individual are Predicted

Each individual has only a very small subset of the diversity at the population level. This is an evolutionary paradox. If having many MHC loci is better than having one, why are there not many more MHC loci? Duplication of loci would be an easy way to increase number of loci [47]. Sex would be unnecessary for maximizing resistance if everybody has all MHC variants present in the population. However, whenever a distinct MHC molecule is added to the MHC repertoire, all T-cell lines that recognize self-peptides bound to that molecule must be removed in order to maintain self-tolerance and to avoid auto-immune responses. The low number of MHC loci, present in, e.g., humans, sticklebacks and mice is probably about optimal to balance out the advantages of presenting an increased range of foreign peptides and the disadvantages of an increased loss of T-cells from the repertoire [11,48]. An optimal individual MHC diversity is thus predicted to have the highest immunocompetence.

Therefore, no individual can be a high responder to all potential pathogens. An individual with all the MHC molecules required to present the necessary peptides would probably have no T-cells left to respond to them [48]. An optimal number of different MHC alleles per individual providing the highest immunocompetence were theoretically predicted [49-52]. Borghans et al. [51] used experimental estimates for positive and negative selection in a mathematical model and predict that resistance to pathogens only decreases at unrealistically high MHC diversities. An updated model [52] based on more recent findings on T-cell selection can predict an intra-individual MHC diversity in the range 3–25 MHC molecules, which is the same order of magnitude as that typically observed in individuals.

The first evidence for an immunogenetic optimum was found in three-spined sticklebacks [18,53] and experimentally proven (Figure 3) [54]. An optimal individual MHC diversity maximizes both lifetime reproductive success [55] and survival in the wild [56]. This kind of immunogenetic optimum has been shown also for other vertebrates, e.g. house sparrows [57], turkeys [58], pythons [59], trout [21], voles [60], turtles [61], and cichlids [62]. The optimal MHC diversity may be part of a co-adapted gene pool providing resistance to local parasites [63]. For inbreeding avoidance it would help to prefer partners with *MHC* alleles that differ from those of self, which might be important for mice [16]. In fish where juveniles disperse, inbreeding avoidance does not need an extra mechanism [18].

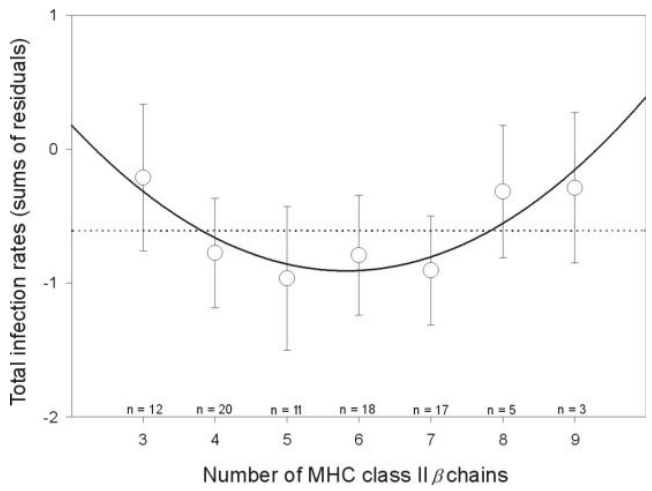

Figure 3: Relation between number of expressed MHC class II molecules and mean parasite load, expressed as summed residuals from GLM analysis. The function matches a quadratic polynomial with a minimum of 5.82 alleles [54].

Parasites Drive MHC Polymorphism

Sticklebacks in lakes harbour different parasites communities than those in rivers, even though the rivers are connected with the lakes [64,65] and exhibit different, locally adapted MHC allele pools [24, 66]. Given the choice between the odour from the tank of a river and that of a lake male, a gravid female stickleback prefers the lake male's odour if she is a lake female and the river male's odour if she is a river female [24]. For choosing the male from their own habitat, female sticklebacks employ MHC-dependent olfactory signals to select mates with which they can achieve a habitat-specific MHC gene structure that optimally protects their offspring against local parasites (Andreou et al. unpublished). Habitat specific parasites may have selected for the possession of MHC alleles that provide resistance against them. Therefore, *MHC* allele pools became locally adapted.

In order to test experimentally whether a parasite against which a specific MHC haplotype provides resistance can increase the frequency of this haplotype at the population level, three of six experimental stickleback populations were exposed to nematode *Anguillicoloides crassus*, the three other populations to the nematode *Camallanus lacustris*. Only those *MHC* alleles that provided resistance to the respective parasite, that a population had been exposed to, increased in frequency in the next host generation (Figure 4). When the offspring were exposed to the parasite to which their parents had been exposed to, those fish within sib-ships that had the respective *MHC* alleles were more resistant than their sib-mates without those alleles (Figure 5). Thus, the first episode of parasite Red Queen driving resistance genes has been experimentally demonstrated [67].

