far-side effect generates heterogeneity on a hemispherical scale, because an impact hits only one side of the planet. Second, portions of the mantle may have been isolated from mixing with the rest of the mantle. Perhaps such a hidden reservoir has existed at the base of the mantle (see the figure). Alternatively, self-gravitating cores may have plunged through the mantle without appreciable emulsification, thus preventing enough metal to mix with the silicate mantle down to small enough length scales for chemical equilibration to occur (*9*).

What is surprising is that such an initial W isotope heterogeneity could be preserved in the mantle today. The mantle source reservoir for the flood basalts is a matter of contention. One candidate is the large low–shear velocity provinces (LLSVPs) at the base of the mantle (see the figure). These regions consist of dense, hot material (*10*) and are thought to be stable at their present antipodal position on the core-mantle boundary close to the equator (*11*). Rizo *et al.* suggest that these regions have existed for essentially all of Earth's history.

Previous analyses of oceanic basalts thought to be derived from deep mantle plumes, including samples from the Ontong Java Plateau, found no ^{182}W excesses (±5 ppm) (*2*). If we accept both studies at face value, then the chemical heterogeneity apparently exists within a single source domain, excluding W heterogeneity created by the far-side effect.

Future studies must first rule out the possibility of analytical artifacts, because several processes may obscure high-precision isotope analyses of W poor samples (for example, lavas), including isotope fractionation in the laboratory, contamination, and interferences. In the end, identifying primitive signatures in Earth's mantle today elucidates the style of Earth's core formation and requires certain parts of the mantle to stay sufficiently buoyant to escape convective mixing throughout essentially all of Earth's geodynamical history. ■

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EVOLUTION

Toward a prospective molecular evolution

Fitness landscapes provide a prospective understanding of chance and necessity in evolution

By **Xionglei He** *and* **Li Liu**

The field of molecular evolution is concerned with evolutionary changes in genes and genomes and the underlying driving forces behind those changes. Current studies in molecular evolution are almost entirely retrospective, with a focus on the mutations that were fixed during evolution, and the conclusions are often explanatory, offering no predictive insights. Because only a tiny fraction of all mutations that have ever occurred during evolution have been fixed, the "successes" that we see today provide an incomplete or even biased understanding of the evolutionary process. One way to circumvent this problem is to obtain the whole fitness landscape of a gene to understand, prospectively, chance and necessity in evolution (see the figure). Two studies in this issue, by Li *et al.* on page 837 (*1*) and Puchta *et al.* on page 840 (*2*), each take on this challenge by characterizing the in vivo fitness landscape of two RNA genes.

"One of the most intriguing aspects of a fitness landscape is...the interactions seen between mutations."

The enormous mutational space of a typical gene poses a considerable challenge to the characterization of fitness landscapes. For example, there are a total of 4^{100} (or 10^{60}) possible variants for an RNA gene of 100 nucleotides, and 20^{100} (or 10^{130}) for a protein of 100 amino acids. The advent of second-generation DNA sequencing goes some way toward addressing this problem. For example, in 2010 a pioneering study used second-generation DNA sequencing to measure the in vitro biochemical activities of millions of variants of a gene (*3*). Li *et al.* and Puchta *et al.* both go one step further than this in vitro study. Li *et al.* generated a library comprising >65,000 mutant alleles of a 72-nucleotide transfer RNA (tRNA) gene of the yeast *Saccharomyces cerevisiae*. They then competed all the yeast strains—each carrying a different allele of the tRNA gene—in a liquid coculture. The frequency of each allele was determined by sequencing the amplicons of the target tRNA gene pool. The increase or decrease in the frequency of a mutant allele relative to the wild-type allele during the competition represents the relative fitness of the allele. In the second study, Puchta *et al.* adopted largely the same strategy and estimated the relative fitness of ~60,000 mutant alleles of a 333-nucleotide small nucleolar RNA (snoRNA) gene, also in yeast. Although the number of mutants they examined is still a small fraction of all possible variants of the genes, most of the possible genotypes that differ from the wild-type by one or two point mutations were characterized. Thus, a high-quality local fitness landscape of a gene has been constructed.

The capability to map large fitness landscapes opens the door to study gene evolution prospectively. Both studies used the landscape constructed to understand the various conservation levels of different sites in the two RNA genes. The same idea could be applied to the study of among-gene differences in evolutionary rate. An outstanding question here is why expression level acts as the most important determinant of sequence conservation (*4*). Mapping fitness landscapes of the same gene expressed at different levels, or different genes expressed at the same level, by manipulating promoter activity would help test many competing hypotheses (*5*).

