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LICR/UCSD Team Solves Mystery Of Centromeres, The Genetic Machinery For Proper Cell Division

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Researchers at the Ludwig Institute for Cancer Research at the University of California, San Diego (UCSD) School of Medicine have solved one of genetics' mysteries - how a segment of protein on each of the body's DNA-carrying chromosomes is able to form a rigid structure called a centromere, leading to proper cell division and the faithful inheritance of genes.

Published in the July 29, 2004 issue of the journal *Nature*, the study utilized a sophisticated new form of mass spectrometry developed at the UCSD School of Medicine to determine how a protein called CENP-A, turns the normally flexible center section of a rod-shaped chromosome into a steel-like structure called a centromere.

A crucial player in the complicated process of cell division, the centromere is responsible for moving the correct number of chromosomes into a new cell. Learning how a centromere forms is an important step in understanding what goes wrong in cell division. When either too many or too few chromosomes end up in newly formed cells, the catastrophic result is often birth defects, spontaneous abortion, or cancer. For example, Down syndrome is a disorder caused by one too many copies of chromosome 21.

During cell division, each cell makes a duplicate copy of its chromosomes. Each pair of identical chromosomes forms a centromere that holds them together in the center, like a cinched waist in an "X". From opposite poles of the cell, microtubules called spindle fibers, extend down to the centromeres and act as ropes to pull the centromere and paired chromosome apart, so that half the centromere/chromosome moves to one side of the cell, while the other half goes to the opposite pole. Cell division follows, resulting in two identical daughter cells.

"Ever since Mendel's original genetic studies, we've wondered how it is that centromeres function to assure that chromosomes are faithfully inherited," said the study's senior author, Don Cleveland, Ph.D., UCSD professor of medicine, neurosciences and cellular and molecular medicine, as well as a member of the Ludwig Institute for Cancer Research.

While many genes have similar DNA sequences in all organisms (yeast, flies, worms, mice, humans, etc.), researchers have determined that the DNA in centromeres varies markedly from species to species.

"It has been perplexing," Cleveland said. "Although the DNA sequence doesn't matter, we've been able to show that a particular protein, CENP-A, determines where the centromere is located and copies this same location to a newly synthesized chromosome. The presence of CENP-A turns the centromere into a staff DNA and protein complex, and ensures that the centromere is maintained every time a cell duplicates. This is a critical component of the cellular machinery that provides every person on earth with a nearly identical set of chromosomes."

In the UCSD investigation, researchers made purified, synthetic copies of human CENP-A protein, which they studied in the laboratory. CENP-A, which binds only to centromeres, is a variation of the more common histone 3 (H3), a protein located throughout all regions of chromosomes.

The study's first author, Ben E. Black, Ph.D., a post-doctoral fellow in Cleveland's laboratory, was able to characterize the function of CENP-A with a UCSD School of Medicine invention called enhanced amide hydrogen/deuterium-exchange mass spectrometry, or DXMS*. This methodology, developed by Virgil L. Woods, Jr., M.D., associate professor of medicine and one of the paper's corresponding authors, enables rapid analysis of protein structure and motion (dynamics) at the molecular level.

Black performed DXMS analysis of CENP-A in the Woods' lab and identified a region of the protein that was much more rigid than similar regions of H3. He then genetically "transplanted" this small, stiff region of CENP-A into H3, and found that the "stiffened-up" H3 acted just like CENP-A, binding to centromeres.

"With DXMS, we were able to find the small region within CENP-A responsible for its ability to locate and then rigidify the centromere," Black said.

Cleveland added that "biologists have been able to take what are, in essence, snapshots of the structure of proteins for many years, but you couldn't see whether regions of the protein were rigid or flexible. Now, with DXMS, we're able to see something more like a movie that shows how flexible the regions of a protein are."

Woods noted that "this work demonstrates the ability of DXMS to precisely localize protein features responsible for function, even when the function is a very complex one - in this case, the initiation of centromere formation."

In addition to Cleveland, Black and Woods, researchers involved in the study were Daniel R. Foltz, Ph.D., a postdoctoral fellow in Cleveland's laboratory; Srinivas Chakravarthy, a graduate student at Colorado State University; and Karolin Luger, Ph.D., a Colorado State University associate professor of Biochemistry and Molecular Biology.

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