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Single-DNA images give clues to breast cancer

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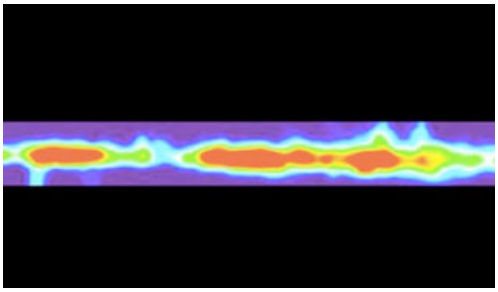

For the first time, researchers at the University of California, Davis, have watched single strands of DNA being prepped for repair. The research, published this week in the journal Nature, has implications for understanding the origins of breast cancer.

"It's clear that in cells, DNA breaks all the time, and there's machinery to repair those breaks and retain genetic integrity," said Stephen Kowalczykowski, distinguished professor of microbiology and of molecular and cellular biology at UC Davis. Kowalczykowski is senior author of the paper.

To repair a break in the DNA double helix, a single strand has to seek out and find its matching sequence on the opposite strand -- a task that Kowalczykowski compares to finding a needle in a haystack. To do that, the single strand first has to be coated with a protein called RecA.

"The RecA/DNA filament is the machine that looks for that needle," he said.

In the new study, graduate student Jason Bell used technology developed in Kowalczykowski's lab over the past decade to image individual strands of bacterial DNA as they were coated with a protein called RecA. Studying how this process works gives insights into the "mediator" proteins responsible that facilitate it, Kowalczykowski said. In humans, one of those mediators is the protein BRCA2, which is strongly associated with breast cancer.

RecA, called Rad51 in humans, helps the single strand of DNA find its complementary, matching strand elsewhere in the chromosome. The RecA protein has to displace another protein, imaginatively named single-strand DNA-binding protein, to get to the DNA.

The researchers were able to watch in real time as the RecA units displaced single-strand DNA-binding proteins and then spread in both directions until the whole strand was covered.

They found that the process has to start with two molecules of RecA attaching to the DNA. Then single molecules of RecA can be added at either end, similar to adding beads on a string.

One surprise was that in the absence of mediators, the process was relatively slow, Kowalczykowski said. It took about 30 minutes to coat a strand -- longer than the time E. coli takes to go through a cell division cycle.

The mediator proteins are crucial for controlling the speed at which RecA assembles on the single strand of DNA, Kowalczykowski said. Too slow, and DNA breaks would not be repaired properly; too fast, and it would capture and coat the short pieces of single-stranded DNA briefly produced during normal DNA replication. Instead, the process only works on DNA that persists because it is actually damaged or broken.

"I'm sure that BRCA2 works in the same way," he said.

UC Davis is a leading center for basic research into DNA repair, a crucial process in understanding the origins of both cancers and birth defects. In 2010, Kowalczykowski's laboratory and another team led by UC Davis Professor Wolf-Dietrich Heyer were the first in the world to purify the human BRCA2 protein from human and engineered yeast cells, respectively. Kowalczykowski and Heyer are also members of the UC Davis Comprehensive Cancer Center, a National Cancer Institute-designated research and treatment center.

Co-authors of the Nature paper are UC Davis postdoctoral researchers Jody Plank and Christopher Dombrowski. The work was supported by grants from the National Institutes of Health.

About UC Davis

For more than 100 years, UC Davis has engaged in teaching, research and public service that matter to California and transform the world. Located close to the state capital, UC Davis has more than 32,000 students, more than 2,500 faculty and more than 21,000 staff, an annual research budget that exceeds $684 million, a comprehensive health system and 13 specialized research centers. The university offers interdisciplinary graduate study and more than 100 undergraduate majors in four colleges — Agricultural and Environmental Sciences, Biological Sciences, Engineering, and Letters and Science. It also houses six professional schools — Education, Law, Management, Medicine, Veterinary Medicine and the Betty Irene Moore School of Nursing.

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