Neuronal molecule makes prostate cancer more aggressive

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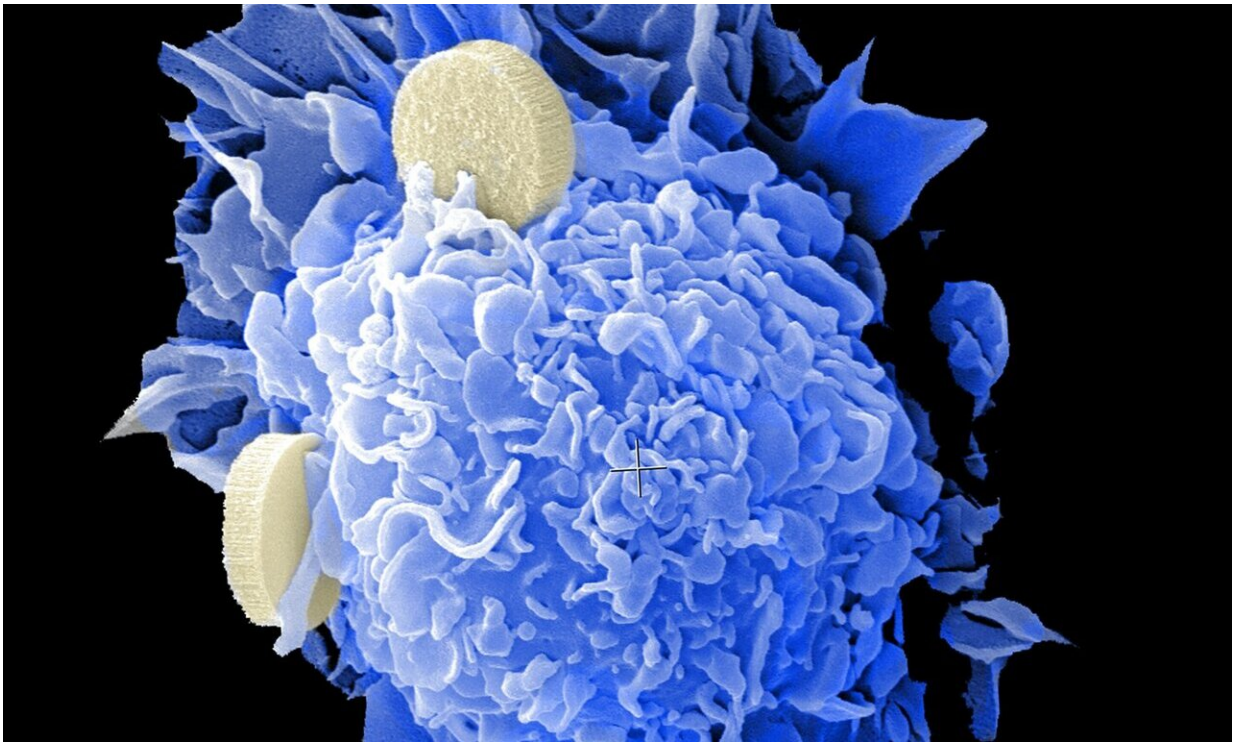

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Prostate cancer is the second most common cancer and the second leading cause of cancer death among American men. Now, researchers have discovered key molecular players that drive prostate cancer to progress into a highly aggressive form of the disease called neuroendocrine prostate cancer that currently has no effective treatment.

The finding uncovers new avenues to explore for therapeutics to treat neuroendocrine prostate cancer.

"We have found novel pathways that promote neuroendocrine prostate cancer," says senior author Lucia R. Languino, Ph.D., a professor in the department of Pharmacology, Physiology and Cancer Biology and director of the Genetics, Genomics, and Cancer Biology Ph.D. Program at Thomas Jefferson University. She and her team published the new research online on November 7, 2022 in the journal *Scientific Reports*.

Most prostate cancers are a type of disease called prostate adenocarcinoma. Other types of prostate cancer, including neuroendocrine tumors, are rare. However, unlike prostate adenocarcinoma, neuroendocrine prostate cancer is very aggressive and can quickly spread to other parts of the body. Treatments that are effective for adenocarcinomas in the prostate do not work against neuroendocrine prostate cancers.

Adenocarcinoma prostate cancers can progress into neuroendocrine prostate cancer. Until now, how this transition occurs has been a mystery.

To better understand how neuroendocrine prostate cancer develops, Dr. Languino and colleagues looked for biomarkers of the disease. In previous work, they discovered that a molecule known as aVb3 integrin is abundant in mice and humans with neuroendocrine prostate cancer, but missing in prostate adenocarcinoma.

To look for molecules unique to neuroendocrine prostate cancer, the researchers found that aVb3 integrin expression in prostate cancer cells bumped up the expression of a known marker of neuroendocrine prostate cancer and significantly increased the expression of a molecule called Nogo receptor 2 (NgR2).

The finding "was a big discovery," Dr. Languino says, who is also a researcher with the Sidney Kimmel Cancer Center—Jefferson Health. That's because NgR2 is a protein found in nerve cells, where it contributes to neuronal functions. It has never before been studied in cancer, of any kind.

Dr. Languino and her colleagues wanted to find out what this molecule, a neuronal protein, is doing in cancer.

An initial experiment revealed that NgR2 binds the aVb3 integrin. The scientists also saw that in mice with neuroendocrine prostate tumors, aVb3 integrin and NgR2 were both present in the primary tumor and in cancerous lesions that had formed in the lungs of the animals. A follow-up experiment made it clear that both aVb3 integrin and NgR2 are necessary for neuroendocrine prostate cancers.

When Dr. Languino and her team lowered the amount of NgR2 in neuroendocrine prostate cancer cells, neuroendocrine markers also decreased. The results suggest that NgR2 plays a role in the development of neuroendocrine prostate cancer. Lowering the amount of NgR2 also reduced the ability of cancer cells to grow and move, indicating that NgR2 may have a hand in cancer spreading to other parts of the body, in a process known as metastasis. Metastases are often what makes cancers fatal.

"These two molecules, aVb3 integrin and NgR2, seem to create a combination that is lethal," Dr. Languino says.

She and her colleagues are now looking for a molecule or antibody that would block the effect of NgR2, or the aVb3 integrin/NgR2 complex, to inhibit their ability to promote neuroendocrine prostate cancer growth and development, and make the cancer more susceptible to therapy.

More information: Fabio Quaglia et al, The NOGO receptor NgR2, a novel αVβ3 integrin effector, induces neuroendocrine differentiation in prostate cancer, *Scientific Reports* (2022). DOI: 10.1038/s41598-022-21711-5