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How prostate cancer packs a punch

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Some types of prostate tumors are more aggressive and more likely to metastasize than others. Nearly one-third of these aggressive tumors contain a small nest of especially dangerous cells known as neuroendocrine-type cells. More rarely, some aggressive prostate tumors are made up entirely of neuroendocrine-type cells. The presence of neuroendocrine-type cancer cells is associated with a poor prognosis, but spotting these rare cells can be like finding a needle in a haystack. Now, in a study published in the July 13 issue of *Cancer Cell*, a team of investigators led by Ze'ev Ronai, Ph.D. at Sanford-Burnham Medical Research Institute (Sanford-Burnham) has identified a series of proteins that might make it easier for doctors to better diagnose the more metastatic forms of prostate cancer.

"In identifying this protein pathway, which determines the formation of neuroendocrine tumors, we've identified new markers that can be used to distinguish the dangerous cells and find new targets for therapy," said Dr. Ronai, associate director of Sanford-Burnham's National Cancer Institute-designated Cancer Center.

This study uncovers a protein named Siah2, which initiates a cascade of molecular events that turns a non-malignant tumor into a metastatic neuroendocrine tumor. In collaboration with four other medical centers across the United States, Dr. Ronai and his colleagues analyzed human prostate cancer samples and found that Siah2 and the other proteins it triggers is detected more often in the aggressive neuroendocrine forms of prostate tumors than in other types. By acting as markers for particularly aggressive prostate cancers, Siah2 and its partners could

provide doctors with an early warning sign for tumors that are likely to metastasize.

To further validate these findings, the Siah2 gene was inactivated in mice already prone to developing aggressive prostate tumors. Although benign growths still appeared, they failed to develop into neuroendocrine tumors.

"When we inhibit the Siah2 pathway in mice, we eliminate the neuroendocrine-type cells from the prostate tumors," explained Jianfei Qi, Ph.D., postdoctoral researcher in Dr. Ronai's laboratory and first author of the study. "Since prostate cancers containing neuroendocrine-type cells are resistant to current therapies, we are pleased to find that targeting Siah2 might provide an alternate approach to treating this disease."

Members of the Sanford-Burnham research team are now looking for chemical compounds that inhibit the activity of Siah2 or other proteins along the chain. They hope to find a new drug that will block the series of molecular events leading to the formation of neuroendocrine-type cancer cells, thus keeping prostate tumors in check.

More information: Qi J, Nakayama K, Cardiff RD, Borowsky AD, Kaul K, Williams R, Krajewski S, Mercola D, Carpenter PM, Bowtell D, Ronai ZA. Siah2-dependent concerted activity of HIF & FoxA2 regulates formation of neuroendocrine phenotype & neuroendocrine prostate tumors. Cancer Cell. Published July 13, 2010.

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