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The Hypothesis of Immune Testing of Partners—Coordinated Adaptations and Changes in Mating Preferences

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Abstract—Reproductive isolation plays the key role in speciation. According to the prevailing ideas, the main speciation mechanism is gradual accumulation of genetic differences in isolated populations (allopatric phase of speciation) based on mutations, selection, and genetic drift. In this case, reproductive isolation emerges as an occasional byproduct of adaptation to different conditions (ecological speciation) or accumulation of random changes in the gene pool resulting from long-term isolation. Pure sympatric speciation assumes isolation as a direct product of selection (divergent or disruptive selection) that favors individuals selectively mating with their likes. A third possibility is substantiated below. We believe that isolation can be a regular and determined product rather than occasional byproduct of divergence. It can rely on the friend/foe discrimination mechanisms, some of which can be "immune-based" and compare the partner's and own properties (signaling molecules, pheromones, and other antigens in a broad sense). Antigens of the major histocompatibility complex (MHC) can play a substantial role in such testing of potential mates.

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The mechanisms of premating isolation (PI) or mating preferences remain largely enigmatic (Kirkpatrick and Barton, 1997; Schluter, 2001). While postzygotic isolation (decreased viability or fertility of hybrid offspring) can be more or less satisfactorily explained as an occasional byproduct of accumulation of genetic changes, which can, for instance, decrease the compatibility between haploid chromosome sets, this explanation is hardly applicable to PI. The effect of PI is mediated by possible adequate mutual perception of mates and involves specific signals triggering or maintaining the mating behavior program in the partners. Note the crucial importance of this particular stage in the formation of isolating barriers between species. It provides for the evolutionary fundamental transition from populations with different ecological adaptations and stable intrapopulation gene flow, which integrates the genotypes into the common gene pool of species, to species with independent gene pools and further evolutionary fate.

Genetics pins great hopes in this respect on the reinforcement mechanism, which should theoretically act in the sympatric phase of speciation, thus, maintaining any changes decreasing the level of hybridization (Kirkpatrick, 2001). At the same time, there was no sympatric phase in experiments initiated in early 1960s on the development of various adaptations and the associated violation of panmixia, so that the reinforcement mechanism does not apply.

These experiments were based on two different approaches—development of adaptations to stress conditions for a given species and disruptive selection on quantitative characters. The resulting lineages were tested for reproductive compatibility. Experiments involved "stress" substrates for aphid *Dysaphis anthrisci maicopica* (Shaposhnikov, 1961, 1965, 1966; Sapunov, 1983) and flies *Drosophila pseudoobscura* (Dodd, 1984, 1989; Powell and Andelkovič, 1983), exposure of *Drosophila melanogaster* populations to contrast (cold-dry-dark and warm-damp-light) conditions (Kilias et al., 1980), artificial disruptive selection on bristle number in *D. melanogaster* (Thoday and Gibson, 1962), and eye stalk size in male flies *Cyrtodiopsis dalmanni* (Wilkinson and Reillo, 1994). In all cases partial PI emerged, which cannot be attributed to the accumulation of some random genetic changes in isolated populations. PI did not appear between isolated lineages incubated under the same conditions and was manifested for lineages exposed to contrast conditions. Clearly, PI induced in these experiments had regular (determined) rather than random nature and was associated with specific living conditions of several tens of ancestral generations exposed to unidirectional selection. Thus, PI is not an occasional byproduct of adaptation to different conditions but rather a determined and regular consequence of it.

The phenomenon revealed in these experiments is clearly observed in nature. This can be illustrated by studies on drosophilids living on different slopes of the "Evolution Canyon," Mount Carmel, Israel. *D. melan-*

ogaster populations living on different slopes at a distance of as low as 100–400 m (i.e., within several minutes of flight) demonstrate significant mating preferences to avoid partners from different slopes. At the same time, no preferences for different isofemale lines from the same slope were observed. The conditions on both slopes are extreme for *Drosophila* and significantly differ since the south-facing slope receives 6 times more solar radiation compared to the north-facing one (Korol et al., 2000).

A similar situation is observed in representatives of gammarid amphipods, whose populations live on different substrates (different algal species). These substrates can be quite close in nature so that crustaceans can migrate between them (but prefer not to). Representatives of different populations demonstrate clear preference for mates from their own population. Experiments with Y-shaped maze demonstrated that gammarid males significantly preferred females lived in nature on the same substrate (N.S. Mugue, Institute of Developmental Biology, Russian Academy of Sciences, personal communication).

