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

CREDIT: SUZANNE RUTHERFORD

chief sponsor, Senator Spencer Abraham (R–MI), are meant to increase the pool of technologically adept U.S. workers available to fill vacancies at domestic information technology companies. Many of those jobs now go to foreign workers. "We wanted to look beyond the immediate crunch and get at the long-term problem of training more Americans," says an Abraham staffer who follows the issue. "And NSF has a good reputation for running quality programs."

The legislation was a last-minute addition to the bill, which raises the cap on so-called H-1B visas from 65,000 to 115,000 this year and next before dropping back to 65,000 in 2002. The scholarship provision calls for NSF to run a competition that would award up to 10,000 $2500-a-year scholarships to low-income students pursuing associate, undergraduate, or graduate degrees in mathematics, engineering, and computer sciences. The exact income level has yet to be determined. In addition, NSF would receive roughly $6 million to be divided between systemic reform efforts in elementary and secondary schools (see p. 1800) and year-round enrichment courses in science, mathematics, and engineering. The money would be available annually through 2001.

Although they welcome the money, NSF officials are concerned about the administrative burden of a new program. They would prefer to make the scholarships part of NSF's existing stable of programs aimed at strengthening the U.S. scientific labor force, including a rapidly growing advanced technology education initiative at community colleges. "A national scholarship program is a huge undertaking," says Joseph Bordogna, acting deputy NSF director. "We haven't decided anything, but we're hoping to do something that is consistent with what we are already doing."

The closest thing to a scholarship program at NSF now is the agency's graduate research fellowships. But those awards are based on merit, not need, and they go to the institutions that students attend rather than to the students directly. "We're not geared up to run an individual scholarship program, including cutting thousands of checks," says one senior education official. NSF officials are also disappointed that the bill appears to exclude most of the natural sciences, noting that science is increasingly interdisciplinary and that graduates often take jobs outside their academic specialty. Abraham's aide says those restrictions "were a deliberate attempt" to train people for the information technology industry.

Educators at institutions that serve large numbers of low-income students say that the scholarships should help those already planning careers in information technology. But they warn that efforts to increase the flow of students into the field must start much earlier. "They may be interested, but many of our students don't have the skills to pursue the degrees that offer the high-paying jobs," says William Edmonson, president of Panola College, a community college in east Texas with an NSF grant to reform undergraduate science and math instruction. "The foreign students who come here are at a distinct advantage because they've already taken the necessary courses in high school."

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>
> **—William Edmonson**

–JEFFREY MERVIS

NEUROBIOLOGY

Drug May Suppress the Craving for Nicotine

They are tired of the scornful glances of strangers, of shivering in cold entranceways, of the fear they will die from their habit. For these reasons and more, each year 35 million smokers in the United States alone try to quit. But more than 90% start again within a year. Now, new evidence suggests that a drug used to treat epilepsy in Europe may one day help smokers kick the habit.

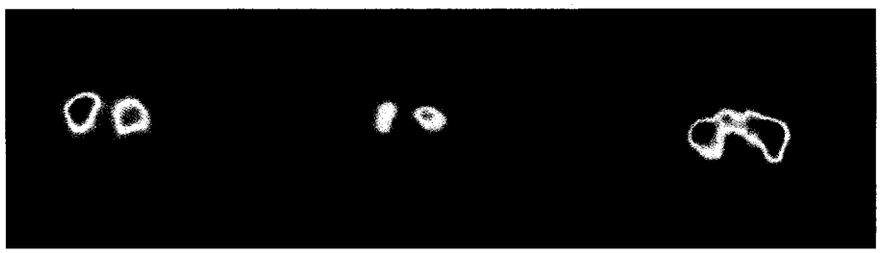
In the January 1999 issue of *Synapse*, neuroanatomist Stephen Dewey at Brookhaven National Laboratory in Upton, New York, and his colleagues report that in baboons and rats, an epilepsy drug called gamma vinyl-GABA (GVG) suppresses a neurochemical hallmark of nicotine and other addictive drugs: a rise of the neurotransmitter dopamine in the brain's "reward centers." It also stops behaviors in rats thought to mirror human cravings for nicotine.

Current smoking cessation aids either deliver nicotine more safely, via patches, gums, or sprays, or combat depression in former smokers. But the Dewey team's work, if confirmed in human studies, may lead to a drug that could help many people stop smoking in a different way: by suppressing their "need" for nicotine and possibly by reducing the "high" as well.

GVG may also have potential as a therapy for cocaine addiction, because the same team reported similar findings for that drug in the August issue of *Synapse*. "These preclinical data are tremendously interesting and provocative," says Alan Leschner, director of the National Institute on Drug Abuse, who nevertheless cautions that further study is needed to determine whether GVG will be a useful—and safe—treatment for addiction.

Dewey didn't originally set out to find an addiction drug. Although not approved in the United States, GVG has been used for years to treat epilepsy in 60 other countries. It works by irreversibly blocking a brain enzyme that breaks down the neurotransmitter γ-aminobutyric acid (GABA), which inhibits neural activity. Thus, brain GABA levels rise, dampening the excessive nerve firing that can lead to epileptic seizures. In 1990, Dewey, psychiatrist Jonathan Brodie at New York University School of Medicine, and their colleagues set out to see whether GVG could also treat schizophrenia. Some of this disease's symptoms have been linked to higher than normal levels of the neurotransmitter dopamine in certain brain areas, and the researchers reasoned that GVG might help by suppressing the dopamine-producing cells.

In 1992, Dewey and Brodie showed that GVG does lower dopamine in a region of the baboon brain. But before pursuing GVG as a schizophrenia treatment, Dewey became intrigued by a Brookhaven colleague's work on drug abuse that focused on dopamine. "I thought, 'I bet [GVG] will work' " to block the dopamine surge caused by addictive drugs, Dewey recalls. This surge is thought to underlie the "high" that keeps addicts coming back for more and



CREDIT: BROOKHAVEN NATIONAL LABORATORY

Craving suppressor? The PET images show the binding of a radioactive drug to dopamine receptors in the baboon brain. Compared to the control (left), nicotine (center) reduces the binding, indicating increased brain dopamine levels, while the drug GVG (right) prevents that effect.