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Memorial Sloan Kettering Cancer Center

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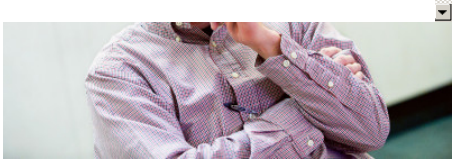
The standard treatment, androgen receptor (AR) therapy, works for a while by blocking receptors for male sex hormones that are known to fuel prostate tumor growth. But the disease usually becomes resistant and progresses.



Brett Carver

One reason may be that a large proportion of such prostate cancers — those with a mutation in a tumor-suppressor gene called *PTEN* — rely on a separate disease pathway called PI3K that helps tumors survive when the AR disease pathway is thwarted. However, attempts to block the PI3K pathway in *PTEN*-deficient prostate cancer have failed to shrink tumors in animal models.

Now Memorial Sloan Kettering researchers have discovered that the AR and PI3K pathways regulate each other through reciprocal negative feedback. The pathways naturally inhibit each other, so impeding one merely strengthens its counterpart. The finding, published in the May 16 issue of *Cancer Cell*, might help explain why AR therapy eventually fails and suggests that therapy blocking both pathways could be effective. [PubMed Abstract]

Using *PTEN*-deficient mouse models, the researchers found that blocking the PI3K pathway alone increases the levels of the proteins that help drive the AR pathway. Conversely, inhibiting the AR pathway in the *PTEN*-deficient mice activates a key protein in the PI3K pathway. In both cases, the animals' prostate tumors persisted despite losing an important survival mechanism.

"Within the last few years, the right agents have become available that allow us to break apart the components of these pathways and see exactly how they interact," says Memorial Sloan Kettering urologic surgeon Brett S. Carver, who led the study along with senior author Charles L. Sawyers, Chair of the Human Oncology and Pathogenesis Program. "Once we understood the crosstalk, we saw that hitting both pathways could produce a profound tumor response."

When the researchers combined an AR inhibitor called MDC3100 with a PI3K inhibitor called BEZ235, tumors receded in the mouse models, and *PTEN* deficient human prostate cancer cells were destroyed in culture and in immune-deficient mice. Memorial Sloan Kettering plans to test the combination approach in phase II clinical trials under the direction of Howard I. Scher, Chief of the Genitourinary Oncology Service.

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