Rapid emergence of reproductive isolation at diverging ecological parameters seems to be typical not only for arthropods, although not much data for other groups are available. This is due to the complexity of such experiments as well as to the inability to determine the duration of isolation in natural partially isolated populations. Still, sometimes this problem can be solved. For instance, partial reproductive isolation was demonstrated for two populations of sockeye salmon (*Oncorhynchus nerka*) that radiated from the common ancestral lineage after 1937, when it was introduced into Lake Washington (United States) and soon formed a large local population in the Cedar River flowing into the lake. In 1957, a fraction of individuals was shown to spawn in the lake rather than in the river. In 1992, the river and lake forms represented partially isolated populations with slight morphological differences. Representatives of different populations mated notably less frequently than could be expected from simple probability considerations. In this case, reproductive isolation developed within at most 56 years roughly corresponding to 13 generations (Hendry et al., 2000).

HYPOTHESIS OF IMMUNE TESTING OF PARTNERS

We believe that the amazing coordination between ecological adaptations and changed mating preferences in the above-mentioned cases can hardly be realized through different mechanisms. There seem to be a common mechanism underlying the changes in mating preferences corresponding to quite diverse ecological adaptations. The appearance of endogamy was observed in all considered cases when like "friends" are preferred to unlike "foes." This requires a tool to distinguish friends and foes.

The problem of coordinated changes in the "signal" and "receptor" in changing mating preferences. The assumed common mechanism would seem to provide changes in some aspects of premating behavior in both males and females and these changes should be strictly coordinated in both sexes. For instance, a changed style of male courtship should be matched with a correspondingly changed female's preferences for this new courtship style, or changes in the pheromones should be matched with adequate changes in the pheromone receptors (Kirkpatrick and Barton, 1997). It seems highly unlikely that such complex and coordinated transformations could occur as a result of random mutations and selection within one or two tens of generations as observed in the above experiments. Unlikelihood of such assumption is further corroborated by the absence of selection factors specifically targeted to premating ritual or mating preferences.

Apparently, the observed coordinated shift of mating preferences during adaptation to new conditions occurred rapidly, smoothly, inevitably, and determinedly—in short, automatically. As we learn new facts, this automatism seems more and more embarrassing and encourages vague reasoning about possible linkage of genes responsible for ecological adaptations and mating preferences, about concerted mutations, etc. (Korol et al., 2000).

Possible immune-based automatic coordination of changes in the "signals" and "receptors." At the same time, there is a simple mechanism that can provide for such automatism. This mechanism relies on the involvement of the immune system components in the friend/foe discrimination.

All multicellular animals have special cells and molecules discriminating self and foreign antigens. In vertebrates and possibly many other animals, an initially large set of cells producing recognition molecules is reduced to eliminate those producing the molecules recognizing self antigens in early ontogeny. As a result, the adult animal possesses a set of recognition molecules binding a great set of foreign (but not self!) antigens (Burnet, 1959; Galaktionov, 1995). Thus, the immune system is a highly efficient tool to discriminate between friends and foes.

A group of individuals adapting to changing conditions usually benefits from limiting the flow of external genes, since such flow blurs the adaptation and introduces hybrid offspring with reduced viability. Immune testing (IT) of potential mates can be an optimal solution of the problem for representatives of any diverging populations.

Such IT can be proposed during premating ritual. In this case, specific sets of antigens released onto the skin surface and/or to the environment provide for a more or less complete description of their physiological and biochemical state. These antigens are perceived by a potential partner and immune-tested, possibly, involving MHC antigens. An optimal number of antigens identified as foreign increases the partner's appeal, while their too high or low number has an inverse effect.

According to the proposed immune hypothesis, isolation in the above-mentioned experiments is not mediated by new isolating mechanisms and requires no new formations at all. We see an ancient mechanism developed in animal ancestors millions of years before the experiment. The main advantage of this hypothesis is that it exhaustively (and simply) explains the most complex problem of the strictly coordinated changes in mating signals and their receptors (preferences) indispensable to rapid establishment of a new endogamous group, while it is hardly explicable in terms of classical views.

The hypothesis allows us to consider reproductive isolation not as an occasional byproduct of adaptation to different conditions (or any other physiological and biochemical changes, e.g., induced by a genetic drift or mutations) but rather as a regular and determined result of these changes. The hypothesis notably extends the possibility of speciation in general by introducing a general mechanism to decrease the blurring flow of external genes to any group of conspecifics deviating from other ones by any biochemical parameters (irrespective of factors that induced this deviation). Such mechanism is particularly useful when contrasting conditions requiring mutually exclusive adaptations exist in the immediate vicinity as in the case of opposite slopes of the Evolution Canyon, where virtually isolated *Drosophila* populations developed (Korol et al., 2000).

Receptors of mating signals do not need to be components of the proper immune system. These can include their modifications or other molecular receptors, however, developed using the same rules, which can be reduced to two main variants: (1) direct replica yielding a polypeptide complementary to the specific antigen, and (2) inverse replica yielding a set of polypeptides with potential affinity for various antigens except their own.

Essentially, the system cannot be completely innate but rather should be formed (or at least adjusted) during the whole body life in both cases. Only such intravital adjustment of the system of mating signal receptors can provide for automatic coordination between their changes and changes in the proper signals. Direct interaction between components of the autoimmune system and olfactory receptors in mate testing has been recently confirmed in vertebrates.

