Researchers solve first structure of a key to intact DNA inheritance

December 20 2007

Researchers have solved the structure of a DNA-protein complex that is crucial in the spread of antibiotic resistance among bacteria. Knowing this structure also provides fundamental insight into how cells successfully divide into two new cells with intact DNA.

The report in the Dec. 20th issue of *Nature* focuses on how DNA separates and maintains its integrity when a cell divides. Using X-ray crystallography, the team led by structural biologists at The University of Texas M. D. Anderson, with colleagues at the University of Sydney, Australia, produced clear 3-D images of the structure that results when two proteins connect with a DNA site to "segregate" DNA during cell division.

"We solve structures to answer questions about how molecules carry out their biological functions. Without knowing the structure, you can't understand molecular mechanisms at a detailed level," says lead author Maria Schumacher, Ph.D., associate professor in M. D. Anderson's Department of Biochemistry and Molecular Biology.

In this case, Schumacher and colleagues answer a basic science question and flag a possible target for clinical attack on antibiotic-resistant Staphlococcus Aureas, a tenacious and often lethal staph infection.

"The plasmid segregation system we are working on, called pSK41, is found in S. aureus and confers resistance to multiple antibiotics, including the drug of last resort, vancomycin," Schumacher says.

"Because the segregation systems are essential for the retention of these multidrug resistant plasmids, they represent wonderful drug targets."

Plasmids are additional strips or circles of DNA found in bacteria that provide the bacterium with some mechanism of defense - in this case, protection against antibiotics. Plasmids can be transferred from one type of bacteria to another through a number of mechanisms.

Plasmids are also a great model for understanding cell division and segregation, Schumacher says, because plasmid segregation is relatively simple: two proteins connect to one DNA site to launch the process. Cells divide to multiply and it's crucial for this split to go smoothly so each daughter cell ends up with the DNA it needs to function.

"If these plasmids don't divide and go to the next generation of cells, those bacteria cells lose their drug resistance," Schumacher notes.

In the Nature paper, the scientists capture the first structure ever solved of a segrosome complex that partitions and divides DNA.

A protein called ParR connects with a centromere DNA site, a round string of DNA repeats in the plasmid, to form the segrosome complex, which then completes itself by attracting filaments of another protein called ParM. The ParM filaments grow, literally pushing the two replicated plasmid segrosomes apart, resulting in two copies of the plasmid with intact DNA.

"An important question in segregation biology has been 'what structure does the segrosome adopt"' Our segrosome structure answers that question. We now have a molecular model for the segregation of DNA," Schumacher says.

Solving the structure is necessary to understand how these molecules

function. "If we know these details we can design highly specific drugs to disrupt their actions," Schmacher notes.

The researchers used a technique called X-ray crystallography to discern the structure of both proteins connecting to the plasmid DNA. This technique first requires purification and crystallization of the protein or, in this case, the more challenging DNA-protein complex structure. These are usually the most difficult steps of the process.

Next, the crystal sample is mounted on a tiny loop in an X-ray diffractor and X-rays are beamed through it. Bending around the lattice of atoms in the crystal, the X-rays produce a diffraction pattern, which can be seen as a dot pattern on a monitor.

A state-of-the-art X-ray diffractor shoots a different angle of the crystallized protein every few minutes. Taking between 180-300 images will produce 100,000 to 300,000 data points.

Mathematical analysis of those points reveals a three-dimensional structure. The first image is an electron density map, which illustrates a protein's hills and valleys based on the position of the electrons of the atoms that compose the complex. This leads to the more exotic ribbon diagram, a spiraling, looping almost skeletal representation of the complex's crucial components.

The researchers used the Advanced Light Source (ALS) synchrotron at the U.S. Department of Energy's Lawrence Berkeley National Laboratory a fast, powerful diffractor that shoots a new diffraction pattern every half second, to solve this structure.

Source: University of Texas M. D. Anderson Cancer Center

Citation: Researchers solve first structure of a key to intact DNA inheritance (2007, December 20) retrieved 25 April 2024 from https://phys.org/news/2007-12-key-intact-dna-inheritance.html

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