Models of Host-Parasite Interaction and MHC Polymorphism

In arguing that natural selection at major histocompatibility complex (MHC) loci is frequency-dependent rather than overdominant, SLADE and MCCALLUM rely heavily on previously published theoretical models of host-parasite interactions. While such models can yield valuable insights, it is important to recall that they are based on assumptions which are not necessarily justified for real host-parasite interactions. Here we point out several assumptions crucial to SLADE and MCCALLUM's argument that are not consistent with what we know about the interaction of parasites with the vertebrate immune system.

SLADE and MCCALLUM write that host-parasite interactions "are intrinsically frequency-dependent and dynamic, because transmission efficiency increases with the frequency of susceptible hosts." While this assumption is commonly made in theoretical models, it need not be true in practice. If a particular host genotype is quickly killed by a given parasite, transmission of the parasite will actually be decreased rather than increased. For example, in the case of *Plasmodium falciparum* malaria, a highly susceptible patient who dies in childhood shortly after initial infection may not spread the parasite at all, whereas an individual who remains infected throughout a long life without suffering any serious illness can be a source of numerous additional infections.

In modeling the interaction of a parasite with the host's MHC, it is important to incorporate the basic features of the MHC's function. The MHC encodes cell surface glycoproteins that function to bind foreign peptides and present them to T cells, thereby triggering an appropriate immune response (LAWLOR *et al.* 1990). Note that any given MHC allelic product can bind several hundred different peptides, which have certain sequence characteristics in common (FALK *et al.* 1991). Since allelic products differ in their capacity to bind different peptides, it has been argued that an allelic product that does a particularly good job of binding a peptide from a given parasite should enhance the host's resistance to that parasite (DOHERTY and ZINKERNAGEL 1975).

Therefore, MHC-linked resistance to an infectious disease is expected to be at least semidominant if not completely dominant. This prediction is supported by the finding that a class I MHC allele and a class II MHC haplotype are associated with resistance to *P. falciparum* malaria, whereas no single allele or haplotype associated with susceptibility to this parasite was found (HILL *et al.* 1991). However, in postulating that a particular MHC allele can be "attacked" by a particular parasite genotype, SLADE and MCCALLUM are in effect hypothesizing that resistance to this parasite genotype is a completely recessive trait. Models that make this assumption are not really applicable to the MHC.

Furthermore, the models cited by SLADE and MCCALLUM make the rather curious assumption that an allele that confers resistance to one parasite genotype will invariably be susceptible to other parasite genotypes. In the simplest case, such models postulate a parasite species with a single immunogenic protein encoded by a single locus and a host with a single MHC locus. Initially, we can assume that both host and parasite are monomorphic, and that the one host MHC allele (A_1) is not able to present any peptide from the protein encoded by the single parasite allele (P_1). A new mutant MHC allele (A_2) that can present a peptide from the protein will have a selective advantage and will increase in the population. This in turn will create a situation favoring any new mutant (P_2) that is not presented by A_2. The increase in frequency of P_2 will of course favor any new MHC allele (A_3) that can present it. However, the idea that, when P_2 again becomes rare, A_3 will be at a selective disadvantage in comparison to *A2* depends on the assumption that A_3 cannot present a peptide from P_1 as well as A_2 can. There is no good biological reason for making such an assumption in the case of the MHC. Given the fact that a particular MHC molecule can present hundreds of peptides and that new MHC alleles often seem to arise via rather minor changes in the antigen recognition site (for example the numerous "subtypes" of the human class I *A2* allelic family), it seems more reasonable to predict that often a new allele arises that can bind one or more new peptides without losing the ability to bind the peptides bound by its ancestral allele.

Many models of frequency-dependent selection considered by HAMILTON (1980), MAY and ANDERSON (1990), and others certainly produce cyclic changes of allelic frequencies. However, these models deal with the case of two alleles in one or both of the host and parasite species; and both host and parasite are assumed to be haploid. Therefore, they are not directly relevant to the MHC. In the case of the MHC, new alleles are produced continuously by mutation and interallelic recombination (WATKINS *et al.* 1992), and allele frequencies change by genetic drift as well as selection. There is no reason to believe that allele frequency changes at MHC loci are cyclic.

Of course, careful studies on natural populations will be necessary in order to distinguish between the hypothesis of frequency-dependent selection and that

of overdominant selection. It is worth emphasizing that a true test of the hypothesis of overdominant selection requires studying simultaneously alleles conferring resistance to at least two different parasites (DOHERTY and ZINKERNAGEL 1975; HUGHES and NEI 1988, 1989). These might be separate parasite species or might be strains of a single parasite bearing different alleles at some immunologically important locus. This point was missed by HILL *et al.* (1991); therefore their study did not constitute a test of the overdominance hypothesis (HUGHES and NEI 1992). In the meantime, our reason for preferring the overdominance hypothesis is that there is a plausible biological mechanism, based on what is known of MHC function, that would give rise to overdominant selection (NEI and HUGHES 1991). So far such a mechanism has not been proposed in the case of frequency-dependent selection.

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