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High levels of PEA-15 shrink breast cancer tumors

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Overexpression of PEA-15, which binds and drags an oncoprotein out of the cell nucleus where it fuels cancer growth, steeply reduced breast cancer tumors in a preclinical experiment, researchers at The University of Texas M. D. Anderson Cancer Center reported at the 100th annual meeting of the American Association for Cancer Research.

Human breast cancer grafts in mice dropped to nearly undetectable levels after 35 days when treated with an adenoviral PEA-15 vector that overexpressed the protein in tumors.

"Treated mice had a dramatic response, while tumors continued to grow in control mice," said first author and presenter Chandra Bartholomeusz, M.D., Ph.D., a post-doctoral fellow in M. D. Anderson's Department of Breast Medical Oncology. Bartholomeusz presented the findings at a minisymposium titled "Up and Coming Targeted Biologic Strategies."

"This first animal model experiment demonstrates the therapeutic potential of PEA-15," said senior author Naoto Ueno, M.D., Ph.D., associate professor of breast medical oncology. "PEA-15 is a different way of modulating growth because it's based on location of the protein in the cell rather than, for example, protein regulation by phosphorylation."

Ueno and colleagues previously showed that PEA-15 stymied ovarian cancer in lab experiments, and that high expression of the protein in tumors is tied to improved overall survival. They had also examined PEA-15 expression in 26 breast cancer specimens and found the protein

was more heavily expressed in the 13 low-grade tumors analyzed.

In the breast cancer experiments, the team first tested overexpression in three breast cancer cell line cultures. Lines treated with PEA-15 developed 30 to 60 percent fewer colonies of cancer cells than did control cultures. Further analysis of one cell line showed that adenovirally delivered PEA-15 overexpression inhibited cell growth and reduced DNA synthesis.

They also found that activated ERK - a protein active in growth, differentiation and mobility of cells that can fuel cancer growth when in the nucleus - was sequestered in the cell's cytoplasm. This is consistent with previous research by Ueno's team that showed PEA-15 works by binding and dragging ERK and phosphorylated ERK from the nucleus, inducing cell death.

Cell cycle analysis indicated the onset of apoptosis - programmed cell death - in breast cancer cells treated with PEA-15. In the case of ovarian cancer, the team found evidence of death by autophagy - cellular self-consumption - rather than apoptosis. The varied forms of cellular death may indicate that the protein's mechanisms differ from one form of cancer to another, Ueno said.

PEA-15 is a versatile protein, serving multiple cellular functions, including glucose metabolism and regulating the tumor necrosis factor (TNF) pathway in addition to its role regulating ERK, Ueno said.

"We are committed to further developing PEA-15 and making it a druggable target," Ueno said. The team is developing a non-gene therapy treatment because adenovirally delivered gene therapies such as those used to overexpress PEA-15 in the mouse experiments have had less success in humans.

Source: University of Texas M. D. Anderson Cancer Center (news : web)