Gene fusions may be the 'smoking gun' in prostate cancer development

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These are study authors Arul Chinnaiyan and Scott Tomlins. Credit: University of Michigan Health System

Prostate cancer treatments that target the hormone androgen and its receptor may be going after the wrong source, according to a new study. Researchers have found that when two genes fuse together to cause prostate cancer, it blocks the receptor for the hormone androgen, preventing prostate cells from developing normally.

The study, from the University of Michigan Comprehensive Cancer Center, suggests that the gene fusion - not the androgen receptor - is a more specific "bad actor" in prostate cancer and is the real smoking gun that should be targeted by treatments.

"We need to begin to think about targeting prostate cancer by targeting

the gene fusion, and not confining our approaches to androgen receptor. If we're going to find a more durable therapy, we need to get at the gene fusion," says study author Arul Chinnaiyan, M.D. Ph.D., director of the Michigan Center for Translational Pathology and S.P. Hicks Endowed Professor of Pathology at the U-M Medical School. Chinnaiyan is also a Howard Hughes Medical Institute investigator and an American Cancer Society research professor.

The study is featured on the cover of the May 18 issue of *Cancer Cell*.

Treatments for prostate cancer typically include drugs to moderate androgen, a male hormone that controls the normal growth of the prostate. These drugs typically work at first, but over time the cancer cells become resistant to the therapy and the cancer returns. Because it's no longer responsive to currently available hormone deprivation therapies, the recurrent cancer is usually more difficult to treat.

In 2005, Chinnaiyan and his team identified a prostate-specific gene called TMPRSS2 that fuses with a cancer-causing gene called ERG. The team's earlier research has shown that this gene fusion acts as an "on switch" to trigger prostate cancer.

This new study used sophisticated sequencing technologies to map the genome-wide location of androgen receptor and the TMPRSS2-ERG gene fusion in prostate cancer cells. The researchers found that the gene fusion blocks the androgen receptor directly and also interferes with it at the genetic level to prevent normal androgen receptor signaling. With the androgen receptor blocked, prostate cells stop growing and developing normally, allowing cancer to develop.

"Our study shows the underlying problem in prostate cancer is the presence of a gene fusion, not the androgen receptor. In many contexts, androgen signaling is actually a good thing, but the presence of the gene

fusion blocks androgen receptor signaling, which alters normal prostate cell development. While current treatments for advanced prostate cancer are focused on hormone deprivation and are quite effective, at least initially, future therapies need to be developed that target the prostate cancer gene fusion," Chinnaiyan says.

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