IMMUNE TESTING, CHEMORECEPTION, AND MATE SELECTION IN VERTEBRATES

Many animals use chemosensory receptors (olfactory, vomeronasal, and taste) to select mates. The problems solved by the chemosensory and immune systems are generally similar: they examine a great variety of molecules both self and foreign (Rodriguez, 2004). Hence, both systems face the problem of receptor diversification. The immune system in vertebrates solves this problem largely by somatic diversification (combinatory rearrangement of genes and somatic mutations). The chemoreception system largely prefers genomic diversification (amplification of chemoreceptor genes in the germ line).

Genes of chemoreceptors are very numerous and diverse in mammalian genomes and can amount to 1% of the whole genome (Mombaerts, 1999). About 1500 genes presumably coding for various chemoreceptors (including about 1000 active ones) were identified in the mouse genome; a similar diversity is observed in other mammals (Young et al., 2002). The structure and functioning of these receptors let alone the mechanisms of expression control of the corresponding genes and splicing of transcribed RNAs remain underexplored (Sullivan, 2002; Young et al., 2003). Nevertheless, currently available facts point to possible realization of the immune patterns in the formation of individual set of olfactory receptors in mammals. First, this is the one cell (neuron in this case), one chemoreceptor dogma (Rodriguez, 2004), which resembles the situation in the immune system (one B cell clone, one specific antibody; or one T cell, one antigen-specific T cell receptor). Second, genes of different olfactory receptors can demonstrate sharply different expression levels (up to 300 times) in the olfactory epithelium of the same individual (Young et al., 2003). This suggests the presence of analogs of the clonal selection mechanism that also provides for sharply different levels of receptor molecule expression. Third, highly active alternative splicing takes place during the expression of these genes (Young et al., 2003). The latter is particularly important since it can point to the mechanisms of selecting the structure of receptor molecules for adaptation of the individual set of chemoreceptors to particular environmental or internal factors. This can form the basis for both olfactory imprinting, discrimination between familiar (including self) and unfamiliar odors, and immunity-based *de novo* formation of specific receptors complementary to self or foreign key antigens (signaling molecules). Finally, similar to MHC proteins and cell adhesion molecules (CAM) containing C2-type immunoglobulin domains, chemosensory receptors are involved in the homing function for axons of chemosensory neurons in the corresponding brain sections (Mombaerts, 1999; Key and John, 2002; Oliveira et al., 2004).

The deep relationship between the chemoreceptor and immune systems is essentially confirmed by the linkage of MHC and olfactory receptor clusters in the genomes of many studied animals (Jordan and Bruford, 1998; Amadou et al., 2003). This assumes a coordinated expression control and functional relationship between these genes.

Very recent data allow us to consider this assumption experimentally confirmed. Thus, mouse vomeronasal epithelium demonstrated coordinated combinatory coexpression of olfactory (vomeronasal) receptor genes and MHC genes; moreover, their products form joint receptor complexes (considered in detail below in the section about the vomeronasal organ).

These facts together with recent data on the expression of olfactory receptor and heavy chains of MHC class I genes in spermatozoa formed the basis for the "sperm-receptor-selection" hypothesis (Ziegler et al., 2002). This justified hypothesis assumes a purely immune mechanism of formation of individual olfactory receptor set expressed on the spermatozoon surface. According to this hypothesis, genes of heavy chains of MHC class I and olfactory receptors, including vomeronasal receptors V1R, linked to the MHC cluster, are expressed during spermatogenesis. Transcribed genes of olfactory receptors are subjected to alternative splicing to select those not binding to self MHC class I proteins (present in the same cells). These receptors are further expressed in mature spermatozoa (or spermatozoa expressing correct receptors after alternative splicing are selected for further maturation). As a result, mature spermatozoa have the set of olfactory receptors not binding self MHC proteins but recognizing foreign MHC proteins in the female genital tracts. Ultimately, this helps the spermatozoon to find and fertilize the egg but only if the female has a different set of MHC class I allelic variants. Indeed, a negative correlation between the probability of successful fertilization and the degree of genetic relationship between parents has been demonstrated for some animals (vertebrates and insects) (Markow, 1997; Kraaijeveld-Smit et al., 2002).

Thus, the mechanism of formation of individual set of chemoreceptors in spermatozoa mediated by MHC molecules is substantially similar to the mechanism of formation of individual sets of T cell receptors. Similar mechanisms can also underlie formation of individual sets of receptors in the olfactory and vomeronasal epithelium (immune selection of chemosensory receptors). This possibility is indirectly confirmed by the presence of numerous stem cells with properties identical to embryonic cells in the olfactory epithelium and by neurogenesis actively going there throughout the whole life and intensified under stress (Feron et al., 1999).

