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Minireview

Environmental stress and the effects of mutation

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Abstract

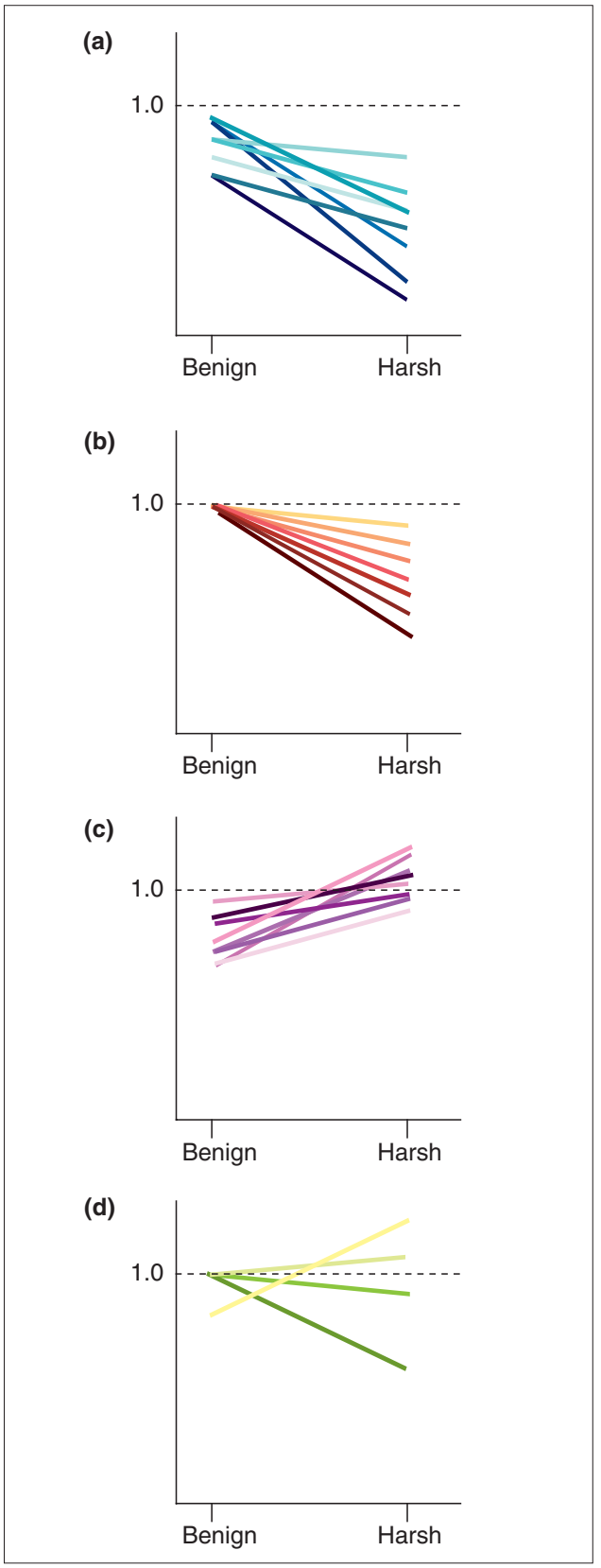
Mutations are the ultimate fuel for evolution, but most mutations have a negative effect on fitness. It has been widely accepted that these deleterious fitness effects are, on average, magnified in stressful environments. Recent results suggest that the effects of deleterious mutations can, instead, sometimes be ameliorated in stressful environments.

When considering how individual organisms and populations evolve, key issues are the genotype of the organism(s), how the genotype is manifest as phenotype and how it contributes to the fitness of the organism(s) under different environmental conditions. One of the basic genetic concepts learned by undergraduate students in evolutionary biology is the 'reaction norm', a mathematical function - usually presented as a graph - that describes the range of phenotypes that can arise from a given genotype in response to variation in the environment. Especially interesting from an evolutionary standpoint is the fitness reaction norm - the range of possible fitnesses in different environments - since it describes the evolutionary potential of an individual in alternative environments. The range of fitnesses seen among different mutant genotypes in a given environment is termed the mutational variance. Examples of hypothetical fitness reaction norms are shown in Figure 1.

