Gene-Duplicating Proteins Isolated

Like a cook sharing recipes, a dividing cell must copy its DNA — which contains instructions for how to make all of its proteins — and pass the information on to its offspring. But what tells the cell where to begin copying this genetic cookbook? And exactly how does the cell perform the Herculean task of reproducing it?

Roughly 20 years ago, molecular biologists discovered specific proteins that start the DNA-copying process in viruses and bacteria. The proteins bind to a certain stretch of these simple organisms' DNA, which comes in the form of a single circle. Since then, scientists have struggled to understand how higher organisms — whose much larger quantity of DNA comes tightly wound in multiple bar-like structures called chromosomes — copy their genes.

Now, biologists Stephen P. Bell and Bruce Stillman at Cold Spring Harbor (N.Y.) Laboratory have isolated a cluster of proteins that initiates copying of the chromosomes of baker's yeast. At a conference on the cell life cycle held at the laboratory last week, they predicted they will soon find that a similar protein complex initiates copying the genes of other higher organisms, from fruit flies to mice and humans. Compounds that block this process, they add, might prove useful as anticancer drugs.

Earlier this year, Stillman and Cold Spring Harbor researcher York Marahrens identified a set of so-called origin DNA sequences, where DNA replication in yeast begins. In the new discovery, Bell and Stillman have found a complex of seven proteins that binds to these origin sequences, setting the replication process in motion.

Bell and Stillman used a technique called DNA "footprinting" to track down the new proteins. Unlike DNA *finger*printing, which can highlight tiny discrepancies between the genetic material of two individuals, DNA footprinting reveals where proteins stick to DNA. Such DNA-binding proteins usually serve to turn genes on or off.

The researchers treated origin DNA sequences from yeast with an enzyme that chops DNA into fragments. When they sorted the DNA fragments by size on a gel and exposed the gel to photographic film, the different-size fragments showed up as a ladder of dark smears.

At several places in the ladder, Bell and Stillman observed missing rungs. These gaps indicated the presence of DNA-binding proteins, which protected the DNA from cleavage by the enzyme. The researchers, who also report their finding in the May 14 NATURE, named the proteins they isolated ORC, for origin replication complex.

"We propose that this complex initiates DNA replication in yeast," Stillman says. "And . . . we believe that it has been conserved through evolution and appears in the cells of other [higher animals], including humans."

An experiment by two researchers at the Imperial Cancer Research Fund in Hertfordshire, England, has already confirmed the findings of Bell and Stillman. Using a different approach, John F. X. Diffley and Julie H. Cocker reported at the conference and in the same issue of NATURE that they have found the signature footprint of ORC on yeast DNA.

Joachim J. Li of the University of California, San Francisco, who also studies DNA replication, says the discoveries constitute "a quantum leap to a new level" in understanding how the cells of higher organisms copy their genes. He asserts that the findings should enable researchers to work backward and discover what prompts a cell to start replicating its DNA, and to figure out how a cell knows to stop after making only one copy.

Stillman says the discoveries might lead to new types of anticancer drugs, because cancerous cells must replicate their DNA more rapidly than normal cells in order to create tumors. "I don't think it's completely off the wall to think about new protein complexes like this as potential targets for chemotherapies," he says. "It's certainly something that should be looked at by drug companies." — *C. Ezzell*

Mystery gamma rays yield nearest pulsar

For nearly two decades, Geminga — one of the three brightest sources of gamma rays in the sky — stood alone. Unlike the other two sources, associated with the Crab and Vela pulsars, Geminga apparently showed no pulsations and no traces of accompanying X-rays, radio waves or visible-light emissions.

"This was a big mystery for a long time because Geminga could not be identified with anything else at any other wavelength," says astronomer Charles D. Bailyn of Yale University.

Using data collected by instruments aboard orbiting observatories, astronomers have now detected pulsations in Geminga's gamma-ray emissions, allowing them to match Geminga with a weak, pulsating X-ray source and an extremely faint, visible-light source in the same part of the sky. The evidence also suggests that Geminga lies closer to Earth than any other known pulsar.

"With this discovery, we consider the mystery of Geminga largely solved," Jules P. Halpern of Columbia University in New York City and Stephen S. Holt of NASA's Goddard Space Flight Center in Greenbelt, Md., conclude in the May 21 NATURE.

Three sets of observations proved crucial to making the identification. Using data from the orbiting X-ray observatory ROSAT, Halpern and Holt showed that the X-ray source in the same neighborhood as Geminga pulsates with a 0.237-second period. Prompted by this finding, Goddard's David L. Bertsch and his collaborators looked for and found pulsations with an identical period in Geminga's gamma-ray emissions, as detected by NASA's Gamma Ray Observatory.

Finally, a team of scientists in Italy demonstrated that earlier Geminga gamma-ray data also showed signs of this periodicity, but the evidence had been overlooked. From the historical record available, the researchers could deduce that the Geminga pulsar, already spinning less rapidly than the Vela and Crab pulsars, has continued to slow gradually — just as expected for an ordinary, spinning neutron star.

The dearth of radio emissions probably indicates that Geminga's magnetic field points in the wrong direction for Earth-based observers to intercept its signals. Moreover, the pulsar's long period and the absence of a visible supernova remnant suggest that Geminga is significantly older than the much more energetic Vela and Crab pulsars.

"The reason we see it at all at these other wavelengths . . . is that it's probably very close to us," Bailyn says. Astronomers estimate that Geminga may lie no more than 30 parsecs, or about 100 light-years, from Earth. That puts it much closer than any other known neutron star.

Geminga's value to astronomers now rests on its very ordinariness. It's much more typical than the Crab and Vela pulsars. "It's nice that what seemed such a bizarre object fits into the scheme of things so well," Bailyn says.

Theorists have proposed that all pulsars emit most of their energy as gamma rays. They can now use the Geminga gamma-ray data to refine their ideas of how pulsars manage to generate such prodigious outpourings of radiation. — *I. Peterson*