Targeting aggressive prostate cancer

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A team of researchers from UC Davis, UC San Diego and other institutions has identified a key mechanism behind aggressive prostate cancer. Published on August 14, 2013 in *Nature*, the study shows that two long non-coding RNAs (PRNCR1 and PCGEM1) activate androgen receptors, circumventing androgen-deprivation therapy. In their active state, these receptors turn on genes that spur growth and metastasis, making these cancers highly treatment-resistant. The study illustrates how prostate cancer can thrive, even when deprived of hormones, and provides tempting targets for new therapies.

"Androgen-deprivation therapy will often put cancer in remission, but tumors come back, even without testosterone," said contributor Christopher Evans, professor and chair of the Department of Urology at the UC Davis School of Medicine. "We found that these long non-coding RNAs were activating the androgen receptor. When we knocked them out, cancer growth decreased in both cell lines and tumors in animals."

Evans' UC Davis group was part of a larger team, led by Michael Geoff Rosenfeld, professor at the Howard Hughes Medical Institute in the School of Medicine at UC San Diego, which has been eager to determine how androgen-dependent cancers become androgen-independent (also called castration-resistant). These prostate cancers are very aggressive and usually fatal, but their continued growth, despite being deprived of hormones, is just now being better understood. It's not unlike removing the key from a car ignition, only to have the vehicle re-start on its own.

In this case, the aberrant starting mechanisms are long non-coding RNAs, a class of genetic material that regulates gene expression but does not code for proteins. Using patient samples from UC Davis, the group determined that both PRNCR1 and PCGEM1 are highly expressed in aggressive tumors. These RNAs bind to androgen receptors and activate them in the absence of testosterone, turning on as many as 617 genes.

Further investigation determined that one of these long non-coding RNAs is turning on androgen receptors by an alternate switching mechanism, like a car with a second ignition. This is critically important because many prostate cancer treatments work by blocking a part of the androgen receptor called the C-terminus. However, PCGEM1 activates another part of the receptor, called the N-terminus, which also turns on genes—with bad results.

"The androgen receptor is unique, if you knock out the C-terminus, that remaining part still has the ability to transcribe genes," said Evans.

In addition, about 25 percent of these cancers have a mutated version of the androgen receptor that has no C-terminus. These receptors are locked in the "on" position, activating genes associated with tumor aggression.

Regardless of the receptor's status, PRNCR1 and PCGEM1 are crucial to prostate cancer growth. In turn, knocking out these RNAs has a profound impact on gene expression, both in cell lines and animal models. The team used complementary genetic material, called antisense, to knock out the RNAs and observe how the tumors and cells responded. In each case, there was a direct relationship between RNA activity, gene expression and cancer growth.

"These long non-coding RNAs are a required component for these castration-resistant cancers to keep growing," said Evans. "Now we have

preclinical proof of principle that if we knock them out, we decrease cancer growth."

The research team's next step is developing treatments that specifically target these long non-coding RNAs. That process has already begun.

"Most treatments for castration-resistant prostate cancer will get us around two to three years of survival," said Evans. "We rarely cure these patients. The tumor will continue to evolve resistance mechanisms. But now that we have additional insight into what's activating these receptors, we can begin developing new types of therapies to prevent it."

Provided by UC Davis