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Scaffolding protein promotes growth and metastases of epithelial ovarian cancer

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Researchers from Fox Chase Cancer Center have shown that NEDD9, a scaffolding protein responsible for regulating signaling pathways in the cell, promotes the growth and spread of epithelial ovarian cancer.

Previous studies have demonstrated the protein's importance in tumor invasion and spread of some lymphomas and many solid tumor types, including melanoma, neuroblastoma, and breast cancer, but its role in gynecological cancers has been poorly understood. The new data, to be presented on Sunday, April 6 at the AACR Annual Meeting 2014, suggest the protein activates known oncogenic signaling pathways in cancer cells, encouraging metastases.

"NEDD9 expression is usually associated with metastasis," says lead author Rashid Gabbasov, a graduate student in Fox Chase's Developmental Therapeutics Research Program and a researcher in the laboratory of Fox Chase Associate Professor Denise C. Connolly, PhD. "We've shown in two mouse models that expression of the protein probably plays an important role both in the initial development of ovarian cancer and tumor dissemination."

Because it lacks catalytic activity that might be inhibited, NEDD9 (neural precursor cell expressed, developmentally downregulated 9) itself is unlikely to be a suitable candidate for targeted therapy, says Gabbasov, and because it's not present in the blood it may not be suitable for diagnosing ovarian cancer. However, because the protein serves as a scaffolding molecule for other signaling proteins that play significant

roles in cancer development and is important in several molecular pathways, it can inform future investigations of the biology of ovarian cancer in human cancer specimens. Researchers can investigate pathways downstream of the protein that are active in ovarian cancer to identify those which may be used as potential diagnostic or therapeutic biomarkers.

Epithelial ovarian cancer is diagnosed in more than 22,000 women every year. The disease kills about 14,000, according to the American Cancer Society. It is the fifth leading cause of cancer death in women and one of the most common gynecologic cancers. In most patients, the disease has already metastasized at the time of diagnosis.

Connolly, whose research focuses on understanding the molecular underpinnings of epithelial ovarian cancer, says she and her colleagues became interested in NEDD9 after learning about its role in other cancers. The protein was discovered in 1996 by Fox Chase Professor Erica A. Golemis, PhD, Co-Leader of the Center's Developmental Therapeutics Research Program and a co-author on the ovarian cancer study.

Proteins like NEDD9 control and regulate the signaling mechanisms between the surface and interior of a cell.

"At the time our research started, we saw an early report suggesting that high-level NEDD9 expression was part of a gene signature related to advanced stage ovarian cancer," says Connolly, senior author on the study.

To study the protein's role in epithelial ovarian cancer, Gabbasov and his colleagues compared tumor growth in two groups of mice bred to spontaneously develop ovarian tumors. Mice in one group lacked NEDD9, and mice in the other group expressed the protein. Using MRI

scans, the researchers observed delayed tumor development in the NEDD9-null mice, compared to mice that expressed NEDD9. Analysis of tumor tissue showed more activity in several well-known oncogenic signaling pathways in the mice expressing the protein.

"When we compared the gene expression in these tumors, we were able to see how NEDD9 depletion really affects overall gene expression," says Gabbasov. "It really does affect numerous genes, and we will try to pursue these gene products to better understand the role of NEDD9."

Connolly says that even though this study looked at the ovarian cancer in mice, some of the genes that turned up in the gene expression analysis can be further evaluated in human cell lines and tumors. "We want to make sure we're studying something that's not only important in mice but can also give us clues about human cancers."

Provided by Fox Chase Cancer Center

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