Chemoreception and mate selection. Let us consider some cases of chemoreceptor identification of conspecifics and potential mates in mammals. Some of these cases can confirm the involvement of immune mechanisms in the friend/foe identification in higher vertebrates.

It is common knowledge that many animals can distinguish friends (relatives) and foes by smell. This is also true for humans (Stricker, 2000). For instance, humans can determine the sex and relation degree of other individuals by smell (Russel, 1976; Porter and Moore, 1981). In a different experiment, probationers compared smells of mothers and their children, couples, and unrelated pairs all unfamiliar with probationers. The smells of mothers and their own children were significantly identified as similar, while those of individuals with no blood relationship (including couples) were considered as different (Porter et al., 1985). Use of individual olfactory information for mate selection can be exemplified by experiments on pygmy slow loris *Nycticebus pygmaeus.* Exposure of loris female to urine of a particular male sharply increase its chances as a mate (Fisher et al., 2003). This can be attributed to olfactory imprinting realized by both the nervous system and modification of individual set of chemoreceptors, possibly immune-based.

The relationship between mating preferences and certain immune indices, particularly, allelic state of MHC genes, has been experimentally confirmed in mammals. An organism with heterozygous MHC genes is thought to recognize a wider range of antigens and, accordingly, has a more efficient immune system (Palmer and Palmer, 2001).

In the general case, vertebrates prefer partners with a different MHC allelic state. Such selectivity can be related not only to a more efficient immune system in the progeny. Negative assortativeness of crosses by MHC can also be targeted to avoid inbreeding and to provide for the highest offspring heterozygosity (Wedekind and Furi, 1997). The key role in the evaluation of the partner's MHC allelic state can belong to peptide ligands of MHC present together with MHC proteins in the urine, saliva, sweat, and other body discharges (Montag et al., 2001). Each class of peptide ligands of MHC corresponds to a particular allelic variant of a particular MHC gene, and the classes usually differ by only two key amino acids. Hence, an individual set of these ligands carries information primarily about individual allelic state of MHC and secondarily about individual genetic, biochemical, and immune state as a whole (complete sequences of peptide ligands of MHC can be used in this case). The hypothesis about the involvement of MHC in the formation of individual odor (odortype) was first proposed by Thomas (1975) and later confirmed by numerous experiments (Wysocki et al., 2004).

Both male and female mice identify individuals with different MHC locus by smell and usually prefer them as mates (Yamazaki et al., 1988; Jordan and Bruford, 1998). As a result, natural populations produce notably less homozygous mice than could be expected under panmixia (Potts et al., 1991). Similar mating preferences have been revealed in some fish, lizard (*Lacerta agilis*), and bird (*Passerculus sandwichensis*) species (Mays and Hill, 2004).

Similar preferences have been revealed in humans (Milinsky and Wedekind, 2001). In one of experiments, probationers evaluated undershirt smell of other people. Thus, a correlation between the smell rating and matching of MHC allelic states in the probationer and smell carrier has been revealed. Both males and females preferred smells of people with the maximum difference in MHC allelic state from their own. Women taking oral contraceptives were an exception: they conversely preferred the smell of people with a similar MHC state. This can be attributed to a different adaptive behavior of pregnant women: staying with close relatives rather than search for a mate (Wedekind and Furi, 1997; Ober et al., 1997). Similarly, female mice rearing their offspring in communal nests prefer neighbors with a similar MHC allelic state (Manning et al., 1992). In this case, MHC allelic state is important not as an immune system property but rather as an individual genetic marker that allows the relation degree to be evaluated.

Apparently, individual olfactory information used by animals to select mates is not limited to MHC proteins and their peptide ligands. For instance, a group of major urinary proteins (MUPs), used in communication, personal identification, and sexual attraction, has been identified in rodents. These proteins are numerous and variable and the set of MUPs is individual (Beynon and Hurst, 2004). Most likely, these proteins are the key antigens carrying the information about the genetic state of the body that, according to our hypothesis, are presented to other animals for testing. MUPs can bind and release small volatile molecules (such as (R,R)-3,4-dehydro-exo-brevicomin, E,E-alpha-farnesene, E-beta-farnesene, 6-hydroxy-6-methyl-3-heptanone, etc.) with signal functions. In particular, some of these substances act as male pheromones and accelerate female maturation (Brennan, 2004). Recall that MHC proteins also bind various peptides and their set carries individual-specific information. The combinatory variation in expression levels of different MUPs is comparable to that of MHC proteins, while their urinary levels are higher by many orders of magnitude (Hurst et al., 2001).

Widely known Bruce effect consists in a sharply decreased probability of pregnancy when female after mating is exposed to another male odor (Bruce, 1959). In this case, females identify individual males by the set of urinary peptide ligands of MHC (Leinders-Zufall et al., 2004).

