CRISPR Screen Reveals New Targets in Squamous Cell Carcinomas

"The challenge now is to exploit this knowledge for therapeutics," says researcher Joaquin Espinosa, PhD.

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A little p63 goes a long way in embryonic development — and flaws in p63 can result in birth defects like cleft palette, fused fingers or even missing limbs. But once this early work is done, p63 goes silent, sitting quietly in the genome from that point forward. Unless it is accidentally reactivated. When p63 comes back to life within the adult genome, the result can be cancer. More than half of all squamous cell carcinomas, often found in the skin, lung, breast, and head/neck, involve excess p63 activity.

Researchers have known that p63 drives squamous cell cancers. The question has been what to do about it. Unfortunately, it has been impossible to simply switch off p63. And so the question becomes how else can doctors and researchers interfere with the action of p63 to shield patients from its cancerous effects.

Today, a team of University of Colorado Cancer Center researchers working in the lab of Joaquin Espinosa, PhD, sheds light on p63 activity in squamous cell carcinoma of the lung, providing an actionable path forward to drug development against this known cause of cancer. The study is published in the journal Cell Reports.

"The question that initiates this study is what is this oncogene, p63, doing to drive cell proliferation and why too much of it would cause cancer," Espinosa says.

To answer this question, Espinosa and colleagues including first author Christopher Abraham, PhD, used the CU Cancer Center Functional Genomics Shared Resource to run cells through a genome-wide CRISPR screen — a cutting-edge technology that enables the analysis of thousands of genes in a single experiment. The group started with lung squamous cell carcinoma cells that require the oncogenic product of the p63 gene, namely a protein called ΔNp63α, in order to proliferate. Then the group turned off the production of ΔNp63α in these cells.

Of course, at that point, these cancer cells that needed ΔNp63α stopped proliferating. Espinosa and colleagues hypothesized that ΔNp63α had been suppressing the action of key tumor-suppressor genes (turning off the genes that turn off cancer), and now without ΔNp63α, these key

anti-proliferative genes were again allowed to take over and stop cell division.

“It’s an example of the classic tug-of-war between oncogenes and tumor-suppressor genes — based on this balance, you either have cancer or you don’t,” Espinosa says.

In order to identify these tumor suppressor genes playing a tug-of-war with ΔNp63α, the group used the CRISPR screen to turn off thousands of genes across the genome to discover which genes, when inactivated, would allow these cancer cells to restart their growth (and thus, which genes ΔNp63α suppresses to aid the growth of cancer).

“We screened the entire genome and there was one molecular pathway, super clean and super clear, that ΔNp63α needed to turn off to drive the growth of squamous cell carcinoma cells,” Espinosa says.

The key tumor suppressor genes in this pathway are TGFB2 and RHOA.

When the group looked in the Cancer Genome Atlas at published data of 518 samples of lung squamous cell carcinoma, they found that in cancers with activated ΔNp63α, about 80 percent also showed inactivated TGFB2 and RHOA.

“ΔNp63α shuts off TGFB2 and RHOA to promote cancer progression, and this is clearly a widespread phenomenon in squamous cell carcinomas,” Espinosa says.

The path to a therapy against ΔNp63α seems clear: activate TGFB2 and RHOA.

“If there was a way to deliver something that mimics TGFB2, perhaps we could stop proliferation of squamous cell carcinoma,” Espinosa says.

Or, RHOA is an enzyme that can switch between active and inactive forms.

“So if you can find drugs that lock RHOA in its active form, that would shut down cell proliferation, as well,” Espinosa says.

“This is a potentially druggable pathway that is driving the progression of squamous cell carcinomas,” Espinosa says. “The challenge now is to exploit this knowledge for therapeutics, to find a way to reactivate the TGFB/RHOA pathway to save the lives of patients with cancers.”

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