Evolutionary genetics

Unravelling gene interactions

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Genome sequencing projects have generated a flood of information about the molecular basis of life. As the catalogue of genes has grown, so too has our understanding of gene function. For example, of the 4,288 protein-coding genes in the bacterium *Escherichia coli*, 62 per cent have been assigned to a functional class[1]. Yet we remain quite ignorant about how these genes work together to create a whole organism. Understanding how genes interact is important in its own right but also has profound implications for evolutionary biology[2].

On page 395 of this issue[3], Elena and Lenski provide the clearest picture to date of the ways in which genes, randomly chosen from throughout the genome, interact to affect fitness. They inserted a known number of transposable elements into random positions of the *E. coli* genome, and calculated growth rate over a six-day period for bacteria with different numbers of mutations. If the function of a gene relies on a complex web of interactions, the effect of a mutation on fitness will depend on which other mutations are present. In this case, evolutionists say that there is 'epistasis' between the genes, because the effects of mutations are not independent of one another. In these experiments, however, the authors found that, on average, each additional mutation slowed the rate of cell division by roughly the same amount, suggesting that epistasis was not present.

Just as one settles into the comfortable interpretation that random mutations affect such different aspects of cell performance that they are effectively independent, Elena and Lenski demonstrate that there are interactions between many pairs of mutations. In an additional set of experiments, they created recombinant *E. coli* with different pairs of mutations and compared them to parental strains carrying each of the mutants separately. In 14 out of 27 cases, the fitness of the double mutant was significantly different from that expected from the product of the single-mutant fitnesses (the probability of observing so many significant differences is $<10^{-11}$). No epistasis was observed on average because the pairs of mutations ameliorated each others' effects about as often as they exacerbated them. This result is remarkable and has a number of implications.

With interactions between fully half of the pairs of mutations, we must re-evaluate the importance of gene interactions. Why would a pair of genes randomly chosen from a genome be sensitive to each other's action? This result cannot be explained by the existence of protective mechanisms that break down as more mutations accumulate (mutations would then only exacerbate one another's effects). Perhaps enzymatic pathways and regulatory networks are longer, more interconnected and more sensitive to structural changes in the cell than is often appreciated.

Indeed, this explanation is consistent with an experiment in *Drosophila melanogaster*, where characteristics such as protein, glycogen and fat content, and body weight and enzyme activities, were examined in lines containing transposable-element insertions[4]. Epistatic interactions were rampant, with insertions often affecting several characteristics. It is also consistent with the observation[3] of great variability in the form of epistasis between pairs of genes, because different epistatic relationships are expected to occur within different enzymatic pathways[5]. The availability of the entire genome of *E. coli*[1] should make it possible to identify the genes affected in such experiments and, for many of them, their putative function. We will then be able to determine more precisely the nature of epistatic interactions.

The observation that genetic interactions are common but highly variable will have an even greater impact on the evolutionary theory of sex and recombination. One of the more popular theories for why sexual reproduction is ubiquitous, despite being a risky and costly mode of reproduction, is that sex allows deleterious mutations to be eliminated more efficiently from a population (the mutational deterministic hypothesis[6,7]). Sex only facilitates the elimination of deleterious mutations, however, when fitness decreases faster than predicted with each additional deleterious mutation, a phenomenon called synergistic epistasis (see Fig.1; refs 8–10). If each additional mutation has less and less of an impact on fitness (antagonistic epistasis), then sex actually hinders the elimination of deleterious mutations. The fact that epistasis was not predominantly synergistic in the new experiments[3] therefore contradicts the main requirement of the mutational deterministic theory for sex. Even if synergistic epistasis were present, sex and recombination need not evolve. Variance in the extent of gene interactions, as found by Elena and Lenski[3], reduces selection for sex and recombination (see Fig. 1; ref. 9). So the absence of synergistic epistasis and the great variance in epistatic interactions observed are double blows to the mutation-elimination hypothesis for sex and recombination.

One might object that, after all, *E. coli* bacteria rarely exchange genetic material[11] and may not be subject to the type of genetic interactions typical of sexual organisms. There is, however, no obvious reason why genetic interactions in sexual eukaryotes should necessarily differ from those in *E. coli* — all cells must perform housekeeping tasks and use similar, often homologous, genes to do so. Perhaps sexual eukaryotes have evolved elaborate protective mechanisms that minimize the effects of a few mutations but fail under the burden of many mutations (resulting in synergistic epistasis). Or perhaps sexual eukaryotes face different metabolic demands compared with bacteria, such that the balance between enzyme pathways is altered and synergistic epistasis is made more common[5]. Studies similar to Elena and Lenski's, but in a number of different species, are needed to determine the nature and variety of genetic interactions — information that is of fundamental importance to both molecular and evolutionary biology. □

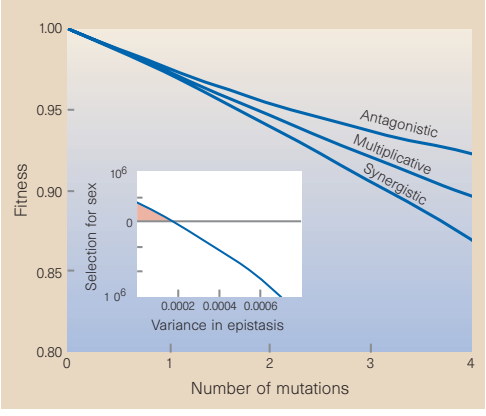

Figure 1 **Fitness versus the number of deleterious mutations. The main figure shows fitness as a function of the number of deleterious mutations under conditions of synergistic, multiplicative and antagonistic epistasis. The inset shows the strength of selection favouring an increased amount of sex as a function of the variance in epistasis (calculated from ref. 9), assuming that, on average, there is synergistic epistasis (necessary for sex to be advantageous). Sex and recombination are able to evolve only when there is little variability in the amount of epistasis (shaded area).**

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