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Critical protein helps mend damaged DNA

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In order to preserve our DNA, cells have developed an intricate system for monitoring and repairing DNA damage. Yet precisely how the initial damage signal is converted into a repair response remains unclear. Researchers at the Salk Institute for Biological Studies have now solved a crucial piece of the complex puzzle.

In a forthcoming article in the Dec. 24 issue of *Molecular Cell*, they show that a protein named CtIP plays an essential role in the DNA damage "signal-to-repair" conversion process. "Being able to repair damaged DNA is extremely important; the cell has to know when it has received this type of damage and respond appropriately," explains Tony Hunter, Ph.D., American Cancer Society Professor in the Molecular and Cell Biology Laboratory and director of the Salk Institute Cancer Center, who led the study. "Failure to do so can have disastrous consequences."

The DNA in our cells is under constant attack from reactive chemicals generated as byproducts of cellular metabolism. In addition, it is assaulted by x-rays, ultraviolet radiation from the sun, and environmental carcinogens such as tobacco smoke. As a result of this continuous bombardment, some studies have estimated that the DNA in a single human cell gets damaged over 10,000 times every day.

If not repaired properly, the damage leads to mutations, which over time can cause cancer. "As a result, individuals with an inherited impairment in DNA repair capability are often at increased risk of cancer," notes first author Zhongsheng You, Ph.D., a former postdoctoral researcher at the Salk Institute and now an assistant professor at Washington

University School of Medicine in St. Louis.

DNA consists of two intertwined strands so that when the DNA is broken, two ends are revealed, one from each strand. In order to repair the DNA break, one strand is trimmed away—or resected—like a loose thread, leaving only the second strand. This exposed strand then searches for a copy of itself (located on its sister chromosome), and "photocopies" past the broken region, repairing the DNA and zipping itself back up.

In yeast, CtIP is required for resection of the broken end, and since it is also recruited to sites of DNA damage in human cells, Hunter's team wanted to know whether CtIP plays a similar role there. To find out, they depleted CtIP from human cells and caused DNA damage. Without the CtIP, they discovered, the cells could no longer trim back the damaged DNA strands, which brought the whole repair process to an abrupt halt.

"It looks like CtIP recruitment is a very important control point in the DNA repair process," You observes. "Once CtIP is recruited, resection and repair begin, so regulating CtIP recruitment is one way to regulate DNA repair itself."

In order to understand the process better, the researchers then asked which regions of the CtIP protein are involved in binding it to the broken DNA ends. By testing small portions of the protein, they found that a region in the central part of CtIP helps recruit the protein. They named this region the "damage recruitment" (DR) domain.

Further studies suggested that the DR domain within CtIP is normally hidden inside the folded protein. Only when the cell sends a DNA damage signal is CtIP's DR domain exposed, and only then can CtIP bind to the broken DNA. In this way, CtIP is like a switchblade that cells

open only in the presence of DNA damage.

The authors believe that exposure of CtIP 's DR domain and its recruitment to the site of DNA damage triggers a chain reaction that results in DNA repair, and they now want to understand exactly what CtIP does to start the DNA repair process.

You is also trying to understand the modifications in CtIP that cause the DR domain to be exposed, and is looking into the role of CtIP in cancer. "Mutations in CtIP have not been mapped extensively in human tumors, but from this data, we predict that mutations to the DR domain would lead to cancer," he says.

In the long term, the team hopes that a better understanding of the DNA damage pathway may provide clues for cancer treatment in the future. "CtIP is another important player in the double-strand break response," says Hunter. "We have added another piece to the complex puzzle of DNA repair."

Along with Drs. Hunter and You, researchers who contributed to the work include Linda Shi, Ph.D. , and Andrew Basilio at the University of California, San Diego; Quan Zhu, Ph.D., Nina Tonnu, and Inder Verma, Ph.D. in the Salk Institute's Laboratory of Genetics; Peng Wu, Ph.D., in You's lab at Washington University School of Medicine; You-Wei Zhang, Ph.D. , now at Case Western Reserve University; and Michael W. Berns, Ph.D., at UCSD and University of California, Irvine.

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