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Counting the cost of disease resistance

A well-known fictitious race of predatory alien would always admonish the species they intended to subjugate with the unforgettable phrase 'RESISTANCE IS USELESS'. A recent paper in *Nature*[1] shows that an animal's ability to mount a robust immunological response to incoming pathogens, while being far from useless, may indeed be less than useful in certain circumstances. Evolutionary biologists have suspected this for some time. The central observation fuelling these suspicions is that genetic variation exists among conspecifics in the capacity to repel or control infection successfully. If resistance is useful, in the sense that it contributes positively towards an individual's fitness, then why are some genotypes refractory to disease and others congenitally defenceless? Why does natural selection not fix genes conferring resistance throughout animal populations?

There are numerous explanations[2]: for example, large asymmetries between host and parasite generation times may leave hosts 'lagging' behind pathogens in coevolutionary arms races. Alternatively, substantial genetic variance, for instance due to the effects of dominance, can remain at the limits of artificial selection, and similar constraints might obtain in nature. Nonetheless, a major possibility is that resistance correlates negatively with other important fitness components (a so-called 'cost' of resistance). Consequently, so the idea goes, resistance genes are subject to antagonistic selective forces which conspire to impose an equilibrium frequency somewhere short of complete fixation.

So far, so good. The great problem with the cost of resistance model, however, has been a continuing lack of direct evidence identifying the all-important costs themselves. Recent years have seen a quickening of interest in this problem, and now in an elegant experiment with an insect host–parasitoid system, Kraaijeveld and Godfray[1] add convincingly to a small but expanding body of empirical data in support of the 'cost' hypothesis.

Using the parasitoid wasp *Asobara tabida*, a common biological enemy of several European *Drosophila* species, the authors selected replicate lines of *D. melanogaster* for increased resistance to parasitoid attack. Ovipositing females of *A. tabida* lay their eggs in the body cavity of larval flies. The young wasp then develops within its host, ultimately causing its death. Occasionally, however, a larval fly successfully contains the intruder within multiple layers of immune cells and deposits a dark pigment upon its surface. If this process, known as melanotic encapsulation, is successful, the invading parasitoid is destroyed and the larval fly can develop to adulthood. The dark melanotic capsule remains visible through the fly's abdominal wall so that as an adult, a larva that survives parasitization displays the little black spot like a badge of honour.

Kraaijeveld and Godfray used these spots as the phenotypic marker in their selection regime, choosing only those flies with a melanotic capsule to parent subsequent generations. The response to selection was rapid and substantial. In the original field isolate, *c.* 5% larval flies encapsulated wasp eggs, a figure typical of northern European *D. melanogaster* populations. After eight generations, encapsulation rates in the selected lines exceeded 50%. Aside from confirming the genetic basis of encapsulation ability, the magnitude of this response suggests that in wild populations there may be considerable constraints on the evolution of resistance.

The authors then turned their attention to locating possible costs associated with the resistant phenotype. Comparison of a battery of traits between selected and control lines revealed that at high population densities resistant larvae suffer a significant decline in ability to compete for a limited food supply when measured against a genetically marked 'tester' strain of *D. melanogaster*. According to Kraaijeveld and Godfray, the population densities imposed in these competition assays are frequently encountered by developing larvae in the field. By demonstrating a negative genetic correlation between larval encapsulation ability and competitive performance, these experiments provide hard evidence of a trade-off between resistance to parasitoids and other components of fitness.

Data pointing to a cost of resistance are now accruing in a diverse assemblage of host–pathogen systems. The conditional inferiority of resistant phenotypes has been demonstrated in the interactions of bacteria with bacteriophages[3] and moths with viruses[4] as well as mosquitoes with protozoan[5] and nematode parasites[6]. These latter two results have implications for the successful control of debilitating human diseases – specifically malaria and the tropical filariases, in which mosquitoes act as vector. Eradication programmes based on the release of pathogen-resistant vectors to the field could ultimately prove futile if resistant mosquitoes pay too high a fitness cost in the absence of parasitism[5].

In plant[7] and vertebrate[8] biology, the genetics of resistance mechanisms have been intensively studied. Our understanding of the genetics underlying host resistance mechanisms in invertebrates is less impressive, but progress is being made. In the case of mosquito refractoriness to *Plasmodium* spp., both susceptibility and resistance respond to selection in the laboratory[9] and, more recently, QTL mapping suggests a complex basis to the mode of inheritance of resistance[10]. For some parasitoid systems at least, the genetic basis of resistance may be much simpler. For example, melanotic encapsulation ability of *D. melanogaster* larvae

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infected by eggs of the wasp *Leptopilina boulardi* may be largely dependent on a single autosomal locus with complete dominance of resistance-conferring alleles[11]. Such a situation apparently does not pertain in the experiment reported in the recent *Nature* article[1], where a cross of selected and control lines produced an F_1 showing intermediate levels of encapsulation capacity.

A fitness 'price tag' attached to disease resistance has repercussions in several areas of evolutionary biology, including the study of virulence[12], ecological immunology[13], genetic diversity and coevolution[12] (the rates of which are crucial for parasite models of sex and sexual selection). But Kraaijeveld and Godfray's experiment[1] may indicate the sort of data that will allow progress in a challenging area so far avoided by most evolutionary biologists.

Optimal immunology

Cellular and molecular biologists have accumulated an enormous collection of facts about the diversity of host responses to infection. NeoDarwinism successfully makes sense of a number of equally disparate facts from other branches of natural history. Yet there is currently no evolutionary synthesis underpinning immunology. What generates quantitative variation in responsiveness? When does natural selection favour qualitatively different responses (e.g. behavioural or physiological; specific or non-specific)? It is possible that much of this variation can be understood in terms of the relative costs and benefits of particular resistance mechanisms. Immunological effectors in the vertebrate gastrointestinal tract, for example, are frequently non-specific. They include widespread inflammatory responses and result in drastic changes in gut motility and mucosal structures. In contrast, tissue responses (e.g. in the eye or testes) are typically more specific, localized and often very muted. Is this because the fitness consequences of major trauma in the gastrointestinal tract are smaller than for other organs? Temporarily impaired digestion is probably less harmful than impaired vision or reproductive function[14].

These kinds of answers lie outside the traditional interests (or training) of immunologists, but may have considerable medical and veterinary relevance. To our knowledge, the first coherent case for an optimality approach to immunology was put in a seminal paper by Behnke, Barnard and Wakelin[15]. Amongst other things, they argued that it may not be desirable (or even possible) to produce vaccines capable of eliciting sterilizing immunity against parasites of domestic animals: the fitness costs associated with responses of sufficient efficacy may simply exact too high a price. This reasoning holds for other immunoprophylactic attempts at disease control. Selective breeding to enhance resistance offers a potential solution to increasing levels of drug resistance in the helminth populations of domestic animals. But the economic viability of selective breeding depends crucially on the direction of correlated responses in production traits and, so far, what little evidence we have is mixed[16].

All of this points to the need for comprehensive data of the sort obtained by Kraaijeveld and Godfray on *Drosophila*[1]. In the context of vertebrate immunology, obtaining analogous data may seem a tall order. But the availability of antigen- and germ-free environments, and the existence of pharmacological and genetic technology designed to disable particular components of resistance, may actually make vertebrate work more tractable. And the questions are important: just when resistance is useful is of interest to more than just the fans of Dr Who.

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