Crystallized 'coiled coil' zaps leucine zipper

Forty years ago, a young British physical chemist predicted a structure for an important class of proteins called coiled coils – including keratin, the basic structural ingredient of skin and hair – based on X-ray diffraction data and some fiddling he did with a broomstick and modeling clay. Until then, scientists thought two spiraling polypeptide strands might twist around one another and join together because a ridge formed by one strand fit into a groove in the second.

In his doctoral thesis, Francis H.C. Crick suggested instead that these helical strands snapped together: Knobs of one fit into holes created by the arrangement of amino acids in its partner, forming a protein with tighter connections than the ridge-in-groove configuration would allow. "It was a very reasonable idea, but it was impossible to check out at the time," recalls Crick, now a Nobel laureate and neuroscientist at the Salk Institute for Biological Studies in San Diego.

Now, researchers have determined that the crystal structure of part of a gene-regulating protein in yeast has exactly the shape Crick proposed. Their work, described in the Oct. 25 SCIENCE, verifies Crick's predictions about the structure of coiled coils, says study director Peter S. Kim, a biochemist with the Howard Hughes Medical Institute at the Whitehead Institute for Biomedical Research in Cambridge, Mass.

The new work also clarifies the atomic nature of so-called leucine zippers – stretches of amino acids that bind two proteins into two-molecule complexes called dimers, which regulate gene activity. Confirmation that leucine zippers are actually coiled coils will help scientists understand how these proteins regulate the on-and-off switching of genes, comments Steven L. McKnight of the Carnegie Institution of Washington's embryology department in Baltimore.

"But [the discovery] has much broader implications than just gene expression," McKnight told SCIENCE NEWS. "It's the first structure of a coiled coil protein, and there are many proteins that use this architecture" – proteins not involved in gene regulation.

The leucine zipper usually consists of a short string of amino acids embedded within a long protein. The sequence on this string repeats so that leucine – a water-repelling (hydrophobic) amino acid – shows up in every seventh slot. The sequence spirals in such a way that all of the leucines face outward on the same side of the spiral, explains McKnight.

When two proteins come together, their hydrophobic amino acids tend to face each other. In 1988, McKnight named this hydrophobic section the leucine zipper because he and his colleagues thought the leucines from two proteins lined up in such a way that they interlocked like teeth in a zipper.

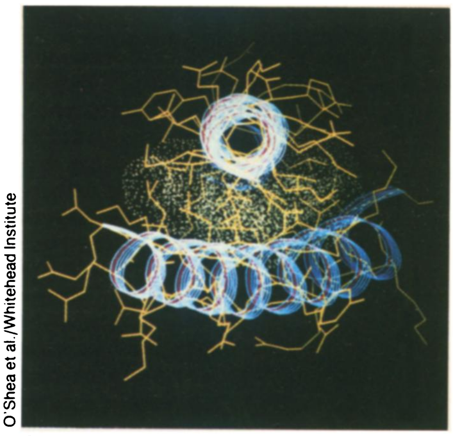
In 1989, Kim's team proposed instead that every third amino acid, and then every fourth one, is hydrophobic – so that amino acids other than leucine are involved.

"It's not a zipper at all," Kim says. Parts of one leucine and three other hydrophobic amino acids in one zipper form the sides of a "hole" into which leucine from the other zipper fits, he explains.

Coiled coils include cell-surface proteins, muscle fibers and structural proteins in bone and hair, but many are so long that they defy crystallization, says Tom Alber of the University of Utah in Salt Lake City, who supervised the crystallography work in the new study.

Erin O'Shea, a graduate student working with Kim, synthesized the 33-amino-acid zipper from the yeast protein. Already, this segment and its crystal structure are helping scientists understand what makes some proteins stay together.

The crystal structure "shows how the amino acid side chains fit in to stabilize the structure," says biophysicist William F. DeGrado, who designs proteins for Du Pont Merck Pharmaceutical Co. in Wilmington, Del. By making systematic changes in the sequence of amino acids, he can control that stability.



O'Shea et al./Whitehead Institute

Computer image of a leucine zipper shows one strand head-on and one twist of another around it. The zipper (stippled) links the two strands.

In addition, researchers hope to gain new insights into the workings of more complex gene-regulating proteins. Sometimes the leucine zipper helps two different molecules link up, says Kim. He, Alber and others plan to study these zippers further to find out why some molecules link up and others do not.

"I'm very pleased," Crick told SCIENCE NEWS. "It's nice to have an idea bear out."

– *E. Pennisi*

Prairie dogs beware: The ferrets are back

Wyoming Fish and Game Dept.

As of five years ago, predators and back-to-back epidemics had all but extinguished the black-footed ferret. With the help of state and federal scientists, however, the species is weaseling its way out of extinction. Biologists rounded up the last surviving community of these ferrets in 1986 to launch a captive-breeding program (SN: 9/6/86, p. 151). Those 18 wild animals provided the 49 juveniles that researchers have just finished releasing into a prairie dog village in Shirley Basin, Wyo.

Resident prairie dogs are already feeling the sting. Weaned on prairie dog meat, the newly released, 10- to 14-week-old ferrets "know how to kill prairie dogs," says Stephen C. Torbit of the U.S. Fish and Wildlife Service in Cheyenne, Wyo. Besides serving as the main source of ferret food, prairie dogs dig the burrows these masked squatters call home.

But the newcomers don't have it easy. Since the ferrets began arriving in September, coyotes and a badger have killed five. Such casualties were bound to occur among animals lacking experience with predator avoidance, Torbit notes. "We had talked about mortality rates after a year – or by next spring – of 85 to 90 percent," he says. Two other ferrets – one with an eye infection, the other injured in a fight with a prairie dog – are temporarily back in captivity for nursing.

Some 260 black-footed ferrets remain in captivity. If the breeding program goes as planned, says Torbit, another 100 youngsters should be available for release next fall.