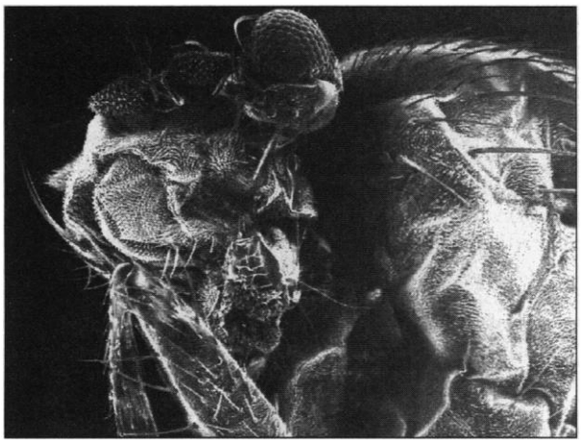
EVOLUTION

Heat Shock Protein Mutes Genetic Changes

When Charles Darwin formulated his ideas about evolution, he did not really understand the source of its raw material: the inherited variation that he saw in plants and animals. And even modern evolutionary biologists struggle to explain how closely related organisms could come to look and act quite differently, sometimes in a relatively short period of time. New work now points to one possible explanation: Genomes apparently have a way of saving up mutations for a rainy day.



Mutations unmasked. Physical abnormalities appear in fruit flies lacking the heat shock protein HSP90.

In the 26 November issue of *Nature*, cell biologists Suzanne Rutherford and Susan Lindquist of the University of Chicago reported findings suggesting that the fruit fly genome contains a hidden reservoir of small mutations. Normally, the researchers find, these mutations are masked by HSP90, one of the so-called heat shock proteins that bind to other proteins to protect them against stresses such as high temperatures and also help newly made proteins fold correctly. But when HSP90 is out of commission, as might happen for example when an organism is under stress and the heat shock protein is tied up in its protective role, it can no longer stabilize mutant proteins and keep them working properly. Instead the mutations are revealed. Usually, they alter physical traits in harmful ways but may in some cases produce changes that help the organism adapt to the stress.

Researchers already knew that some organisms have ways to increase mutation rates in response to stress, generating more genetic diversity for natural selection to act on (*Science*, 21 August, p. 1131). But this is the first clear example of any stockpiling of genetic changes. By permitting the organism to harbor a reservoir of mutations without harm under ordinary circumstances, HSP90 "gives [it] the capacity to evolve rapidly" when circumstances change, says Marc Kirschner, a cell biologist at Harvard University. "The work is really very cool," says Patricia Foster, a bacterial geneticist at Boston University School of Public Health. "It's a wonderful concept."

Rutherford and Lindquist first wondered whether HSP90 might protect individuals against genetic mutations when they noticed that a few percent of fruit flies with mutations that disable the protein had any of a variety of developmental abnormalities: misshapen wings or legs, abnormal eyes, face, or bristles, or other odd physical flaws. The researchers then began breeding experiments to determine the cause of these abnormalities and HSP90's contribution to them.

First they mated flies with similar mutations with one another. Not all the offspring were abnormal, however, and "that pattern indicated that there were multiple genes [involved]" even for a single abnormal trait, such as deformed eyes, says Lindquist. Normal flies resulted when a defective gene in one parent compensated for a different defective gene in the other. In addition, after several generations of mating only abnormal flies, further mating of those defective progeny with flies that make normal HSP90 did not make the abnormalities disappear. This suggests, Lindquist says, that the mutant HSP90 gene did not cause the changes directly. It also indicated that these defects had become so concentrated in the genome that HSP90 couldn't prevent abnormalities from showing up.

It seemed to her, however, that when the flies didn't have too many genetic changes, the normal heat shock protein could mask the mutations—a function that is lost when HSP90 is disabled. Subsequent experiments proved that to be the case. When the researchers fed young normal fruit flies a substance that stifles heat shock protein activity, about 8% more of the resulting adult flies were deformed. But perhaps most intriguing, Rutherford and Lindquist found that even fruit flies with a normal HSP90 gene can develop abnormalities when they are raised in either unusually high or low temperatures, 30 or 18 degrees Celsius, well above or below the 25 degrees Celsius they favor.

Based on these findings, Rutherford and Lindquist conclude that under normal conditions, HSP90 compensates for the small genetic glitches that would otherwise alter the stability and function of the fly's proteins. How the protein does so is still unclear. "It's probably fixing things in a variety of different ways," Lindquist explains. For example, HSP90 might help a protein involved in fly development fold properly even when its amino acid sequence is not quite right because of a mutation. As a result, mutations can accumulate without any apparent effects.

But if HSP90 itself is abnormal, or if unusual temperatures or other stresses deplete the supply of HSP90, then the consequences—either good or bad—of those mutations emerge. "If it happens to be good for the flies, then they [will survive] and can continue to express that trait," Lindquist points out.

This picture expands the role of heat shock proteins and other so-called chaperones that help fold proteins, notes Richard Morimoto, a molecular biologist at Northwestern University in Evanston, Illinois. More than just helping other proteins, these molecules may shape an organism's evolutionary potential. Depending on the context—such as the ambient temperature—HSP90 and possibly other chaperones can radically change the way an organism looks or acts. "It's a way you can dramatically change entire classes or proteins," he suggests.

Researchers have yet to learn whether other heat shock proteins work similarly and whether HSP90 masks genetic change in organisms other than the fruit fly. Morimoto expects the answer to be yes on both counts. HSP90's activity in *Drosophila*, he predicts, "is not going to be unique."

–ELIZABETH PENNISI

CAREER TRAINING

Visa Bill Creates NSF Scholarships

A new law that allows U.S. high-tech companies to hire more foreign workers contains a windfall—and a headache—for the National Science Foundation (NSF). The windfall is a $27 million pot of money for college scholarships and school reform efforts, funded through a $500 fee that employers will pay the government for each visa application to bring in a foreign worker. The headache is figuring out how to set up and operate such a program, which would be a first for NSF.

NSF's new responsibility is spelled out in the American Competitiveness and Workforce Improvement Act, which was wedged into the massive omnibus spending package that Congress approved shortly before it adjourned in October (*Science*, 23 October, p. 598). The scholarships, named after the bill's

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