Study pinpoints epigenetic function of common cancer-causing protein—it's not what science thought

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(Medical Xpress)—Squamous cell carcinoma (SCC) is diagnosed in about 700,000 people in the United States every year. Commonly contributing to SCC is a protein called DNp63a – it goes abnormally high and the ability of a patient's body to kill cancer cells goes abnormally low. In many cases of SCC, it's just that simple. And science thought the function of DNp63a was simple, as well: the tumor suppressor gene p53 is responsible for recognizing and killing cancer cells, and in SCC, it's usually inactivated. It looked like high DNp63a repressed p53, made SCC.

A University of Colorado Cancer Center study published today in the journal Genes *& Development* throws the accepted role of DNp63a on its ear. Though high DNp63a and low p53 activity are correlated in SCC, there's no causation – DNp63a doesn't affect p53. Instead, DNp63a employs "epigenetics" to keep cancer cells alive.

"This is a potent oncogene whose mechanism we thought we knew. But basically in this paper we demolish the accepted model. DNp63a doesn't work through p53 – it operates through epigenetic silencing of anti-proliferative genes," says the study's senior author, Joaquin M. Espinosa, PhD, investigator at the CU Cancer Center and associate professor in the Department of Molecular, Cellular and Developmental Biology at CU Boulder.

Genes are blueprints that code for proteins and these proteins in turn drive most things that happen in the body, both good and bad. But between genes and their protein products is the layer of epigenetics – genes may be expressed differently depending on the heritable, epigenetic features that turn them on and off. In the case of DNp63a, it employs a protein partner called H2A.Z, which in volume effectively buries anti-proliferative genes in silt, rendering them unable to go about their anti-cancer duties.

"Independently of p53, DNp63a is shutting down genes that stop cell division – shutting down anti-proliferative genes so that cells can keep dividing and dividing and dividing," Espinosa says.

Now that the function of DNp63a is known, Espinosa is looking inside the chain of events for a breakable link.

"DNp63a itself isn't druggable," he says, "but the enzymes that partner with DNp63a for epigenetic silencing are."

With a mechanism in hand, Espinosa and colleagues can now explore in animal models the possible effects of breaking the DNp63a mechanism. Drug away an essential enzyme and DNp63a may lose its ability to cause cancer.

Provided by University of Colorado Denver