Hormonal treatment for endometrial cancer does not directly target the malignant cells

June 11 2013

Progesterone, a female hormone that can be used as a therapy for endometrial cancer, eliminates tumor cells indirectly by binding to its receptor in stromal or connective tissue cells residing in the tumor microenvironment, according to a study from the G.O. Discovery Lab team and collaborators at UCLA.

Like tumors of the breast and prostate, endometrial cancer is regulated by hormones. Unlike therapies for breast and prostate cancer, where drugs are given to block hormone signaling, in therapy for endometrial cancer progesterone is given to stimulate its hormone receptor. Although it has been used for several decades, no one really knew the mechanisms and site of action for progesterone therapy.

Doctors know that a certain subsets of patients will benefit from treatment with progesterone. However, doctors prescribing the hormone therapy are shooting in the dark because they don't know in advance which patients will respond and which women may have resistant tumors, said study senior author Dr. Sanaz Memarzadeh, an assistant professor of obstetrics and gynecology and director of the G.O. Discovery Lab at UCLA. Therefore, while progesterone can be effective as a therapy in endometrial cancer, its use is not widely embraced in clinical practice.

"When viewing tumors under the microscope clinicians often focus on the cancer cells and neglect the supporting stroma in the microenvironment. In this study we found that all of the progesterone

anti-tumor effects are in fact mediated through the stroma even though it makes up a minor fraction of the tumor," said Memarzadeh, who also is a researcher at the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research and UCLA's Jonsson Comprehensive Cancer Center. "I believe these exciting findings are going to surprise the clinical community and change the way people look at patterns of hormone receptor expression in endometrial tumors."

The results of the three-year study, done using a specially developed laboratory model created by Memarzadeh's team that closely mimics human endometrial cancer, appear in the early online edition of *Cancer Research*, a peer-reviewed journal of the American Association for Cancer Research.

Memarzadeh and her team showed that if you delete the progesterone receptors in the stromal cells in the tumor microenvironment, progesterone therapy will not work. However, in a model of hormone resistant endometrial cancer, the tumor cells became sensitive to hormone therapy when the progesterone receptors are returned to the adjacent cells in the microenvironment.

"We were really surprised to find that when we added back the progesterone receptor to the microenvironment, tumors that before did not respond to the treatment simply melted away," said study first author Deanna Janzen, a senior research associate in the G.O. Discovery Lab. "Making one genetic change in the tumor microenvironment, deleting or adding back the progesterone receptor, completely changed the biology of the tumor. That was a striking finding."

Going forward, Memarzadeh and her team will translate this work into studies of human samples of endometrial cancer to see if their findings apply to patients. They hope to discover biomarkers that indicate response or resistance to hormone therapy. They also plan to find and

test drugs that can reverse progesterone resistance, making cells sensitive to hormone therapy. This approach will provide a potential combination therapy that could prove effective for women with disseminated endometrial cancer.

Currently, the most common treatment for early stage endometrial cancer is hysterectomy, followed by radiation and or chemotherapy. Doctors may prescribe progesterone to endometrial cancer patients who are seeking to preserve their fertility not knowing whether it will be effective, so finding biomarkers that indicate response would provide clinicians with a valuable tool, Memarzadeh said.

Endometrial cancer, which starts in the endometrium or the inner lining of the uterus, is the most common gynecologic cancer in the United States. About 49,000 new cases of endometrial cancer will be diagnosed this year alone, and about 8,000 American women will die from their cancers. The chance of a woman being diagnosed with this cancer in her lifetime is about one in 38, according to the American Cancer Society.

"This finding may have critical clinical implications as it demonstrates that modulation of the tumor microenvironment can reverse hormone resistance in endometrial tumors," the study states. "In future work, we will test if stromal specific delivery of DNA methyltransferase inhibitors may be an effective way to re-sensitize hormone refractory endometrial cancers to progesterone therapy."

Ultimately, the G.O. Discovery Lab team hopes to develop a simple test so that, after biopsy and analysis of an endometrial tumor, physicians will be able to figure out whether or not their patient is a good candidate for hormonal therapy.

Provided by University of California, Los Angeles