Grooving Down the Helix

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Researchers show how proteins slide along DNA to carry out vital biological processes

December 3, 2009

Written by Steven Deitz

UPTON, NY — A team of scientists from the U.S. Department of Energy's (DOE) Brookhaven National Laboratory, Harvard University, and the Indian Institute of Science has made a major step in understanding how molecules locate the genetic information in DNA that is necessary to carry out important biological processes. The research, published in the December 1, 2009 edition of *Nature Structural & Molecular Biology*, confirms that many proteins responsible for interacting at specific sites on DNA find their targets by sliding along one of the grooves of the DNA double helix in a spiraling fashion.

"Essentially, proteins that search for specific information spin down the double helix of the DNA, like traveling along the threads of a screw, until they locate their target," said co-author Walter Mangel, a Brookhaven biophysicist.

This research provides experimental proof of a recent theory put forth by the team and could lead to new ways to alter the behavior of DNA-binding proteins, which are responsible for replicating and repairing DNA, and for turning genes on and off.

For decades, scientists have known that proteins searching for genetic sequences are able to locate them at rates much faster than expected. They found that rather than moving around the entire three-dimensional space inside a cell, they moved in one-dimension, along DNA molecules. The Harvard group showed, in 2006, that the proteins slide back and forth in direct contact with the DNA as part of the search for specific sequences.

Until now, however, the exact nature of the path these molecules take along the DNA has not been known. Competing biological models assert that the proteins either move in a straight line parallel to the DNA axis or trace more complex helical paths, following a strand or groove of DNA around that axis.

One challenge is that the very fine and quick motions occur at extremely small

space and time scales. This means that the precise motions of a DNA-binding molecule are difficult to observe directly. So the researchers used indirect methods to determine the protein's path.

With a special fluorescence microscope, collaborating scientists led by Sunney Xie at Harvard University observed single protein molecules labeled with a fluorescent dye binding to and then sliding along the DNA. Although they could not see the exact path the molecules were sliding on, they could measure how fast the molecules were going.

Depending on how a protein moves along a DNA axis — either in a linear or helical pattern —it will encounter different degrees of resistance, as shown in the earlier paper. If protein motion is linear, its speed will decrease proportionately as its radius increases. If a protein exhibits helical motion, it will experience additional friction and its speed will decrease much faster as its radius increases.

Using a human DNA repair protein as a test for the protein rotation model, Paul Blainey, now at Stanford University, found the latter case to be true. When he increased the size of the protein, the rate of motion decreased much more rapidly than it would have for a simple linear motion.

Relying on the same technique, the group went on to analyze the diffusion rates of eight different proteins of various sizes. These molecules had highly diverse functions — such as DNA replication, cleavage, and repair — and DNA-binding mechanisms. They were also taken from a range of organisms, including mammals, bacteria, and human viruses.

The researchers observed the same pattern: The speed of each protein decreased dramatically as its radius increased, as predicted by the theory for helical sliding.

"The data present strong evidence that proteins seek out targeted DNA sequences by spinning down the helix rather than linearly sliding along its axis," said Biman Bigachi, a co-author from the Indian Institute of Science.

This work validates the new equation for describing and predicting the motion of protein molecules along strands of DNA with a higher degree of accuracy than ever before. It enhances the possibilities of future research in understanding and manipulating the DNA-binding and sliding behavior of proteins.

Said Mangel, "By being able to predict the DNA sliding rate of a protein, one could alter the size of a protein and thereby alter its sliding rate. For example, certain viral proteins need to slide along DNA in order to cause infection. A small protein could be designed to bind to the viral protein to slow down its sliding rate. This might be a useful means to block a virus infection."

This research was funded by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, the National Science Foundation, and the Department of Science and Technology of India.

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