COMMENTARY

Adaptive value of novel MHC immune gene variants

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The major histocompatibility complex (MHC) is a core component of the vertebrate immune system and has puzzled immunologists, geneticists, and evolutionary biologists for more than half a century. The so-called classical MHC genes (in humans also called HLA) code for cell surface molecules that present antigens to immune effector cells and thus play a critical role in triggering a specific immune response. Their exceptional polymorphism had been discovered early on (1), but the exact mechanisms that maintain this polymorphism remain enigmatic up until today. Indeed, one of the first and maybe most intuitive mechanisms, proposed as early as 1972 by Walter Bodmer (2), has remained the hardest to prove: the idea that the fitness advantage associated with an MHC allele is negatively proportional to its frequency in the population, because parasites tend to adapt to the more common alleles in a given host population. This mechanism, called "negative frequency-dependent selection" (NFDS), has become part of the core terminology of any essay addressing the polymorphism in the MHC, despite the continuous lack of robust empirical evidence for this process in nature.

Now, in PNAS, Phillips et al. (3) describe an elegant experiment that uses natural populations of freshwater fish (guppies) and one of their native parasites in controlled infections to test one of the core predictions of NFDS. They show that MHC alleles can confer increased parasite resistance when they are introduced into a host population where they were previously not present, supporting the idea that novel MHC alleles can be advantageous and thus confirming one of the pillars of NFDS.

Sixty-five years ago, the brilliant immunologist Peter Medawar noted the following:

> Although there are no factual grounds for supposing that antigenic diversity is anything but an unfortunate consequence of constitutional differences between individuals of a species, yet one is under some obligation to rack one's brains for evidence of any good it might conceivably do. Only thus can antigenic polymorphism be made genetically respectable. (4)

Since then, countless researchers have indeed racked their brains trying to unravel the complex evolutionary dynamics that lead to the maintenance of the exceptional polymorphism in the vertebrate's MHC. Their combined work has certainly succeeded in making this polymorphism respected, to the extent that the human reference genome now contains several alternative reference haplotypes for the MHC region, and that there are entire conferences (e.g., the International HLA and Immunogenetics Workshop and Conference) and journals (e.g., *HLA*) dedicated to its study. All of this effort is largely a consequence of the realization that genetic variation in the MHC region is associated with many more diseases than any other region in the vertebrate genome (5, 6). However, despite all of the acquired respect and dedicated effort, one of the main hypotheses proposed to explain the polymorphism of the resistance-associated MHC genes, while widely accepted on theoretical terms (e.g., ref. 7), has been very resistant to empirical validation itself.

The NFDS hypothesis, sometimes also called "rare allele advantage," assumes that coevolving pathogens are more likely to adapt to common MHC alleles than to rare MHC alleles, leading to decreasing relative fitness of the common alleles over time (8, 9). In consequence, rare alleles gain a relative fitness advantage over common alleles and are thus expected to rise in frequency until they become common themselves. Such initially rare alleles could be either new alleles, originating by mutation of an existing allele or by introgression from another population or even species (Fig. 1, trajectory 1), or old alleles that were once common but became rare because of NFDS (Fig. 1, trajectory 2). Analogously, a common allele that becomes the target of selection by coevolving parasites declines in frequency until it either starts to benefit from the NFDS dynamics again (Fig. 1, trajectory 2) or gets lost from the population altogether (Fig. 1, trajectory 3).

One of the difficulties of observing NFDS dynamics is their time dependence, indicated by the color shading in Fig. 1*A* (see, for instance, the two very different fitness values at intermediate allele frequency). NFDS-like

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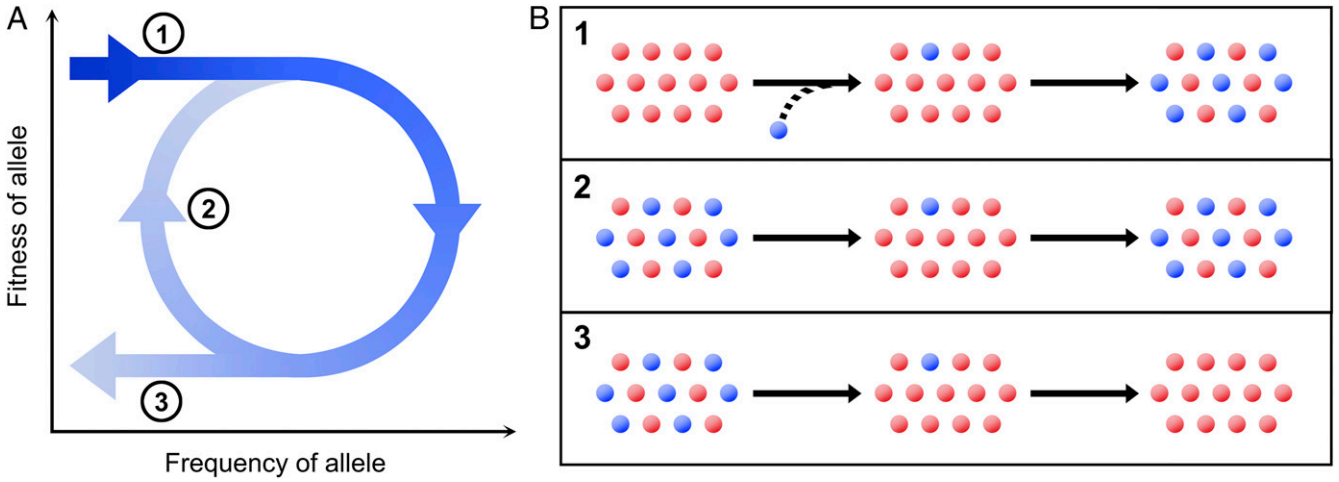