Genotype-environment interactions

It is generally thought that the deleterious effects of mutations on fitness will be exacerbated in stressful environments. But new results [1] suggest that in fact the negative fitness effects of deleterious mutations can be reduced in stressful environments. The dependence of the fitness of a particular genotype on the environment may be classified into one of three categories [2]. In the first category (Figure 1a), mutations are unconditionally deleterious across alternative environments because they impair an essential function of the organism. The relative effect of each of these mutations can change and usually increases with the degree of environmental harshness, but they remain deleterious. In the second category, mutations are conditionally neutral (Figure 1b); that is, they are deleterious in some environments but neutral in others, because they affect the organism's match with specific environmental factors. In the third category, mutations are conditionally beneficial (Figure 1c) - deleterious in some environments but beneficial in others.

Unconditionally deleterious mutations are invariably purged from populations by natural selection, under any environmental conditions, so their long-term impact is limited. But conditionally beneficial variation is of great evolutionary significance because it drives ecological specialization in marginal habitats and, eventually, leads to



speciation [3]. Together, the form of the interaction between genotype and environment, the underlying genetic architecture and the pattern of exposure to the relevant environments direct the outcome of evolution [4]. For example, if the fitness reaction norms for a given set of genotypes decrease monotonically with increasing stress, the mutational variance will increase (Figure 1a and, more obviously, Figure 1b). But, if the rank order of the fitness of different genotypes alters across environments in such a way that the slopes of reaction norms are of different sign - for example with some mutations being unconditionally deleterious but others conditionally beneficial (Figure 1d) - changes in mutational variance across environments are unpredictable. In this case, not all reaction norms go in the same direction and if the environment fluctuates spatially or temporally different genotypes may be optimal in each alternative environment, supporting the situation of a balanced polymorphism.

Measuring the effects of stress

Genotype-environment interactions that affect fitness are widespread in nature, and most studies have found mutations that have unconditionally deleterious or conditionally neutral effects in stressful environments [2,5-13]. In a few cases, individual deleterious mutations have been found that have beneficial effects in a more stressful environment [14-16]. But it is not only mutations with a qualitative change in fitness effect that are important: quantitative changes across environments may also have evolutionary consequences. For instance, of the large class of unconditionally deleterious and conditionally neutral mutations, most show aggravated deleterious effects under stress [11,12], leading to their more efficient removal from the population under these conditions. In contrast to this general view, the study by Kishony and Leibler in this issue of *Journal of Biology* [1] suggests a

Figure 1
Hypothetical fitness reaction norms across two alternative environments, benign and harsh, for different genotypes. Each line represents the behavior of one particular genotype **(a)** These mutations are unconditionally deleterious. Changes are observed in the fitness rank order (the hierarchy of fitnesses among the different genotypes), together with an increase in mutational variance (the range of fitnesses seen among the different genotypes). **(b)** These mutations are conditionally neutral. A net increase in mutational variance is observed. **(c)** These mutations are conditionally beneficial. The fitness rank order changes for some mutations, although the mutational variance remains unchanged. **(d)** These different genotypes carry all three types of mutations: unconditionally deleterious, conditionally neutral and conditionally beneficial. A complex situation is illustrated, in which a net increase in mutational variance is accompanied by a change in fitness rank order. In all cases (a-d), the dashed line at a fitness value of 1.0 represents a neutral effect; we assume that a mutation-free genotype has a fitness of 1.0 in the benign environment.

slightly different picture, in which some environmental stresses alleviate rather than aggravate the deleterious effects of average random mutations.

Kishony and Leibler [1] used a chemical mutagen to induce random mutations in the bacterium *Escherichia coli*, and isolated 65 mutant genotypes under permissive conditions over the course of three days, with about one third appearing after the first day (thus avoiding further selection). They then measured the growth rate of the progenitor strain and the 65 mutants in a relatively permissive environment, as well as in seven different stressful environments. In the seven stressful environments, the growth rate of the unmutated progenitor strain was reduced by 35-98% relative to the favorable environment. By using a strain that constitutively expressed luciferase, the authors were able to measure growth at very low cell densities. The stressful environments were classified according to the kind of stress applied: some environments were stressful only for certain metabolic pathways (for example, antibiotics), while others had a broad cellular impact (for example, temperature or pH). Whereas the growth rate of the 65 mutants was on average reduced by 28% relative to the unmutated strain in the favorable environment, this reduction shrank in four of the seven stressful environments (two antibiotics, a reducing agent and low temperature), and became larger only under acidic stress. (The other two stresses did not change the average relative fitness of the mutants.) Thus, contrary to previous findings, this study found that amelioration of deleterious effects, rather than magnification, was common in stressful environments.