It is quite probable that peptide ligands of MHC act as signaling molecules carrying individual information in many other cases, in particular, in mate selection. However, studies of this mechanism of olfactory communication has just started and the role of peptide ligands of MHC in mate selection has been experimentally confirmed only for threespine stickleback (Milinski et al., 2005).

Let us present some other facts indicating numerous manifestations of the triple relationship MHC–chemoreception–sexual behavior. These include synchronized estrous cycle in a group of women exposed to their sweat scent (Jacob and McClintock, 2000); a similar effect in mice exposed to volatile ligands of MUPs (Brennan, 2004); and inhibiting effect of odor of dominant males on pubescence, testosterone level, and testicle size in rodents and primates (Perret and Schilling, 1995; Kaluev et al., 2000).

Vomeronasal organ. Vomeronasal organ (VNO) plays an important role in olfactory communication and identification of personal scents in land vertebrates (tetrapods). VNO essentially differs from the main olfactory epithelium by the capacity to perceive low-volatile and non-volatile molecules such as proteins and peptides in a close contact with the source of odor (Brennan, 2004). Vomeronasal organ can actively draw in air. Unlike land animals meeting difficulties in olfactory perception of non-volatile molecules, fish express the genes typical for VNO receptors V2R (see below) largely in the olfactory epithelium (Speca et al., 1999; Rodrigues, 2004).

Sensory neurons of VNO respond to pheromones and other chemical signals carrying information about sex, social status (hierarchical position of social animals), and individual properties. In particular, VNO is involved in the above-mentioned Bruce effect (Lloyd-Thomas and Keverne, 1982). However, chemical nature of VNO-perceived odorous substances carrying individual information remained unclear until recently.

VNO removal in mammals has no effect on the perception of normal odors but sharply affects social behavior of animals. Amazingly, the vomeronasal epithelium is ultimately formed in late ontogeny—by pubertal period—in contrast to the main olfactory epithelium completely developed soon after birth (Rodriguez, 2004). One can conclude that functional VNO is essential only for adult individuals, which agrees with facts indicating an important role of VNO in mate selection.

Neuroepithelial cells of VNO express specific chemosensory proteins—vomeronasal receptors containing seven transmembrane domains and interacting with G proteins. Vomeronasal receptors belong to two superfamilies V1R (largely expressed in the central or apical vomeronasal epithelium) and V2R (confined to the peripheral or basal regions). Mice have at least 137 and 100 different V1R and V2R receptors, respectively (Brennan, 2004). Apparently, V1R receptors recognize small volatile molecules including pheromones and volatile ligands of MUPs; they are highly sensitive and selective compared to normal olfactory receptors. For instance, V1rb2 is the (possibly only) receptor responding to 2-heptanone pheromone in mice. Neurons expressing this receptors are excited by tiny concentrations of the pheromone while other molecules resembling 2-heptanone induce no response (Zufall et al., 2002). V2R are responsible for perception of larger protein molecules (Cavaggioni et al., 1999). Genes of vomeronasal receptors feature high allelic polymorphism—which is also typical for genes of the immune system. Sets of vomeronasal receptors considerably vary between species. Rodrigues (2004) proposed that evolutionary changes in vomeronasal receptors could considerably influence or even drive speciation. In addition to the vomeronasal epithelium, V1R gene expression was observed in the olfactory epithelium of goat and humans and, amazingly, in developing germ cells in mouse testis (Tatsura et al., 2001). The latter suggests the involvement of these receptors in partner selection at the level of gametes.

Of extreme interest is the coexpression of V2R receptors and H2-Mv family proteins (this family belongs to non-classical MHC class I genes, MHC Ib) including nine genes (*M1, M9, M10.1–M10.6*, and *M11*) (Ishii et al., 2003; Brennan, 2004). Expression of these genes in mice has not been detected anywhere except VNO sensory neurons expressing V2R. MHC Ib proteins form receptor complexes with V2R proteins and beta 2-microglobulin on the membranes of sensory neurons (Loconto et al., 2003). Noteworthily, each V2R receptor is co-expressed with a strictly specific MHC Ib gene (or several genes) (Ischii et al., 2003; Scott, 2003).

H2-Mv proteins have a variable part in the region of the peptide-binding groove, which suggests it can selectively bind peptide ligands. Apparently, these proteins are directly involved in the receptor function in a complex with V2R receptors. However, they lack several amino acids required for peptide binding by MHC class I proteins suggesting a non-classical pattern of peptide binding by H2-Mv proteins (Loconto et al., 2003).

Thus, MHC or proteins with a highly similar domain structure (immunoglobulin domains) and functional properties to the immune system proteins are directly involved in chemoreception. This involvement takes place in the region of chemosensory epithelium that plays the key role in individual odor recognition and regulation of sexual behavior. This is a material argument for the proposed immune testing of mates.