Fig. 1. Allele frequency dynamics under negative frequency-dependent selection (NFDS). A new allele of a parasite-associated host gene enters the population at low frequency, originating either by mutation/recombination of existing alleles or by introgression from another population/species. Under the NFDS hypothesis, it is expected to confer higher fitness than common alleles, because these have been the main target of selection by coevolving parasites, and thus rises in frequency (trajectory 1 in *A* and *B*). Once common, the allele's fitness is expected to decrease again, because it now becomes itself the main target of selection by parasites, resulting in two possible trajectories: Once the allele is rare again, it loses its fitness disadvantage, because parasites adapt to other, more common alleles, and ultimately gains again in frequency, leading to a full cycle in the allele frequency trajectory (trajectory 2). Instead, the allele can also be lost from the population, because of either continuous fitness disadvantage or neutral drift effects (trajectory 3). *A* and *B* depict different perspectives of the same process. The blue color shading in *A* indicates the time dependency of the allele's frequency trajectory under NFDS. In *B*, the black arrows depict the passing of evolutionary time, and the dashed arrow exemplifies an introgressed allele.

dynamics in the context of host–parasite coevolution have been observed in multigenerational studies of invertebrates (e.g., refs. 10 and 11). Equally conclusive evidence for NFDS-like dynamics at MHC genes in vertebrates has been largely elusive so far. Nevertheless, several studies have provided correlative support for NFDS at the MHC, for instance the observation of cyclic dynamics in MHC allele frequencies in a reed warbler population (12) or an advantage of rare MHC variants against HIV infection in humans (13). Recently, a number of studies have provided first experimental support for certain prerequisites of the NFDS acting on the MHC. One study used laboratory mice to show that viruses can quickly adapt to specific host MHC genotypes, leading to higher viral load, and in consequence become less efficient in infecting other MHC genotypes (14). An experiment using sticklebacks as the host species revealed that MHC alleles providing resistance to specific parasites can increase in frequency in experimental populations already over a single generation, supporting the NFDS prerequisite that selection by specific parasites can rapidly change MHC allele frequencies (15). Another experiment on sticklebacks showed a lower cumulative parasite load in carriers of locally less common MHC genotypes, suggesting that at least some parasites are better adapted to locally common MHC alleles (16). However, an experiment that decisively tests whether rare MHC alleles provide higher resistance against established parasites than common alleles, relying on natural levels of genetic diversity and controlling both initial allele frequencies and parasite doses, was still awaited.

The study reported by Phillips et al. (3) targeted specifically this core prediction of the NFDS hypothesis. Their experimental design relies on natural diversity by using hosts and parasites obtained from natural populations (but controlling for host genetic background by using F_2-generation individuals). It also controls for the novelty of the investigated MHC alleles by introducing them from a foreign population (equivalent to the dashed arrow in Fig. 1B, trajectory 1). This guaranteed the novelty of the alleles, as the local parasite could not have encountered it before, but at the same time allowed for a balanced sample size, which is otherwise an inherent problem of studying novel/rare alleles. Using this setup, the authors observe a reduced infection intensity on hosts carrying novel MHC alleles, despite a standardized infection dose. Their work thus provides direct evidence that novel alleles can carry an advantage over alleles that the parasite has encountered before. Given the experimental settings, this translates into a rare allele advantage, as the novel alleles would initially have been rare in a scenario of natural gene flow/introgression, while the established alleles would necessarily be common, given the limited number of fish sampled for the parental generation. The question whether the advantage of these novel alleles would lead to increased frequencies in the next generations could not be tested in this setting, but it seems likely given the significant fitness cost of the studied parasite. Unresolved remains the question of whether the parasite would then in turn adapt to those novel alleles, once they became more common. The ultimate experiment that describes the entire cycle of NFDS (Fig. 1*A*) in the context of MHC–parasite coevolution thus still remains to be seen.

Interestingly, the approach of Phillips et al. to test for the advantage of immunogenetic novelty, by basically introgressing a novel allele into an established host–parasite system, also highlights another intriguing aspect of MHC evolution. While most "novel" MHC alleles in a given population are thought to originate either from point mutations or from intralocus recombination/gene conversion (17), it has been suggested that introgression of novel MHC alleles from distant populations or even species might also contribute to the excessive polymorphism observed (18, 19). While the initial introgression event by hybridization is certainly conceivable, the reason why such introgressed MHC alleles should be maintained in the population is still unclear. One

possibility is that such alleles are highly divergent in their sequence from established alleles, making them subject to overdominant selection through divergent allele advantage (20). It has also been speculated that introgressed alleles might provide an advantage during invasion of a novel environment (18). The work by Phillips et al. (3) now suggests a third explanation by showing that such introgressed MHC alleles can simply be advantageous because they provide the host with immunogenetic novelty against local parasites that are not adapted to them.

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