One of the most intriguing aspects of a fitness landscape is epistasis, or the interactions seen between mutations. Both studies observed widespread epistasis, especially negative epistasis, meaning that the combined deleterious effect of two harmful mutations is greater than that expected from the individual mutations (*6*). Sign epistasis (*7*), where a deleterious mutation becomes beneficial in the presence of another mutation, is of special interest because it can generate fitness peaks that trap an adapting popula-

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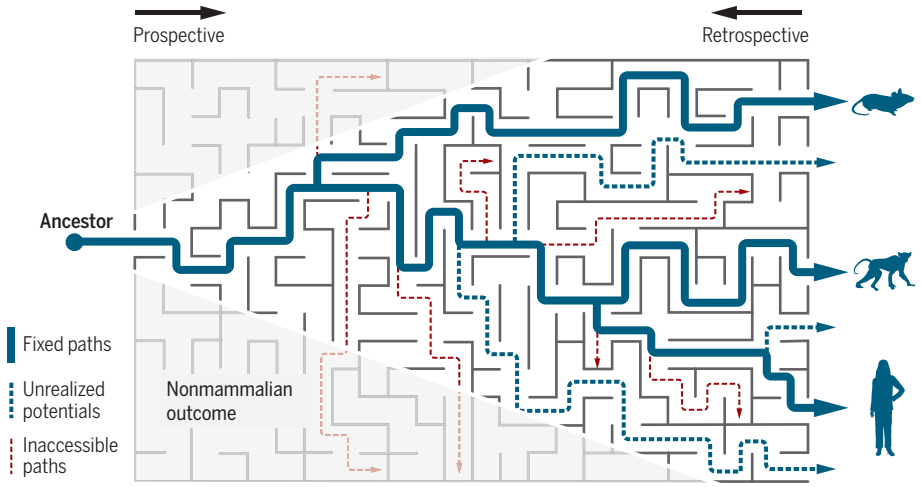

A prospective versus retrospective view of molecular evolution. Current retrospective studies of extant genotypes (e.g., human, monkey, and mouse) provide a necessarily biased and limited understanding of the path of evolution (solid blue lines). Mapping the fitness landscape that confronts the ancestor (shown as a maze) reveals possible paths to either "dead end" local fitness peaks (dashed red lines) or routes to new global fitness peaks (dashed blue lines). Knowing the map of the fitness landscape allows for a prospective understanding of the role of chance and necessity as part of an evolutionary process.

tion moving along the path toward the global fitness peak. Li *et al.* observed 160 cases of substantial sign epistasis, as well as a few dozen cases of high-order epistasis involving more than two mutational sites with opposite signs in different genetic backgrounds. For instance, the interaction of two harmful mutations is negative epistasis when the mutations occur in the wild-type strain, but it is sign epistasis when the mutations occur in a mutant strain. It would be interesting to find out how such roadblocks in adaptation are navigated in nature. A recent study (*8*) showed that antagonistic pleiotropy (*9*), where an allele is deleterious in one environment but beneficial in another, can help a population cross fitness valleys between a local fitness peak and the global fitness peak. This idea can be illustrated with a lock-and-key model for a pair of interacting genes that evolve, say, from genotype A-B to genotype A′-B′. Single mutations (A→A′ or B→B′) would destroy the lock-and-key fit and hence are deleterious in the environment where the fit is required. An environmental change making the fit detrimental would drive the fixation of the first mutation, say A→A′. B→B′ could then follow as a compensatory adaptive change should the environment switch back to the first condition. A more recent study (*10*) using the antibiotic resistance gene *TEM-15* β-lactamase provided another example of how environmental changes help genes cross fitness valleys. Specifically, a mutation that is selected for low antibiotic resistance was found to be a prerequisite for evolving variants of the highest antibiotic resistance. Thus, understanding how different environments can shape fitness landscapes and hence evolutionary trajectories will be of great interest.

Determining fitness landscapes empirically, as Li *et al.* and Puchta *et al.* have done, gives us the power to predict evolutionary trajectories and thus is of immediate practical value, for example, in controlling viral epidemics or preventing antibiotic resistance (*11*). Mapping the complete fitness landscape of a typical gene is presently still an unrealistic goal. Instead, in the near future, we will be able to use local fitness landscapes covering most of the possible genotypes within a few mutational steps of the focal genotype. With the evolution of a target gene (e.g., the hemagglutinin gene of influenza virus), a series of local fitness landscapes with updated focal genotypes could be constructed to keep track—in real time—of the target gene's evolution prospectively. ■

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NEUROSCIENCE

REMembering what you learned

Specific brain activity during REM sleep affects memory consolidation

By **Bernat Kocsis**

Which memories are retained, where, and in what form depends on a long afterlife of the acquired information in the brain. Initial steps of consolidation may be completed within a few hours during wakefulness, but other forms of postacquisition processing take longer, extending into sleep (*1*, *2*). The relationship between brain activity during sleep and memory consolidation remains controversial and poorly understood. On page 812 of this issue, Boyce *et al.* (*3*) demonstrate that a distinct form of hippocampal neural activity, called theta oscillation, is critical for memory formation during the rapid eye movement (REM) phase of sleep.

The two-stage process of memory acquisition and "offline" processing is observed in rodents that experience alternating episodes of exploration and quiet waking, and is also linked to distinct patterns of synchronized hippocampal activity (*1*, *4*). Exploration is characterized by regular theta (6 to 10 Hz) and nested gamma (30 to 90 Hz) oscillatory activity in hippocampal neural networks that are open to new information via cortical input. By contrast, synchronized neuronal activity in quiet waking appears as irregular sharp waves and ripple oscillations, during which processed hippocampal content is transferred to distributed cortical circuits to support memory consolidation. The waking theta-gamma versus sharp wave–ripple dichotomy extends to sleep as the dominant pattern of synchronization in the alternating periods of REM sleep and slow-wave (non-REM) sleep. Extensive evidence supports the role of hippocampal sharp wave–ripple events and related cortical oscillations ("spindles") in non-REM sleep in memory consolidation (*1*, *4*), but the relationship between theta rhythm during sleep and

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