

ESTROGEN INTERFERES WITH IMMUNE SURVEILLANCE IN BREAST CANCER

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CHAMPAIGN, Ill. — Estrogen is known to enhance the growth and migration of breast cancer cells. Now researchers from the University of Illinois at Champaign-Urbana have found that estrogen can also shield breast cancer cells from immune cells.

In a study published online this week in *Oncogene*, the researchers report that estrogen induces the expression of an inhibitor that blocks immune cells' ability to kill tumor cells. This is the first study to identify estrogen's role in shielding breast cancer cells from the action of immune cells.

The researchers analyzed estrogen's role in the cascade of events that occurs when immune cells, called natural killer cells, encounter a tumor cell. Under normal conditions, natural killer cells release granules that contain enzymes, called granzymes, which enter and kill the tumor cell.

The research team found that when estrogen binds to an estrogen receptor the complex promotes production of a granzyme inhibitor, proteinase inhibitor 9 (PI-9). The inhibitor binds the granzyme, preventing it from initiating the molecular cascade that kills tumor cells.

"It wasn't known that estrogen could do this in breast cancer cells," said principal investigator David J. Shapiro, a professor of biochemistry in the School of Molecular and Cellular Biology. "The amounts of estrogen required to do this are quite small."

U. of I. graduate student Xinguo Jiang also found that when breast cancer cells that contain very high levels of estrogen receptor protein are exposed to low levels of estrogen, they produce large quantities of the granzyme inhibitor and become highly resistant to immune attack.

(MORE - Estrogen)

The researchers were able to show that estrogen's effect on PI-9 production was the sole mechanism by which estrogen interfered with the natural killer cells' ability to kill off breast cancer cells. They did so by blocking PI-9 production in the breast cancer cells exposed to estrogen. When these breast cancer cells were targeted by natural killer cells, they were efficiently killed off, even when significant levels of estrogen and estrogen receptor were present.

Estrogens are known to cause only a few types of cancers, said Shapiro, and PI-9 is also implicated in other cancers. High levels of PI-9 in some lymphomas, for example, are associated with poor prognosis.

This study demonstrates how basic research can have important and unanticipated implications for understanding diseases such as breast cancer, Shapiro said. The finding that estrogens stimulate PI-9 production could eventually help drug designers develop new tests – and targets – for breast cancer therapy.

The research team included collaborators from the University of Wisconsin at Madison.

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