EVOLUTIONARY BIOLOGY

# Parasites and polymorphisms

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IT was Haldane's suggestion[1] that there is an evolutionary arms race between hosts and pathogens, one characterized by the host's need for continual adaptation to the coevolving antagonist. In this light, genetic recombination could be advantageous because parasites are believed to adapt primarily to common host genotypes. This so-called Red Queen hypothesis provides a powerful, yet not fully understood, mechanism for the maintenance of genetic polymorphism as found in both plants and animals. The part played by genetic diversity in the coevolution of hosts and parasites was the subject of two interdisciplinary meetings last month*, bringing results together from medicine and theoretical, organismic and molecular biology.

One of the best examples of host evolution in response to a pathogen comes from Africa, where infectious diseases continue to be a major cause of death in human populations. In vertebrates, the highly polymorphic glycoproteins coded by the major histocompatibility complex (MHC) bind foreign peptides in a sequence-dependent fashion, and thereby induce a T-cell immune response against specific pathogens. Evidence for parasite-driven changes in the allelic frequency of MHC genes came from the finding that resistance to *Plasmodium falciparum* malaria in West Africa is associated with a human class I allele, HLA-B53, and an unusual class II haplotype. Both genes are underrepresented in children suffering from severe malaria, and are more common in the overall population than elsewhere in the world, suggesting that selection by malaria has contributed to the increase in frequency of these protective alleles in West Africa[2]. This is in agreement with time-lagged, frequency-dependent coevolution, because it might take many generations for the parasite to evolve an evasion strategy after the host has evolved resistance.

## Complexity

The finding that protection against malaria in East Africa operates with different MHC haplotype associations from those in West Africa highlights the complexity of parasite selection (A. V. S. Hill, John Radcliffe Hospital, Oxford). In particular, it is intriguing that this difference is apparently not due to B53-epitope variation between East and West African strains of *P. falciparum*. The explanation for this spatial variation is probably complicated, as differential selection on MHC genes over time and space is likely to be driven not only by malaria but also by other diseases. The fact that we detect an MHC–malaria association at all underlines the selective strength of malaria in driving host–parasite coevolution.

## Fitness

Differential fitness of host genotypes, as found in the malaria example, might result in a frequent loss of obsolete resistance genes. But because the strong polymorphisms of the MHC and of disease-resistance genes in plants appear to be ancient, a storage mechanism seems to operate to prevent the loss of alleles. The polygene storage concept of Mather[3] suggests that genes can be maintained by keeping them in close linkage, as is the case in both vertebrate (J. Klein, Max Planck Institute for Biology, Tübingen) and plant resistance systems (I. R. Crute, Horticulture Research International, Warwick). Low recombination rates will preserve alleles from extinction, but release them from time to time, and once favourable they might increase again[4]. So during sexual recombination new alleles and gene combinations arise; combinations of linked genes are maintained to some degree, however, facilitating preservation of currently obsolete genes.

In contrast to host evolution, pathogen evolution has been observed since early attempts to select for resistance in crops. But the evolutionary mechanisms involved, and the extent of genetic diversity of parasites, is only beginning to emerge. In Papua New Guinea, polymorphism of merozoite surface antigens of *P. falciparum* was evident in 68 per cent of the infected human population (K. Day, Univ. Oxford). This is probably a result of repeated infections — in areas where malaria is endemic, within-host diversity is correlated with transmission probability, resulting in a variable degree of inbreeding of the sexual state of *P. falciparum*. Similarly, within-host diversity of a trypanosome parasite that infects bumble bees has been found to be unexpectedly high, which is also probably the result of repeated infections (P. Schmid-Hempel, ETH-Zürich).

High frequency of multiple infection is believed to play an important role in parasite evolution[5]. Whereas between-host competition of parasite strains selects for the highest transmissibility, within-host competition selects for survival and reproduction of the parasite. For example, if parasites outcompete each other through rapid reproduction, and if reproduction is correlated with virulence,

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within-host selection for faster reproducing strains will increase parasite virulence and maintain genetic diversity, at the cost of reduced transmissibility (M. Nowak, Univ. Oxford).

To increase survival within hosts, some viruses, such as the human immunodeficiency virus, have evolved high mutation rates. The consequence is the generation of rare genotypes which have temporary advantages in the frequency-dependent race with the host immune response (A. Leigh Brown, Univ. Edinburgh). This high mutation strategy may be disadvantageous to both host and parasites if the within-host competition leads to increasingly higher virulence and rapid death of the host[6]. But it can also generate synergistic evasion strategies of the host immune system, which require epitope variability to operate[7].

High rates of generic change — through mutations, sexual recombination or both — characterize host–parasite co-evolution. Genetic diversity provides the ammunition in this arms race, in which parasites evolve in a constant conflict of within and between-host selection, and hosts are under constant pressure to escape their parasites. Whether or not sex is crucial in this race remains one of the most exciting questions in biology. □

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