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Amplification of a Stat5 gene produces excess oncogenic protein that drives prostate cancer spread

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An international group of investigators, led by researchers at Thomas Jefferson University's Kimmel Cancer Center, have solved the mystery of why a substantial percentage of castrate-resistant metastatic prostate cancer cells contain abnormally high levels of the pro-growth protein Stat5. They discovered that the gene that makes the protein is amplified—duplicated many times over—in these cancer cells, which allows them to produce excess amounts of the oncogenic protein.

The study, reported in the May 7 issue of the *American Journal of Pathology*, found a direct association between the number of Stat5 genes in human prostate cancer cells and Stat5 protein levels, and also revealed that gene amplification and protein levels increased as prostate cancer metastasized and became resistant to castration (anti-androgen) therapy.

The finding is important since agents that inhibit the Stat5 pathway are currently entering clinical trials, says the study's senior author, Marja Nevalainen, M.D., Ph.D., associate professor of Cancer Biology, Medical Oncology, and Urology at Jefferson.

"Our latest findings on Stat5 provide further support for the idea that targeting Stat5 protein pharmacologically might provide powerful therapy for advanced prostate cancer," she says. "Our hope is that a successful agent might prevent some prostate tumors from spreading and might be able to contain metastasis that has already occurred and

become castrate-resistant."

The discovery also suggests that testing Stat5 gene amplification in patients could provide a biomarker that identifies those patients most likely to respond to Stat5 inhibition, Dr. Nevalainen says.

Not only is Dr. Nevalainen testing Stat5 inhibitors developed by Astra Zeneca and Novartis in preclinical studies, her lab has also developed its own inhibitor, which is also being tested.

Dr. Nevalainen has long studied Stat5 in prostate cancer, and with her colleagues, has authored a number of crucial studies demonstrating the impact the gene and its protein can have on prostate cancer progression. "Stat5 isn't the only protein that drives prostate cancer, but it is a very important one," she says.

Stat5 is a transcription factor – a protein that can regulate expression of other genes. In 2003, Dr. Nevalainen discovered that Stat5 protein is critical for viability of prostate cancer cells and growth of prostate tumors in mice. In 2004, Dr. Nevalainen found that Stat5 inside a cell's nucleus is often over-expressed in high-grade human prostate cancer, and in 2005, she demonstrated that Stat5 activity was associated with recurrence of prostate cancer in patients who had already been treated. Then, in 2008 she showed that nuclear Stat5 was especially prevalent in recurrent prostate cancers that are resistant to hormone therapy. Most importantly, her research has demonstrated that blocking Stat5 in laboratory and in animal models effectively destroyed prostate cancer. "We know that Stat5 is absolutely critical to the survival of prostate cancer cells," she says.

In 2010, Dr. Nevalainen found that excess Stat5 in prostate cancer cells is linked to metastasis, and excess Stat5 expression predicts early disease recurrence and death from prostate cancer. This study was conducted to

investigate why such over-expression of the protein occurs.

The researchers found amplification of the Stat5 gene in a significant fraction of 128 prostate cancer specimens from patients, and that Stat5 gene amplification was more frequently found in metastatic cancers that are no longer responsible to castration treatment (29 percent) and in high histological grade cancers (40 percent). Experiments in cell culture and in mice showed that increased Stat5 copy numbers conferred a growth advantage for tumors.

"Lots of cancers have chromosomal rearrangements that lead to amplification of pro-growth genes," says Dr. Nevalainen. "We don't know exactly why this happens, but it is related to imperfect cell division and unstable genomes."

While it is known that excess Stat5 protein predicts early recurrence of prostate cancer, development of metastatic disease and death from prostate cancer, researchers will need to determine if Stat5 gene amplification is also linked to those outcomes, she adds.

Researchers who contributed to the study included investigators from Georgetown University, the University of Helsinki in Finland, the University of Basel in Switzerland, and the University of Tampere in Finland. The authors declare no conflicts of interest.

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