second network that creates the opportunity for the material to adapt to mechanical stress. The second network has much greater slack in its average constituent strand, so it remains fully intact while the first network starts to break. Because the two networks are intertwined, the second network effectively holds the shape of the initial DN gel in place, even as the first network is breaking. The intertwined structure also greatly enhances the toughness of the DN gel, so that far greater mechanochemical response, and subsequent polymerization, can be realized than in a single network alone. The net mechanochemical response leads to soft materials that respond to damage to their underlying molecular scaffold by building both mass and strength at the sites of activation. As in the muscles that inspire the design, this response is localized to the regions of stress concentration, as demonstrated by stamping experiments.

Looking ahead, the demonstration by Matsuda *et al.* offers several opportunities for broadening its scope. For example, the reactive monomer in these systems is simply included in the aqueous content of the gel, but reactive monomers could instead be supplied by flow through a vascular network akin to a circulatory system (*5*). If this supply were regulated, the chemical nature and properties of the added mass could be varied. In addition, the range of mechanochemical responses that is now available extends far beyond homolytic bond scission, offering the potential for even greater control of the polymerization, the range of functional responses, or both (*3*, *6*). Also, because the changes in mechanical properties of the DN gels are localized, there is the possibility for engineering nonlinear adaptive behavior, in which a response in one region of the material makes it either more or less likely for a subsequent response to occur in another region. This approach would create an opportunity for complex, patterned structural evolution of a material with properties that might not have been predicted in advance—a material smart enough to solve problems that its creator could not anticipate. ■

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EVOLUTION

Testing evolutionary predictions in wild mice

An experimental demonstration of a "simple" evolutionary path for camouflage in nature

By **Fanie Pelletier**

Four decades ago, Dougal Dixon used "thought experiments" based on evolutionary and ecological principles in his book *After Man* (*1*), to imagine what adaptations species may develop in a future after humans disappeared. For example, he imagined that pytherons, a group of carnivorous mammals evolved from rats, would fill the ecological niche currently occupied by seals in the polar oceans. Pytheron evolution included fin-shaped limbs and a streamlined body, better adapted for swimming. His book on "speculative evolution" is a reminder that making specific predictions about trait evolution in nature, in many cases, belongs more to science fiction than to science. Indeed, evolutionary ecology has yet to build a predictive framework that allows forecasting how genetically encoded traits may respond to known selective pressures (*2*, *3*). On page 499 of this issue, Barrett *et al.* (*4*) take advantage of recently evolved traits in wild mice (*Peromyscus maniculatus*) with known genetic architecture to experimentally simulate the ecological context and evolutionary forces that may have led to the evolution of differences in coat color according to soil color in Sand Hills, Nebraska.

Evolutionary adaptations are affected by many factors, including mutations, complex selective pressures, genetic architecture, epigenetic effects, and other random processes (*5*, *6*). Recently, however, our knowledge of how genetic architecture and natural selection may interact to affect trait evolution has increased rapidly (*7*, *8*). Despite this progress, predicting the most probable evolutionary path of traits under different ecological scenarios is not a simple task. Our ability to predict how a specific trait will respond to a particular evolutionary pressure in the wild is usually limited (*2*, *9*) and a source of debate (*9*). Yet, laboratory experiments involving microbial and viral systems suggest that evolution should be predictable (*3*). Those contrasting results suggest that without detailed biological knowledge, forecasting evolutionary trajectories remains challenging (*3*, *9*). To succeed, we urgently need studies that use integrative frameworks mapping genetic changes to phenotype, fitness, and

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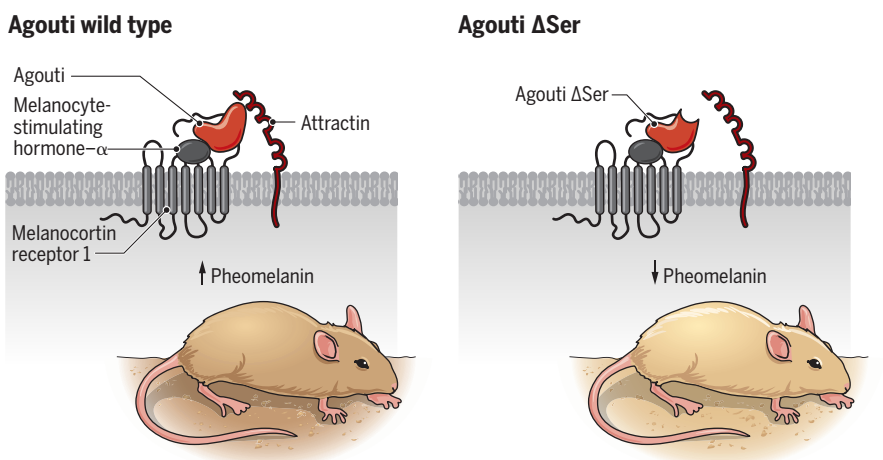
Changing coat color in wild mice

The serine mutation in the agouti protein affects the interaction between agouti and attractin, lowering pheomelanin production and leading to lighter coat color in wild mice inhabiting areas of the Sand Hills with lighter soil color.