In late 2004, the capacity of neurons in the basal vomeronasal epithelium (those that carry V2R/MHC Ib receptor complexes) to selectively respond to peptide ligands of MHC molecules has been experimentally demonstrated (Leinders-Zufall et al., 2004). The significance of this finding in the context of the proposed hypothesis cannot be overestimated. Previously we only knew that MHC proteins and their peptide ligands carry individual information which can be potentially used for communication and that such information is somehow perceived and accounted in mate selection. Now a real molecular mechanism of such perception has been found. Olfactory (vomeronasal) receptors forming complexes with non-classical MHC proteins on the surface of sensory neurons can perceive it directly through the interaction with peptide ligands of MHC, i.e., with the key components of the immune system of another (tested) individual.

Chemical signals perceived by VNO directly influence social and sexual behavior as well as mate selection (Meredith, 1998; Halpern and Martinez-Marcos, 2003). In particular, nerve fibers go from VNO through the region of hypothalamus responsible for reproductive behavior control and secretion of gonadotropic hormones (Kaluev et al., 2000; Makarchuk and Kaluev, 2000). Hence, immune testing of mates should be considered as a fact rather than hypothesis for mice.

Thus, both main functional units of the system of communication of information about individual genetic status (transmitting and receiving) are tightly associated with MHC components. These are, on the one hand, peptide ligands of MHC class I acting as signaling molecules and, on the other hand, receptor complexes including MHC class Ib proteins.

Amazingly, vomeronasal receptors in studied mice proved capable to respond to both self peptide ligands of MHC and foreign ones, i.e., those for which there are no corresponding MHC molecules. However, the threshold concentration required for neuron excitation was by one order of magnitude higher for self than for foreign ligands (Leinders-Zufall et al., 2004). Such low sensitivity of vomeronasal neurons to self odors can be one of primary mechanisms to discriminate friend and foe at the olfactory level.

Note that the system of olfactory personal identification is quite complex and is not limited to vomeronasal receptors V2R recognizing peptide ligands of MHC. This is confirmed by the experiments on mice with removed VNO. This operation not only reserved their capacity to discriminate MHC-based odortypes but also did not notably decrease this capacity. It follows that the main olfactory epithelium also has tools to discriminate individual odors reflecting allelic state of MHC (Wysocki et al., 2004). In this context, one should mention a valid hypothesis claiming that MHC proteins released from the cell surface can lose their peptide ligands. In this case, their binding sites become vacant and can interact with various small volatile molecules. Together with MHC proteins, such volatile ligands can enter urine and other body discharges, where they can be released again from protein carriers to exert an impact on individual odor. Such volatile ligands can be recognized by the main olfactory epithelium (Singh, 2001; Brennan, 2004).

Effect of degree of relation on mating behavior. One can say that mammals (and vertebrates in general) demonstrate a more pronounced tendency to select unrelated individuals as mates compared to insects. Vertebrates demonstrate more efficient mechanisms to prevent inbreeding. This can be mediated by specific properties of the immune system, which is very complex and efficient in vertebrates (for instance, the structure of MHC clearly favors the development of the preference for different partners and for overall heterozygosity). This can partially explain certain features of evolution of vertebrates and insects (different degrees of endemism, numbers of eurybiontic and polymorphic species, diversity level—mammalian species demonstrate a lower disposition to radiation, etc.). At the same time, the preference of foreign mates is relative; absolutizing this pattern would provoke large-scale remote hybridization and species degradation. The optimal similarity/dissimilarity is clearly the point.

For instance, female threespine sticklebacks evaluate a set of peptide ligands of MHC class IIb released by males and use this information to select mates. However, not the most dissimilar allelic state of MHC is preferred but rather an optimal genetic similarity with that of the female. Both too close (similar) and too remote (dissimilar) sets of peptides are repulsive (Milinsky, 2003). The interaction of the mechanisms of kin selection and heterogeneous advantage crosses at the background of clear predominance of the latter has been demonstrated in natural populations of Atlantic salmon *Salmo salar* (Griffiths and Armstrong, 2001).

It is quite probable that particular conditions (e.g., stress, high death rate in a population, etc.) can shift the optimum immune similarity of mates in vertebrates to prefer kin, i.e., genetically similar individuals, in order to maintain hereditary changes, valuable under specific critical conditions, in the overall genetic pool. Possible changes in the pattern of olfactory perception and the related preferences as a function of conditions is supported by neurogenesis activation in the olfactory epithelium of mammals exposed to stress (Feron et al., 1999).

Generally, it is clear that individual odor (a set of signaling molecules or key antigens) in vertebrates is, first, individual-specific and, second, carries a lot of information about its genetic status. This information can be adequately interpreted by conspecifics and this interpretation involves the comparison of the own and tested statuses. Mate selection often relies on the result of such comparison.

