Scientists shed light on how DNA is unwound so that its code can be read

November 24 2008

Researchers at The Scripps Research Institute have figured out how a macromolecular machine is able to unwind the long and twisted tangles of DNA within a cell's nucleus so that genetic information can be "read" and used to direct the synthesis of proteins, which have many specific functions in the body.

The scientists say that their findings, published in the November 23, 2008 online issue of *Nature Structural & Molecular Biology*, provide important new insights into this critical DNA unwinding.

"This is a fundamental processes that takes place countless times inside each of our cells every day, but how it happens had not been understood." says the study's lead investigator, Francisco Asturias, Ph.D., associate professor in the Department of Cell Biology at Scripps Research. "The structure we have solved provides important clues into one of the first steps in gene expression regulation."

To accomplish this feat, the scientists used a technique called macromolecular cryo-electron microscopy, in which images of individual molecules preserved at extremely low temperatures are recorded and used to determine the molecule's structure. Using samples from the yeast Saccharomyces cerevisiae, the scientists were able to take thousands of individual pictures of the RSC chromatin remodeling complex—a large and flexible protein machine that unwinds the DNA—in complex with the nucleosome, the basic organizational unit into which DNA strands are wrapped.

The scientists then used mathematics and intensive digital processing to translate what were two-dimensional snapshots of single RSC molecules into a detailed picture of the three-dimensional molecular machine at work.

"Remarkable Unpacking and Repacking"

To understand the complexity of the process, it is important to know that if the DNA in each cell were stretched out, it would be more than three feet long—and given the trillions of cells within a human body, it has been calculated that a single individual's DNA could stretch to cover the distance to the sun and back many times over.

So DNA must be packaged into tidy little chromosomes. The DNA in each gene first assembles into what looks like a string of beads: the string is the DNA and to compact its length, it is wrapped two times around a spool-like bead of histone protein, to form a nucleosome. But there is so much DNA in a single gene that each gene is packed into a necklace of nucleosomes on a DNA string. These beads then become further compressed into twisted ropes that eventually form chromatin, in which DNA is compacted about 10,000 times from its extended length.

What the Scripps Research scientists set out to do is to understand how the RSC complex unwinds DNA from the many histone beads within a gene so that other molecular machines can read the genetic code.

RSC is a huge complex of 13 different proteins and the scientists first found that it holds an individual nucleosome in what looks like a vise grip. They then found that RSC creates a little bulge in the DNA that can be propagated around the nucleosome and make possible translocation of the DNA with respect to the histones, exposing the DNA so that it can be read.

"Imagine a rubber band wrapped twice around a water glass. The easiest way to move the band is to pull a little of it away from the glass and then slide it" Asturias says. "By using energy from an external source (ATP hydrolysis) RSC can repeatedly pull DNA away from the histones and eventually expose all of the DNA."

The researchers believe that by translocating a nucleosome along the DNA, RSC eventually slides into the next adjoining nucleosome, causing the histones to be ejected and exposing the DNA. "Interestingly, although its DNA is gradually exposed, the nucleosome to which RSC is bound remains intact," Asturias says.

The structure RSC interacting with a nucleosome explains how previously observed DNA bulges formed by chromatin remodeling complexes are formed, and why a single intact nucleosome appears to be left on a fully activated gene before other cellular machinery scoop up the histones and repack the DNA until it needs to be read again.

"Every time your cell expresses a gene, it goes through this remarkable unpacking and repacking," he says. "We are happy to have provided some clarity to the process."

Reference: For more information, see www.nature.com/nsmb/journal/va… t/abs/nsmb.1524.html .

Source: Scripps Research Institute