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Protein compels ovarian cancer cells to cannibalize themselves

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A protein known to inhibit the growth of ovarian cancer works in part by forcing cancer cells to eat themselves until they die, researchers at The University of Texas M. D. Anderson Cancer Center report in the Nov. 15 issue of *Cancer Research*.

The research team also found that expression of the protein, known as PEA-15, is an independent indicator of a woman's prospects for surviving ovarian cancer, said senior author Naoto T. Ueno, M.D., Ph.D. associate professor of breast medical oncology.

An analysis of ovarian cancer tumors from 395 women showed those with high expression of the PEA-15 had a median survival time of 50.2 months compared with 33.5 months for women with low levels of the protein in their tumors.

"These findings provide a foundation for developing a PEA-15 targeted approach for ovarian cancer and for clarifying whether this protein is a novel biomarker that can predict patient outcomes," Ueno said.

Ovarian cancer kills about 15,000 women in the United States annually, and is notoriously hard to diagnose in its early stages, when it is also most optimal to treat.

A series of lab experiments by first author Chandra Bartholomeusz, M.D., Ph.D., showed that high expression of PEA-15 inhibits the growth of ovarian cancer cells by killing cells via autophagy, or self-

cannibalization, rather than by apoptosis. Removing PEA-15 from ovarian cancer cells led to a 115 percent increase in the number of cells compared with a control group of cells that still had the protein.

In apoptosis, defective cells die from self-induced damage to their nuclei and DNA complex. Autophagy kills when a cell entraps parts of its cytoplasm in membranes and digests the contents, leaving a cavity. When this goes on long enough, the cell essentially eats itself until it dies, its cytoplasm riddled with cavities.

Location, location, location

Ueno's research team has found that the protein works to inhibit cancer in two distinct ways depending on its location in the cell.

First, PEA-15 inhibits one of the prominent actors in the growth, differentiation and mobility of cells, a protein called extracellular signaling related kinase, or ERK. Activated ERK in the cell nucleus fuels cancer growth. The research team earlier found that PEA-15 binds to ERK in the nucleus and moves it out into the cytoplasm, preventing its growth effects.

Now they've found that PEA-15 in the cytoplasm induces autophagy in cancer cells, a second method of inhibiting cancer growth. "These two very different actions by PEA-15 are based on the location of the protein," Ueno said.

ERK is an inviting target for cancer therapy, Ueno noted, but so far no one has been able to develop a successful ERK inhibitor.

"PEA-15 offers us a new dimension for potentially targeting ERK," Ueno said. "We've shown with high levels of PEA-15, women with ovarian cancer are surviving longer." Levels of the protein in tumors also

might affect how other drugs work against the disease. Similar research is under way in breast cancer with. PEA-15, which is short for phospho-enriched protein in astrocytes.

Source: University of Texas M. D. Anderson Cancer Center