Chromatin remodeling complex connected to DNA damage control

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When molecular disaster strikes, causing structural damage to DNA, players in two important pathways talk to each other to help contain the wreckage, scientists at The University of Texas M. D. Anderson Cancer Center report in the August edition of *Cell*.

This connection between a signaling pathway crucial to DNA damage control and a pathway known as chromatin remodeling "opens an entirely new category of targets for potentially attacking cancer," says senior author Xuetong "Snow" Shen, Ph.D., an assistant professor in M. D. Anderson's Department of Carcinogenesis at the Science Park - Research Division in Smithville, Texas.

If DNA damage is like a fire that spreads when impaired cells divide and multiply, then the DNA checkpoint and repair system can be considered a first-response firebreak. Checkpoint genes temporarily halt a cell's division and assess its DNA. The "fire" is either doused by DNA repair or by programmed destruction of the cell.

The ATM/ATR kinases are known to regulate DNA repair and checkpoint pathways, Shen explains, by attaching phosphate groups to other proteins involved in damage control. When ATM and ATR are themselves damaged, they cause genome instability and fuel cancer growth.

"We found that one of the proteins phosphorylated was a unit of a chromatin remodeling complex we call INO80," Shen says. "We subsequently found that phosphoryllation of this subunit regulates checkpoint pathways, but not DNA repair pathways."

A cell's DNA resides in chromosomes found in the cell nucleus, but it's a bit more complex than just DNA itself, Shen explains. DNA is tightly intertwined with proteins known as histones and assembled in histone/DNA units called nucleosomes along the connecting length of a string of DNA.

"This structure is often referred to as beads on a string," Shen says, and is collectively known as chromatin.

"Chromatin creates barriers to DNA against anything that wants access to DNA, such as a transcription factor or DNA repair machinery," Shen says.

"Chromatin remodeling shuffles the nucleosomes around to create access to DNA," Shen says. "This moving and sliding of the 'beads on the string' is accomplished by large protein complexes, ATP-dependent chromatin remodeling complexes."

In this case, the Ies4 subunit of the remodeling INO80 complex is phosphorylated by ATM/ATR, a necessary step for certain DNA checkpoints to work properly.

When Shen and colleagues used a mutant version of Ies4 to mimic constant phosphorylation, more cells were stuck in a checkpoint pause, blocking cell division. When phosphorylation was blocked, the cells' response to replication stress was impaired, greatly slowing down replication in the absence of another replication checkpoint factor called Tof1.

Shen discovered the INO80 chromatin remodeling complex as a post-doctoral fellow at the National Institutes of Health. His research focuses on defining its functions and mechanisms. An earlier paper from his lab in Cell showed that INO80 also is involved in DNA damage repair through its connections to a specific phosphorylated histone.

"Modification of histones has been studied for some time, now we are moving to understand the modification of something that modifies histones," Shen says of INO80.

Shen's research is conducted in yeast, but the pathways involved are conserved in all forms of life with complex cellular organization, known as eukaryotes, right on up to humans, Shen notes.

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