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DNA packaging discovery reveals principles by which CRC mutations may cause cancer

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A new discovery from researchers at Huntsman Cancer Institute (HCI) at the University of Utah concerning a fundamental understanding about how DNA works will produce a "180-degree change in focus" for researchers who study how gene packaging regulates gene activity, including genes that cause cancer and other diseases. The discovery, by Bradley R. Cairns, PhD, Senior Director of Basic Science at HCI and a professor in the Department of Oncological Sciences, is reported in this week's online issue of the journal *Nature*.

Cairns's research focuses on chromatin remodeling complexes (CRCs), which are cellular protein complexes that behave like motors, expanding or compacting different portions of DNA to either express or silence genes, respectively. Before, scientists thought that the motor within CRCs waits at rest until it receives instructions. Cairns and co-author Cedric R. Clapier show that the motor within a key CRC responsible for gene packaging and assembly is intrinsically turned on, and instead requires specific instructions to turn it off.

"Many articles in the research literature show that CRCs are mutated in cancer cells. They are intimately involved in regulating gene expression—responsible for correctly packaging genes that control growth proliferation and for unpackaging tumor suppressors," said Cairns. "This research reveals principles by which CRC mutations could cause cancer."

Chromosomes are made of long DNA strands compressed around nodes

of protein called nucleosomes; when DNA is compressed, the genes in that area are turned off. Some CRCs, called disassembly CRCs, act as motors that unwind sections of DNA chains, making genes active for a given cell process. Another type, called assembly CRCs, rewinds the DNA chain, recompressing it when the process is complete. The unwind-rewind cycle is repeated continuously throughout a cell's life.

In this study, Cairns and Clapier focused on assembly CRCs. "Before this research, we thought that the motor was off unless a protein coming from another part of the cell turned it on," said Cairns. "Researchers have been searching for the switch by looking at the CRC motor to see what binds to it.

"As it turns out, we discovered that the CRC motor already carries on its flank a 'switch' that inhibits its action until a marker sequence, located on the nucleosome, is encountered. The marker flips the inhibitor switch and allows the CRC to crank the DNA chain back around the nucleosome, promoting gene packaging and silencing" Cairns said. "Our results change where future researchers should be looking to understand how CRCs are regulated—not at the CRC motor itself, but at the 'switches' that flank the motor."

The study also describes a measuring function on the CRC that checks for the correct distance between one nucleosome and the next, telling the motor to switch off at the proper time, a function needed for gene silencing.

Cairns's lab will now examine this same switching concept in disassembly remodelers. "There are additional remodeler families with alternative functions, like DNA repair," said Cairns. "We think this concept will apply to them as well."