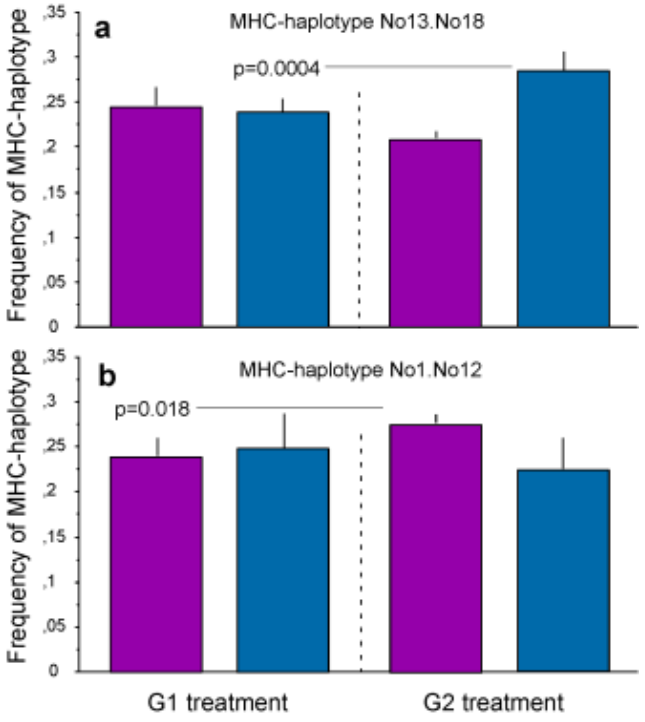

Figure 4: Mean (+1 SEM) frequency changes of the resistance haplotypes between the first generation (G1) and the second generation (G2). (a) The haplotype No13.No18 increases in frequency under *C. lacustris* selection – a parasite to which it confers resistance. (b) No01.No12 increases in frequency under *A. crassus* selection, a parasite to which it confers resistance. Frequencies are averaged over replicated experimental ponds. Blue bars represent fish exposed to *C. lacustris* and purple bars represent fish exposed to *A. crassus* [67].

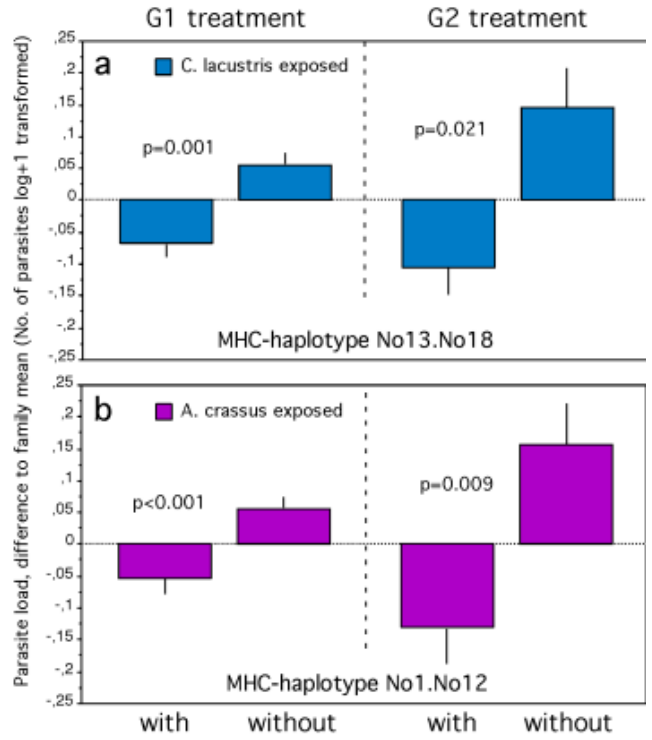

Figure 5: Mean (+1SEM) parasite load as a function of the presence ("with") or absence ("without") of the respective resistance haplotypes (No13.No18 top panel, No01.No12 bottom panel) in G1 and G2 generations. Haplotype No13.No18 confers resistance against *C. lacustris*, while the haplotype No01.No12 confers resistance against *A. crassus*. Parasite load is the difference between the average individual infection with and without the resistance haplotype to the average infection within its family. If values are negative, infection is lower than the average family infection whereas if values are positive, infection is higher than the average family infection. Blue bars represent 13 segregating fish families exposed to *C. lacustris* and purple bars represent 12 segregating fish families exposed to *A. crassus* [67].

Conclusion

Vertebrate hosts and their parasites are involved in a co-evolutionary arms race according to Red Queen dynamics. Mate choice of hosts adjusts the optimal mix of different *MHC* alleles in every generation anew according to the change in prevalence of infectious diseases. Because of high standing variation, i.e. usually more than 1000 *MHC* alleles exist in vertebrate populations, the *MHC* allele providing resistance usually exists in some potential partners that need to be chosen to provide the offspring with the required resistance. Females approach a partner that offers by olfactory signaling the optimally complementary mix of *MHC* alleles and select the males that signal with costly ornaments to be healthy, thus likely to possess the *MHC* allele that provides resistance against the currently dominating infectious disease. Different habitats differing in their parasite community select for different set of *MHC* alleles that provide resistance against local parasites leading finally to speciation.

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