GRAPHIC: KELLIE HOLOSKI/*SCIENCE*

demography in nature (*10*–*12*). Barrett *et al.* tackled this challenge through an elegant experiment linking survival of wild mice to a mutation in a gene encoding a protein that affects coat color.

The authors studied populations of mice in the Sand Hills of Nebraska, where habitats show a sharp contrast in background color, depending on soil type. The sand dunes in this region are formed by fine grains of quartz sand that have been shaped by winds over the last 10,000 years. This recent geological formation has substantially modified the landscape and soil color of this area. Classic ecological and evolutionary principles predict that mice with a coat color that matches the soil would be less exposed to predators. Thus, if evolution is predictable—and coat color heritable—local adaptations should evolve, favoring mice with a light coat color on light soil and mice with a dark coat on darker soil.

To test this hypothesis, the authors set up an impressive experiment simulating the evolutionary forces likely at play in this environment. They built eight large enclosures, four on each of the two types of soil color found at Sand Hills, and removed all native small rodents. They reintroduced 75 to 100 mice in six of the eight enclosures. Each enclosure received equal proportions of mice from each of the two habitats with contrasting soil color. Monitoring of individual fates, affected by predation, confirmed the predicted survival patterns. After 3 months, mortality of "unmatched" mice was much higher than for mice with a coat color that matched the soil type, supporting the hypothesis that divergent selection on pigmentation favored local adaptation. This interpretation was supported by changes in dorsal coat color during the experiment. In the "light" background habitat, surviving mice were 1.44 times lighter than the average for mice first introduced in the enclosure. Correspondingly, surviving mice in the "dark" enclosures were 1.98 times darker than average. Observations during the study suggest that predation at night by owls is the likely selective force driving this adaptation.

Beyond demonstrating selection, Barrett *et al.* also document a genetic evolutionary response. Prior knowledge suggested that changes in allele frequencies at the *Agouti* gene locus affected coat color in mice. Thus, they sequenced all individuals introduced in the enclosure to quantify changes in allele frequencies following selective mortality. They found allele frequency changes at the *Agouti* locus consistent with selection. In the dark habitat, random sampling from the initial population could not explain the observed change in allele frequency, confirming that selective processes were at play. The authors then identified a specific mutation causing a deletion of a serine amino acid in the agouti protein that could explain the change in coat color. Mice carrying the mutation have a lighter coat color than wild-type mice. This change in color appears to be due to reduced interaction between mutant agouti and attractin, lowering production of pheomelanin, a yellow pigment responsible for darker coat color (see the figure). Barrett *et al.* then showed that mice carrying the mutation had higher mortality in dark enclosures. This study is important because it firmly establishes in nature the evolutionary trajectory that was expected from evolutionary theory.

This research provides strong evidence that selection on known genetic targets within the *Agouti* locus was sufficient to lead to rapid change in coat color in wild mice. Studies documenting genetic changes in response to selection on very short time scales under natural conditions are valuable, especially given the current debate about whether evolution should be considered in modeling population responses to human-driven environmental changes. Some have argued that on short time scales, changes in allele frequencies are typically unimportant relative to plasticity (the ability of one genotype to produce more than one phenotype in different environments) and can safely be ignored (*13*). However, others recommend that evolution should be considered (*2*, *14*). Reliable evolutionary predictability to forecast the fate of natural populations affected by human-derived stresses remains an elusive goal. An important step will be to determine whether evolution can be predictable for traits with complicated genetic architecture under more complex selective regimes, driven by multiple ecological factors. ■

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BIOPHYSICS

Membrane protein takes the brakes off

An enzyme family has evolved to distort membranes and diffuse quickly to find substrates

By **Michael S. Wolfe**

Proteases are enzymes that use water to break amide bonds of protein substrates. This process—proteolysis—plays a myriad of roles from digestion to cell signaling, and regulation of protease functions are critical to all life forms. A fascinating class of proteases have their water-wielding active sites immersed in the water-repelling (hydrophobic) environment of the lipid bilayer and cleave the transmembrane regions of their substrates. How these intramembrane-cleaving proteases (I-CLiPs) (*1*) carry out this apparently paradoxical process has intrigued biochemists for 20 years. Among the challenges is deciphering how I-CLiPs diffuse through viscous cell membranes crowded with other membrane proteins to find their substrates. On page 497 of this issue, Kreutzberger *et al.* (*2*) find that one class of I-CLiPs, the rhomboid family, diffuses much faster than other membrane proteins, in violation of estimated speed limits for their size. This implies that these membrane proteins have evolved for rapid diffusion to carry out their functions effectively.

The rhomboid I-CLiP family is defined by the presence of a serine amino acid in its membrane-embedded active site, and this serine is directly involved in proteolysis of rhomboid substrates. Among I-CLiPs, rhomboids are particularly well studied because they have yielded more readily to crystallographic elucidation of structure with atom-level resolution (*3*). Moreover, rhomboid structures have been captured in several different conformational states (*4*). Rhomboid I-CLiPs are found in virtually all life forms, and cleavage of their substrates plays a variety of roles, including cell signaling, mitochondrial function, and virulence of certain human pathogens (*5*). Yet,

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