Understanding the impact of stress

Why would Kishony and Leibler observe, in general, the amelioration of deleterious mutational effects by stress, whereas others found that stress tends to aggravate these effects? Kishony and Leibler discuss three possible explanations [1]. One is that particular stresses (for example, that caused by antibiotics) would confer an advantage on slowly growing cells. This possibility was immediately refuted by their data, as it would imply a positive correlation between fitness reduction and the level of mutation amelioration by the stress, but such a correlation was not observed. The second possible explanation is that the amelioration is an artifact caused by the mutagenic effect of certain stresses, which obscures the effect of the original mutation(s) under study. The third possibility is potentially the most interesting: that stress and mutation do not always affect the same cellular functions. When stress affects only a single function or pathway, as is true for certain antibiotics, and if growth rate is determined by the slowest of a number of parallel pathways, then a mutant cannot grow more slowly under stress than either the mutant growing under favorable conditions or the wild-type under stress. Hence, the mutational effect under stress would always be smaller than the effect under favorable conditions. While the distinction between stresses that target a specific pathway and those that have broad cellular effects is helpful, the 'parallel-pathway model' used to interpret this distinction is something of an oversimplification. For instance, it relies on the independence of the presumed parallel pathways, but the widespread occurrence of epistasis [17] is not consistent with this notion.

Alternative explanations for the discrepancy between Kishony and Leibler's results and those of others are possible as well. First, the stresses applied by Kishony and Leibler are unusual, from an evolutionary perspective, and different from the kinds of stresses applied in other studies, which instead relied on such stresses as starvation, intensified resource competition, population density or parasitism. Why stress caused by antibiotics, a reducing agent or low temperature might be essentially different from these other stresses is unclear, but this would be worth investigating in future studies. The authors' distinction between stresses with particular versus broad cellular effects may help to direct such studies. A second possible explanation for the discrepancy is that Kishony and Leibler used growth rate at low density as a measure of fitness, whereas others have measured fitness under more competitive conditions [2,5,6,8,9], or even in direct competition experiments [14,16]. Competitive conditions may challenge more functions of an organism than non-competitive conditions, increasing the chance that stress and mutation interact in their effect on fitness. It is unclear why this interaction should be synergistic (such that stress amplifies mutational effects) under competitive conditions, but theoretical work [18] predicts that synergistic epistasis among deleterious mutations depends on competitive conditions.

As an extrapolation from their findings, Kishony and Leibler [1] interpret the amelioration of single mutational effects by certain stresses as evidence for epistasis between multiple deleterious mutations, an issue of broad relevance for evolutionary theory [17]. The authors base their argument on the observed lower decrease in fitness of mutants under stressful conditions than under favorable conditions. If this tendency is extrapolated to mutants carrying multiple mutations, the multiple mutants would have higher fitness under stress than under favorable conditions. The authors found this idea unrealistic and invoked epistasis to avoid the potential for this situation to occur and to preclude the crossing of lines on the graph of fitness reaction norms. Conditionally beneficial mutations have in fact been observed previously [14-16], so the scenario may not be as

unrealistic as the authors suggest; support for epistasis from these data is therefore weak.

In conclusion, the classic view that deleterious mutational effects are magnified under environmental stress turns out to be somewhat naïve. As the number of precise studies of this issue increases, a new and more complex picture arises. Some mutations with deleterious effects across most environments appear to have beneficial effects in other environments [14-16]. In addition, stressful environments appear to sometimes alleviate rather than aggravate the deleterious effects of unconditionally deleterious mutations [1]. Although the reasons for these discrepancies are not known at present, some interesting suggestions have been made that should stimulate further studies. In particular, experiments in which the number of introduced mutations is controlled, the evolutionary history of the strain used is known, and fitness is measured in direct competition with the unmutated progenitor, are needed to improve our understanding of the qualitative and quantitative details of genotype-environment interactions. We believe that microbes are well suited for such studies [19].

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