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Macrophage Signaling May Affect Hormone Resistance in Prostate Tumors

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Debra Kain

Interaction between prostate cancer cells and immune cells called macrophages may be a source of inflammatory signals capable of impacting the effectiveness of androgen antagonists, the most common and effective treatment for prostate cancer, according to a new study by researchers at the University of California, San Diego (UCSD) School of Medicine.

Male hormones called androgens are essential for the physiological function and growth of the prostate gland, and anti-androgen treatment, which blocks the expression of androgen target genes, is widely used for the treatment of prostate cancer. Unfortunately, most patients eventually progress to an antagonist-resistant or hormone independent form of cancer, according to David W. Rose, associate professor in UCSD's Department of Medicine, Division of Endocrinology and Metabolism, and Moores Cancer Center. Rose is principle investigator of the study, to be published in the Feb. 10 issue of the journal *Cell*.

"These findings are exciting because we have shown on the cellular level that, when the immune cells interact with the tumor cells, the result essentially negates the effect of the very drug being used to repress the tumor. If we can show the same process occurs in animals and in people, we may be able to block the "de-repression" of these genes, and develop more effective drugs to target prostate cancer tumors," Rose said.

The UCSD research team explored the possibility that external signaling from macrophages in the prostate tumor microenvironment might affect hormone resistance.

Using cell biology methods, they discovered a mechanistic explanation for at least one form of resistance to androgen antagonists.

"It was of particular interest for us to determine whether a macrophage/prostate cancer cell interaction occurs, if it is a common event in prostate cancer, and whether this serves as a source of inflammatory signals capable of impacting the therapeutic effectiveness of androgen antagonists," said Rose.

The research shows at a mechanistic level that the physical interaction of macrophages with prostate tumor cells activates processes in both cell types that cause the activity of androgen antagonists to change, allowing the expression of androgen target genes in the tumor cells. The research team describes the signaling pathway involved in this process, involving several proteins that may be potential drug targets in the future.

Steroid receptors (the proteins that bind and mediate the effects of androgens, estrogens, and progesterone) contain within their structure a novel binding site not previously recognized by researchers, according to the study. This site makes these receptors uniquely responsive to inflammatory signals, because the protein that binds there, called TAB2, is the ultimate target of the signaling pathway. When pro-inflammatory signals cause the chemical modification of TAB2, the activity of the receptors is changed. Drugs that are normally antagonists now activate target genes, many of which are associated with tumor growth.

Media contact: Debra Kain, 619-543-6163.