X-file cracked: Mini-key determines DNA shape

April 20 2023

Benjamin Rowland, research group leader at the Netherlands Cancer Institute. Credit: Netherlands Cancer Institute

We finally know why our DNA has an X shape. This finding by researchers at the Netherlands Cancer Institute may have much broader implications for how our cells behave. "It looks like we have uncovered a universal mechanism by which cells determine the shape of their DNA."

"Would it really work like that?" wondered researcher Benjamin Rowland. He recounts the phone conversation with his colleague from England. "We saw a suspicious similarity between two molecules in the nucleus of our cells. They seemed to have exactly the same building blocks in one place, which could explain a lot of what happens within cells. So of course we had to investigate that." Their findings are published in the journal *Nature Structural & Molecular Biology*.

X in biology textbooks

In our body, cells continuously divide in two to make new cells. In the process, a cell copies its DNA and divides it equally between the two new cells. This is easier said than done. After all, our DNA is several meters long and crammed like spaghetti threads into the invisibly small nucleus of a cell. Try distributing that fairly.

Cells have a clever way to deal with this. They copy their DNA and turn it into compact parcels. In the process, the cells leave the two copies attached in the middle until they divide. Under the microscope, such a parcel looks like an X, as one can see in all biology textbooks.

Exotic name

Just before the cell divides, the X releases in the middle. The arms of the X then each go to a separate cell. If this goes wrong, the new cells get more or less DNA than normal. This can cause them to derail. Cancer cells, for example, often have abnormal amounts of DNA.

"Such a chromosome actually consists of two identical long DNA threads that at first are connected along their entire length," says researcher Benjamin Rowland. A host of ring-shaped cohesin molecules holds the two threads together. "When a cell is about to divide, the cohesin rings open, and the arms of the DNA come apart. The rings in the middle of the DNA remain tightly closed. This is due to a protein with the exotic name shugoshin—SGO1."

Locked rings

Since the late 19th century, textbooks have stated that our chromosomes have this X shape. But the underlying mechanism has remained a mystery for a long time. Rowland's Ph.D. student Alberto García-Nieto has now discovered that shugoshin uses a molecular key that fits precisely into a kind of keyhole in cohesin.

In doing so, it locks the cohesin rings. Because shugoshin works in the center of chromosomes, it is only there that it locks the rings. That gives chromosomes their X shape. Only after the cell has everything neatly lined up to start dividing, does it cut those last rings loose with molecular scissors. The DNA is separated, and the cell can divide.

Universal mechanism

An unexpected similarity pushed the researchers towards this discovery. They saw that a small fragment of shugoshin is identical to a piece of another protein they had previously examined closely—CTCF. Guess what that protein does? CTCF has the exact same molecular key that fits into that same keyhole of cohesin. It also uses this to lock cohesin rings, but in a different context. Cohesin also does something else entirely: it compacts chromosomes by making DNA loops. Different place, same mechanism of locking.

"We seem to have found a universal mechanism by which cells determine the shape of DNA. Indeed, what makes the whole thing more extraordinary is that CTCF and shugoshin don't seem to be the only proteins that use these building blocks." Rowland and his U.K. colleagues have evidence that a variety of important proteins that regulate our DNA use the same molecular key to control cohesin. "By locking cohesin at exactly the right time, as well as at the right place on the DNA, you can determine the shape of our chromosomes."

"Remember: DNA is the code of life. The structure of DNA partly determines the function of DNA and therefore the behavior of our cells. So if you can determine the structure of DNA, this could have huge implications."

More information: Daniel Panne, Structural basis of centromeric cohesion protection, *Nature Structural & Molecular Biology* (2023). DOI: 10.1038/s41594-023-00968-y.
www.nature.com/articles/s41594-023-00968-y

Provided by Netherlands Cancer Institute