SOME CONSEQUENCES OF THE IMMUNE SELECTION OF MATES

Interaction between the random and directed in evolution. Classical models of evolutionary processes in populations developed within the synthetic theory of evolution (STE) are largely based on the Hardy–Weinberg law and the concept of panmixia—equiprobable mating of all individuals (Hardy, 1908). In this case, evolution is a chiefly stochastic and nondeterministic process (tychogenesis). However, complete panmixia is a random event in real populations. If organisms have a choice of mates and specific highly efficient mechanisms for it (such as immune testing), it is hardly possible that these opportunities increasing survival chances of the offspring will not be used.

Long-term human experience of selection (both unintentional and deliberate) demonstrates that valid selection of mating pairs is a powerful tool to briefly make new animal and plant varieties. Elimination of unfit (or undesirable) individuals is subordinate in this case and is not essential for morphogenesis in the long run except conditions of severe competition for the same resources between the deviating and ancestral lineages. Nevertheless, the secondary role of selection is possible only at the first stage of morphogenesis and species divergence. A clear leading role of selection is manifested in the evaluation of nascent adaptations and in the stabilizing effect on each particular ontogeny, which maintains homeostasis at the levels of the body and population.

Recognition of rational mate selection as an important driving force of evolution can explain many facts of observed directional and determined evolution, which are used to substantiate "nomogenetic" theories.

Narrowing the range of tested antigens. One can hardly imagine that IT is always total (i.e., all or a very wide range of partner's antigens are tested). Such total testing could be the primary and most primitive variant of this mechanism in some groups of multicellular animals. Evolution of different animal groups should narrow the range of tested antigens in order to first of all test the allelic state of loci defining progeny survival. Later indirect mechanisms could develop instead of direct testing of vital antigens. In particular, messengers could appear—special signal compounds, the set of which carries (more or less general) information about allelic state of genes crucial for progeny survival. However, this introduces the problem of adequacy of this information, which becomes particularly acute for nascent alleles (e.g., resulting from mutations).

Ultimately, IT can be reduced to a very simple specialized signaling system including a small set of species-specific signal compounds (pheromones) and the corresponding receptors. Such system is very rigid and can hardly mediate optimization of the species population structure. In this case, any evolutionary changes in the pheromone and receptor should be concerted. Pheromones can carry information about the species, sex, physiological state, phase of the estrous cycle, etc. However, pheromone communication gives almost no opportunity to transmit and analyze detailed information about individual genetic status; accordingly, its functional role is limited compared to IT. The system of pheromones is insufficient for optimal selection of mates based on their individual genetic properties.

The concordance of evolutionary changes in the signals and their receptors can be mediated by the immune formation of the receptors. Mammalian olfactory (including vomeronasal) receptors with great diversity and important role in mate selection are probable candidates for such immune-based specific receptors.

It is early to propose candidates for the elements of the testing system in invertebrates yet; however, the presence of this system has been confirmed by the discovery of adaptive immunity in gastropods (Zhang et al., 2004). The involvement of somatically differentiating FREP immunoglobulins in pathogen identification allowed Eason et al. (2004) to propose widespread distribution of immune testing in all multicellular animals. For instance, series of publications from Mackay laboratory on the genetic analysis of odor-guided behavioral mechanisms demonstrated concerted changes in expression levels of odor receptor genes, immune response, and cell adhesion in isogenic lines of *D. melanogaster* with homozygous smell-impaired mutations (Anholt and Mackay, 2001; Anholt et al., 2003).

Repeated emergence of the same species. Note that the immune mechanism of endogamous group formation can sometimes introduce an unusual event of independent repeated emergence of the same species. This statement looks incredible within the frames of the classical STE. Indeed, if reproductive isolation is an occasional side effect of slow accumulation of random genetic differences, the appearance of each new species should be a singular and absolutely unique event since a long chain of random events cannot be exactly reproduced. It is a different matter if endogamy appears automatically as a regular and determined result of adaptive changes based on the mechanism of premating IT.

Only an incomplete PI has been experimentally reproduced by Dodd (1989). Experimental reproduction of a complete isolation (e.g., by increasing its duration) should confirm independent repeated emergence of the same species. After all, there is no PI between isolated populations adapted to the same stress environment. This is also confirmed by experiments of Shaposhnikov (1961, 1965, 1966) where an experimental population became reproductively compatible with another aphid species, thus, demonstrating a repeated emergence of the species already present in nature.

The key factors of such event clearly include close relations between the initial (ancestral) populations and unidirectional selection (with the only limiting factor evenly affecting all experimental populations).

Optimum level of immune similarity. The immune mechanism of mating preference formation can be clearly complemented by other mechanisms (e.g., different courtship rituals) in evolution. In addition, the optimal level of immune similarity, which is considered as the most attractive, can be shifted. For instance, accumulation of recessive lethal or harmful mutations should shift this optimum towards lower similarity (to avoid inbreeding). This introduces a positive feedback (accumulation of lethals—optimum shift towards less similar partners—increased hybridization and heterozygosity levels—favorable conditions for further accumulation of lethals). Thus, harmful genetic load can be a factor increasing population polymorphism. This can be beneficial for a population since polymorphism favors species stability and adaptability to changing conditions (Severtsov, 2000).

