Research on cell-control path gains Nobel

Two U.S. biochemists have won this year's Nobel Prize in Medicine or Physiology for discoveries that led to understanding a process that plays a critical role in cell-protein regulation.

"Their fundamental finding initiated a research area which today is one of the most active and wide-ranging," stated the Nobel Assembly at the Karolinska Institute in Stockholm, Sweden.

Edmond H. Fischer, 72, and Edwin G. Krebs, 74, professors emeritus at the University of Washington in Seattle, will share the $1.2 million prize for work they began in the 1950s and have continued to the present.

Fischer and Krebs made their initial discovery in a study of muscle contraction. They isolated and described a key enzyme in the biochemical process that enables another enzyme within muscle cells to draw energy rapidly from stored body sugars.

This enabling enzyme, one of a class of proteins called protein kinases, later proved to be present in all cell types. Researchers have implicated protein kinases in many critical aspects of cell life, including protein synthesis, cell metabolism, respiration, and hormonal responses to stress. Scientists estimate that as much as 1 percent of the human genetic code holds the programming for protein kinases.

Proteins such as hormones and enzymes perform the essential functions of cell life. In muscle cells, for example, an enzyme called phosphorylase releases stored energy. Biochemists Carl and Gerty Cori won the 1947 Nobel Prize for identifying this muscle enzyme. But a problem remained for biochemists to solve: Just what in muscle cells switches phosphorylase on and off as needed? Fischer and Krebs teamed up in the 1950s to find the answer.

Their solution exposed fertile ground for further biochemical research and ultimately earned Fischer and Krebs their Nobel. The Seattle researchers found that kinases ferry certain chemical subunits, called phosphate groups, from the energy-rich molecule ATP to dormant phosphorylases. The phosphate groups change phosphorylase into an active enzyme, which then breaks down stored sugars to release the energy needed for muscle contraction.

The process works in reverse, too. Krebs and Fischer found that another kind of enzyme, called a phosphatase, strips away phosphate groups, rendering proteins inactive.

This "reversible protein phosphorylation" is a recurrent motif in the complex interplay of proteins that sustains cell life. "Step by step, it has become evident that protein phosphorylation constitutes a fundamental mechanism, influencing all cellular functions," the Nobel Assembly explained in its announcement of the award this week.

Research into the role of phosphorylation has proved medically fruitful. Fischer and Krebs have demonstrated, for example, that the drug cyclosporin blocks the body's immune response to transplanted tissues by interfering with phosphorylation. *— D. Pendick*

Davis Freeman

Edmond H. Fischer (left) and Edwin G. Krebs in a 1983 photograph taken at the University of Washington, where they have worked together for 30 years.

Caffeine: The pain of going cold turkey

It started with a severe headache. Before long, the young woman vomited and began experiencing other flu-like symptoms. "I can only compare that sickness to [last year's radiation and chemotherapy treatment for cancer]," she recalled. "The only difference was that it didn't last as long."

But her "cure" was swift and simple: resuming consumption of the colas and other caffeinated soft drinks she loved.

Physicians know that going "cold turkey" can induce lethargy and headaches among heavy caffeine users. But this "stunning" example "portrays how really incapacitating withdrawal can be" among low and moderate consumers of the drug, notes Roland R. Griffiths of Johns Hopkins University School of Medicine in Baltimore. In the Oct. 15 NEW ENGLAND JOURNAL OF MEDICINE, he and his colleagues document such effects in a study of 62 adults, including this young woman. Half typically consumed caffeine doses equivalent to a cup or two of coffee daily.

After analyzing the volunteers' dietary histories, the researchers prepared two pairs of capsules for each volunteer. One pair contained caffeine tailored to the individual's daily consumption; the other contained an inactive filler. Participants consumed the capsules in Griffiths' lab, taking one in the morning and the second capsule three to five hours later. Neither the volunteers nor the researchers knew whether the capsules administered on any given day contained caffeine. To divert attention from caffeine, researchers instructed volunteers to avoid during the test periods foods that contained chocolate, saccharin, aspartame, and shellfish. They also limited volunteers' drinks to milk, juice, and water.

Thirty or so hours after receiving the first capsule of each pair, participants filled out standard psychological questionnaires designed to assess mood. More than half reported experiencing headaches on the days they went without caffeine, the researchers note. Eight to 11 percent showed signs of depression and anxiety on those days — symptoms that have not previously been associated with caffeine withdrawal, Griffiths says. The occasional flu symptoms may also surprise many physicians, he says.

In an editorial accompanying the research report, John R. Hughes of the University of Vermont in Burlington asserts that these "provocative" data not only suggest caffeine might be considered "a drug of dependence," but also indicate that physicians should rule out caffeine withdrawal before trying to treat patients for headaches, depression, fatigue, or drowsiness. *— J. Raloff*

Death of a Venus pioneer

Planetary scientists mourned an old friend's passing last week. On Oct. 8, researchers lost radio contact with the Pioneer Venus satellite, which finally ran out of control fuel nearly 14 years after it began orbiting Venus — some 11 years longer than expected. Researchers estimate the drum-shaped craft will burn up in Venus' dense atmosphere about Oct. 20.

During its sojourn in the ionosphere of Venus, Pioneer Venus recorded the highest-resolution images of the planet's cloud cover and monitored the atmosphere's circulation pattern. In mapping for the first time 90 percent of Venus' surface, the craft identified mountain ranges, plateaus, and likely volcanoes. It also recorded the ultraviolet spectra of Comet Halley.

As the craft descended last month from the ionosphere to Venus' thick upper atmosphere, researchers calculated that the orbiter might survive until December. But they were fooled by the craft's gas gauge, stuck at an old setting. The craft made history to the very end, skimming 128 kilometers above Venus and recording electronic signals that seem to support previous, controversial findings that it had detected lightning. Pioneer Venus also recorded an unusual ultraviolet glow — a likely sign of its own demise as atmospheric drag began burning the craft. □