EVOLUTION

The treacheries of adaptation

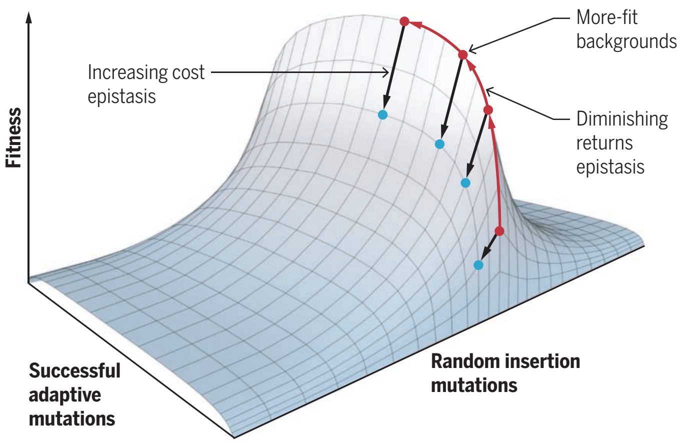
As fitness rises during adaptive evolution, the cost of mutation may escalate as well

By **Craig R. Miller**

One of Darwin's great insights was that he took the widespread observation that organisms are exceptionally well-suited to their environment and turned it on its head. He argued that behind the constructive process of adaptation lies, counterintuitively, a destructive one: Progeny with favorable variations obscure the many progeny who are less well suited and either do not survive or, at best, have fewer offspring. This insight—which Darwin owes in part to Thomas Malthus and shares with Alfred Wallace—is a cornerstone in the theory of evolution by natural selection and raises an important question in biology: What is the nature of the trade-off between the capacity for adaptation and the cost of producing less-fit offspring? On page 490 of this issue, Johnson *et al.* (*1*) find that as adaptation proceeds and fitness gains are expected to diminish, the cost of mutation becomes more severe.

A fitness landscape with two types of epistasis

Disruptive insertion mutations have greater deleterious effects on more-fit backgrounds, called increasing cost epistasis. By contrast, most adaptation experiments show a pattern of diminishing returns epistasis, whereby mutations confer smaller benefit as fitness increases. The different curvatures may reflect differences in how deleterious and beneficial mutations are sampled.



The modern framing of adaptation imagines genotypes as hyperdimensional Cartesian coordinates and fitness as the elevation above them. This gives rise to a fitness landscape that a population must traverse if it is to adapt (see the figure). The landscape metaphor aids visualization of the trade-off. The capacity for adaptive evolution is determined by the curvature of the uphill terrain. This curvature results from how mutations interact, called epistasis. A wealth of microbial evolution experiments (*2*–*6*) suggest that the uphill curvature is usually concave, giving rise to "diminishing returns epistasis" as fitness increases. Thus, the fitness effect of a beneficial mutation is not the same across backgrounds; it gets smaller as background fitness increases. The cost of mutations among offspring is also related to curvature; if the vicinity around a genotype is concave in all directions, the costs will be small and the genotype is considered robust. High robustness occurs when mutations have little effect on phenotype (*7*). Compared to the uphill terrain, the curvature of the downslope terrain has been less well studied in the context of adaptation.

Johnson *et al.* sought to characterize the landscape around genetically distinct variants by estimating the fitness effect of insertion mutations in yeast (*Saccharomyces cerevisiae*). They found that most mutations were deleterious (that is, they reduced fitness) and had larger deleterious effects on higher-fitness backgrounds. They called this pattern "increasing cost epistasis."

Examining mutations individually, they found that most follow the pattern of increasing cost epistasis. A substantial minority, however, either showed the opposite pattern (diminishing costs) or no trend at all. The same backgrounds were previously the subject of quantitative trait loci (QTL) mapping (*8*), whereby genetic differences at tens of thousands of sites are used to find genome locations associated with measurable (quantitative) traits. This allowed the authors to ask how well a QTL model explains fitness effects and compare it to models that include background fitness or both. They found that the QTL model is best for some mutations, the background fitness model is best for others, and, for most, the best model includes both QTLs and background fitness. That QTLs were not consistently the best explanation is surprising because they were very good at explaining variation in quantitative traits (*8*). The implication is that although there is an overarching pattern of increasing cost epistasis, there is also interesting variation at the level of individual mutations. This also suggests that models with mechanistic underpinnings (*6*, *9*) may be more successful than simple models of epistasis (*10*, *11*) in explaining adaptive evolution.

The results of Johnson *et al.* are unexpected because they imply different curvatures of the fitness landscape depending on what type of mutations are tested: Random insertion mutations follow a convex function on fitness, whereas successful beneficial mutations during adaptation follow a concave one (see the figure). Although epistasis scales with fitness in both cases, the relationship is in opposite directions. How can this be? The authors argue that increasing cost epistasis may arise from metabolic flux, whereby a deleterious mutation in a sequential pathway has lesser negative consequences when other enzymes in the pathway have already been adversely affected. If low-fitness backgrounds have less-functional metabolic pathways, disruptions through mutation can do less damage. But this argument, when reversed, is problematic. It implies that beneficial mutations on higher-flux pathways should generate synergies (or convex surfaces)—such mutations are observed (*2*), but rarely. Part of the explanation may be that some adaptive mutations in experimental evolution succeed by disrupting expendable pathways; once such pathways are disrupted, further mutations will be of diminishing benefit. Indeed, beneficial disruptive mutations are not uncommon (*5*, *12*).

