that loss of the protein may have contributed to the cancer development. Other work hints that if the protein is produced, it may end up in the wrong place in the cell. In the 3 November issue of *Science*, Wen-Hwa Lee's team at the University of Texas Health Science Center in San Antonio reported that the BRCA1 protein is located in the nucleus of normal breast epithelial cells, but in the cytoplasm of cells derived from tumors.

Exactly what that means is not yet known, but it suggests that something has gone wrong in *BRCA1* function in the tumor cells. And now that researchers have *BRCA2*, they can begin asking similar questions about that gene's role in sporadic cancers.

The research puzzles aren't the only ones swirling about this new breast cancer susceptibility gene. There's also the matter of who will win the patent on the gene. Meldrum maintains that Myriad should have the edge in the United States because it has the complete sequence. But Guy Heathers, CRC Technology's business manager, says their patent application also claims the whole gene, or at least the coding region. It's far too early to know who will win out. But one thing is certain: The potential payoffs—for science, medicine, and industry—are so high that *BRCA2* will be getting a lot of attention. As King puts it, its discovery "is only the end of the beginning."

–Jean Marx

BIOCHEMISTRY

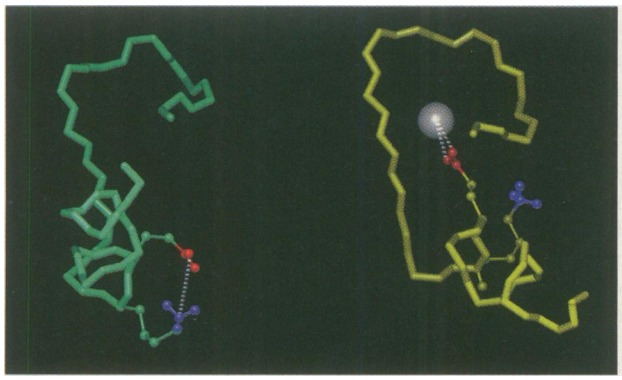
Flexing Muscle With Just One Amino Acid

The workings of muscles interest more than just athletes: For years, scientists have been tracing the cascade of molecular events that trigger muscle contraction. One key player in the sequence is a protein in muscle cells known as troponin-C, which responds to a chemical signal—the release of calcium ions from within the cell—by changing its shape. The contortion alters its chemical interactions with neighboring proteins, and these interactions eventually lead to cell contraction. But just why troponin-C undergoes this crucial shape change has remained murky.

Two weeks ago, however, a group of Canadian researchers, flexing some investigatory muscle of their own at the 1995 International Chemical Congress of Pacific Basin Societies in Honolulu, Hawaii, may have cleared up this mystery. The researchers, led by Brian Sykes, a biochemist at the University of Edmonton in Alberta, Canada, unveiled new studies showing that a single amino acid—glutamic acid, the 41st amino acid in the protein chain—controls this shape change by dragging a section of the protein toward a newly bound calcium ion; mutant proteins without this amino acid didn't budge. Troponin-C comes in two forms, one in skeletal and one in cardiac muscle. These studies were done on the skeletal form, but researchers believe the information may aid the design of drugs, known as calcium-sensitizing drugs, intended to treat heart attack victims by strengthening the contractions of undamaged heart muscle cells.

"It's a very nice study," says Walter Chazin, a molecular biologist at the Scripps Research Institute in La Jolla, California. The new result is the first to suggest that a large shape change can be controlled by the identity of just a single amino acid, he says. But although Chazin finds the evidence compelling, he cautions that some uncertainty remains, because the mutation could also be altering the protein's response by affecting the way it binds calcium.

Sykes's group has been pursuing the relationship between troponin-C's structure and function for some time. Their new result comes just 3 months after they completed the first description of the protein in its calcium-bound state. Past x-ray crystallography studies of the unbound protein had shown that the amino acids in the key regulatory section of the molecule are woven into a series of five connected helixes and a pair of loops. Researchers suspected that the calcium ions were bound inside the loops and played a role in the protein's shape change. But scientists were unable to confirm these suspicions, because they couldn't crystallize the protein in its calcium-bound configuration to study it with x-rays.



B. SYKES

Shaping up. Models of the muscle protein troponin-C show that glutamic acid *(red)* is usually attracted to lysine *(purple)*. But a calcium ion *(white)* pulls it away—bending the protein.

But in the September issue of *Nature Structural Biology*, Sykes and his colleagues Stephane Gagné, Sakae Tsuda, Monica Li, and Larry Smillie addressed the question with a different structure-determining technique, known as nuclear magnetic resonance (NMR) spectroscopy, that doesn't require crystallization. The NMR technique, which determines the position of atoms within a protein from the way they resonate in a magnetic field, confirmed that calcium binding takes place inside the two loops.

The bound structure also revealed a clue to how this might trigger the shape change. The calcium-bound structure showed that a calcium ion in one loop was sitting near a glutamic acid in a neighboring helix; in the unbound structure, the two are farther apart. That difference suggests that upon binding to the protein, the positively charged calcium attracts the negatively charged glutamic acid, which pulls the helix along with it, forcing the protein to change its shape, says Sykes.

But this circumstantial evidence didn't eliminate the possibility that other amino acids were involved in the shape change as well. So in their latest study, the Alberta researchers created a mutant version of the protein in which the key glutamic acid was changed to an alanine, another amino acid—but one with a neutral charge. When the team studied the structure of the mutant protein, they found that it no longer altered its shape even after the two calcium ions bound inside their loops. With no electronic attraction, Sykes suggests, there is nothing forcing the helix to change its position.

The structural information may provide clues to shape changes in the cardiac form of the protein, and thus help to design drugs that strengthen heart muscle contractions by keeping that form in its calcium-bound position, says R. John Salero, a physiologist studying such drugs at the University of Illinois, Chicago. But structural studies on the cardiac form have yet to be completed.

Chazin also notes one complication in studies of the skeletal form. The glutamic acid is normally a key link in the protein's framework that holds the calcium in place, and the mutational change may change the way calcium sits in the binding pocket. That in turn could prevent the shape change by altering the way in which the calcium interacts with neighboring atoms.

But so far Sykes sees no sign of that. "I would say our data show the binding pocket is still as it was," says Sykes. "And there isn't any evidence that the calcium is binding anywhere else." And Chazin says that seeing the full NMR data of the new protein once it's published should help settle the matter. "If he's got the right answer," says Chazin, "then he's on to something very big."

–Robert F. Service