Caught in the act: The dynamic dance of enzymes

December 11 2007

In a new study in *Nature*, Brandeis University Howard Hughes Medical Investigator Dr. Dorothee Kern and collaborators pull back the curtain on the secret lives of enzymes, the ubiquitous proteins that catalyze chemical reactions in the cell. Harnessing a slew of sophisticated technologies to capture a key enzyme changing shape in near real time, Kern was able to show that these proteins are not the wallflowers of the biological world scientists had once thought, essentially passive until catalysis occurs.

Rather, Kern and her team demonstrated that the enzyme adenylate kinase, and presumably many more, engages in a dynamic dance even before its catalytic date—the substrate to which it binds—shows up.

If one of the constants of life is change over time, implicit in this truth is how macroscopic change, such as the growth of a child, is ultimately rooted in microscopic change, such as atoms moving in a protein. Kern's study is remarkable in its ability to document the tiny flutterings of enzymes just before they do their all important catalytic work.

In two *Nature* articles, Kern and collaborators were able, in effect, to create a motion picture of an enzyme as it actually changed shape, or conformations, in the absence of the substrate. "It's really a paradigm shift," said Kern. Earlier studies had been able only to create snapshots of enzymes frozen in time, obscuring their true restless, twitching selves.

The three-year study represents a breakthrough in scientific

understanding of the dynamic personalities of enzymes. For years, Kern has dedicated herself to capturing how enzymes move and change shape through time. She pioneered the use of nuclear magnetic resonance (NMR), which can detect the motion of individual atoms in a protein, in this biophysical application.

But in this study, Kern, who earlier in life was the point guard on the East German national women's basketball team, knew she had to create a gold-standard strategy that would capture not only the motion of a key protein, but its structures, as well. She had to make sure that the fleeting, more infrequent shapes of enzymes couldn't essentially wiggle out of the picture. These rarer enzyme states are critical to understand, as they are the ones most relevant to better drug design.

Ultimately, Kern harnessed five different elegant techniques, including X-ray crystallography, (NMR), single-molecule fluorescence resonance energy transfer (FRET), computer simulations of molecular dynamics, and paramagnetism, to reveal the full picture of how proteins fold in those infrequent, yet lightening-fast intermediate states between inactivity and activity. Each technique provided a piece of the puzzle.

"The big goal here is to understand proteins well enough so that we can actually predict how they will behave," said Kern. These short-lived structures are most likely to have a higher affinity to drug molecules. Instead of relying on trial and error, scientists may be able to rationally design drugs to specifically bind to these intermediate conformations, according to Kern.

With the ability to capture an enzyme in real time as it is moving toward the active state, Kern and co-workers were able to detect picosecond (one millionth of one millionth of a second) changes, the fast smaller conformational motions, as well as the millisecond large-scale motions that are a result of the many fast motions.

“This work will lead to understanding the physical nature of proteins not as a static picture but as an ensemble of structures,” said Kern.

Source: Brandeis University