Another factor of the optimum shift towards lower similarity is highly unstable and unpredictable environmental conditions (in this case, the population benefits from high degree of polymorphism). Conversely, stress factors which caused endogamy in the above-mentioned experiments (which could be mediated, among other things, by a shift of the optimum towards higher similarity) were always constant.

Adaptation to stress conditions, degree of homozygosity, and immune testing mechanism. Rapid adaptation to stress conditions, as in experiments of Shaposhnikov (1961, 1965, 1966), Dodd (1989), etc., should clearly increase the proportion of certain key homozygous alleles in a population. The flow of external genes counteracts such homozygosity. It follows that homozygotes for key adaptive alleles should benefit from shifting the optimum immune similarity of mates towards higher similarity. This can be realized automatically in the case of IT. Indeed, the homozygotes have a smaller set of the corresponding antigenic determinants compared to heterozygotes and the set of their testing mechanisms formed as an inverse replica recognizes more allelic variants as foreign. Why "foreigners" appear outside of the optimum immune similarity under stress conditions? The individuals most adapted to stress factors are likely to share similar genetic mechanisms for favorable adaptation, which distinguishes them from other individuals in a population under these conditions. Considering significant changes in the adaptation-related metabolic and signaling cascades and quantitative changes in the range of proteins involved in signaling peptide production (including MHC ligands), such individuals should significantly differ from other ones by the range of presented antigens and should be more fastidious in mate selection in favor of their likes. A similar situation is observed for blood groups and their compatibility: individuals with the lowest diversity of the key antigens (type 0) have the greatest diversity of the corresponding antibodies and are accordingly fastidious about transfused blood (only blood of the same type fits), while individuals with the highest antigen diversity (AB type) are most tolerant in this respect since they have the lowest diversity of the corresponding antibodies.

If we assume that the degree of homozygosity strongly increases during adaptation to unfavorable (stress) conditions, this can explain several facts of emergence or non-emergence of isolation between substrate-specific populations. Frolov (1994) studied substrate-specific populations of similar moth species *Ostrinia nubilalis, O. narynensis*, and *O. scapulalis.* Although different natural populations feed on strictly specific plants (cereals and dicotyledons), representatives of these species randomly mated under laboratory conditions and demonstrated no notable preferences (with one exception discussed below). In this case, sufficient endogamy in populations is maintained by their feeding on different host plants (assortative mating through habitat choice) (Hawthorne and Via, 2001). A similar situation is observed in other insects, e.g., fly *Rhagoletis pomonella*, whose substrate-specific populations (diverged only 150 years ago) are completely isolated due to the attraction of flies to the odor of apples or hawthorn (Linn et al., 2003).

The only exception in experiments of Frolov (1994) was *O. nubialis* populations living on maize in the northern part of the species range. Representatives of these populations preferred to mate with kin and their isolation was observed both with populations feeding on dicotyledons and maize populations from the southern part of the range. According to Frolov, northern maize populations of *O. nubialis* feed on maize leaf tissues at the leaf funnel stage when the tissues are most toxic. The southern populations feed on maize at later stages (paniculation and later) when the toxicity sharply decreases.

Thus, adaptation to stress conditions caused endogamy. Apparently, this property of the northern maize populations of *O. nubialis* is not of great adaptive significance considering that their feeding on different plant species suffices for efficient isolation of populations. Moreover, a non-adaptive pattern of this isolation is confirmed by the independence of its level from the degree of sympatry of populations tested (Frolov, 1994). In this case, endogamy seems to develop as a determined byproduct of adaptation to stress conditions involving neither the direct effect of selection on ethological isolation nor the reinforcement mechanism. An adequate explanation involves an increased homozygosity in these populations in combination with the immune testing mechanism.

In addition, one can propose that the absence of mating preferences between populations feeding on different (but not "stress") plants or even between different species indicates that the range of tested antigens in these insects is relatively narrow and primarily includes antigens with the key role in adaptation to stress environment, particularly, plant toxins. The development of rapid adaptation to plant toxins, representing the main defense tool of plants against pests, played the key role in the evolution of herbivorous insects (V.V. Zherikhin, personal communication). Naturally, alleles responsible for this adaptability became the key antigens tested in mate selection.

In conclusion, the situation in mammals does not essentially differs from that in insects. Formation of endogamous groups on the basis of chemoreceptive mate selection in any case requires concerted (coordinated) changes in the system of signals and in the system of their perception. Random and independent changes can hardly provide for this, particularly, within a short time period. Formation (or adjustment) of the individual perception system involving immune mechanisms, i.e., through ontogenetic selection of a direct or inverse replica of the self key antigens or signaling molecules, is a simple and convenient solution of this problem.

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