The different curvatures may also reflect how mutations are sampled. Insertion mutations disrupt random pathways; if disrupting a pathway is usually detrimental, it will tend to generate increasing cost epistasis. To quote the singer-songwriter

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Townes Van Zandt, "you don't need no engine to go downhill." Conversely, adaptation is biased. When disruptive mutations can confer fitness gains, they will be selected—even if they return only diminishing benefit.

Returning to Darwin's insight and the question of trade-offs in adaptation, the study of Johnson *et al.* suggests that as organisms adapt through natural selection of beneficial mutations, they will concurrently suffer an escalating burden of producing less-fit offspring. The authors speculate that increasing costs, paired with the reality of diminishing gains, may arrest adaptation before a fitness optimum is reached. An important test of the authors' claim will be to assess if increasing cost epistasis is also observed during an adaptive walk, where the genotypes of increasing fitness differ by a far smaller number of mutations. Moreover, it is unclear how often mutation rates will be high enough and beneficial effects small enough

"...as adaptation proceeds and fitness gains are expected to diminish, the cost of mutation becomes more severe."

for the forces to counterbalance. There is also accumulating evidence that some biological features—gene expression patterns and protein stabilization by chaperones, for example—are robust, meaning they have apparently escaped the treacheries of increasing cost epistasis (*7*). This raises the question, how have they done so? ■

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IMMUNOLOGY

Immune cells for microbiota surveillance

Commensal microbes regulate specialized T cells, which promote wound healing in skin

By **Julia Oh** and **Derya Unutmaz**

The immune system has coevolved with the microbial community that inhabits body surfaces and mucosal barriers. Although this commensal microbiota is critical for maintaining healthy host physiology, it can cause pathology when the body surface barriers are breached. How the immune system maintains this homeostasis with microbiota remains poorly understood. Specialized immune cells, called mucosal-associated invariant T (MAIT) cells, specifically recognize and respond to microbial metabolites and are thought to be important in microbial defense, although their function remains unclear. On pages 445 and 494 of this issue, Constantinides *et al.* (*1*) and Legoux *et al.* (*2*), respectively, show that commensal bacteria control development of MAIT cells in the thymus and their expansion within mucosal tissues. The development of MAIT cells depends on a specific developmental window of early-life exposure to defined microbial communities, and a distinct MAIT cell subset in the skin promotes wound healing.

Conventional T cells recognize peptide antigens presented by major histocompatibility complex (MHC) molecules. However, MAIT cells are nonclassical T cells because they are stimulated by nonpeptide antigens—specifically, vitamin B2 precursor derivatives produced by many bacteria that are bound to an MHC-like protein called MR1. Several studies suggest that MAIT cells play an important role in immunity for controlling bacterial, fungal, and viral infections (*3*). MAIT cells have been further implicated in nonmicrobial diseases, including autoimmune diseases, and have potential roles in tumor immunity.

The intriguing paucity of MAIT cells in germ-free (GF) mice, which are reared in microbe-free conditions, suggested that they require an established microbiota to develop (*4*). Constantinides *et al.* and Legoux *et al.* provide extensive evidence that the development of MAIT cells is tightly linked to the availability of the commensal microbial derivatives, which enable both their development in the thymus and further tissue-specific expansion. In mice, the type and timing of microbial colonization also determine the MAIT cell frequencies in tissues. These findings provide further clues about the high variation in the frequency of MAIT cells in humans, which can vary by 40-fold (*5*).

The findings by Constantinides *et al.* and Legoux *et al.* emphasize the role of microbial colonization in early life because they identify a specific developmental window after birth for MAIT cell education in mice (see the figure). In humans, MAIT cells begin to develop in utero, and all newborns are rapidly colonized by a diverse set of commensal bacterial species and strains (*6*). Although many bacterial species are riboflavin-synthesizing, the synthesis of intermediate metabolites that activate MAIT cells may vary in different bacterial species (*7*). Constantinides *et al.* also found that certain bacteria species—such as Enterobacteriaceae, including *Proteus* and *Klebsiella* species—were most efficient in MAIT cell development, although such interactions appear to have local constraints. For example, *P. mirabilis* colonization of both GF neonates and adults was sufficient to induce mature MAIT cells in the thymus but not in tissues. However, it is not yet known how in humans the dynamic nature of the microbiota through a lifetime contributes to the equally dynamic MAIT cell maturation and expansion, which is gradual during early childhood, peaking in early adulthood followed by decline in the elderly (*8*). Thus, in humans, the frequency and tissue localization of MAIT cells at different stages in life are likely determined both by early life imprinting and expansion based on the presence of different bacterial species colonizing the barrier sites.

A key remaining question is how MAIT cells can respond to a diverse set of microbiota and yet discriminate pathogenic microorganisms from commensals. It appears that MAIT cells have acquired diverse functional programs and can tune their outputs by integrating both antigen

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