Study identifies how tamoxifen stimulates uterine cell growth and cancer

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UCSF researchers have identified a new "feed-forward" pathway linking estrogen receptors in the membrane of the uterus to a process that increases local estrogen levels and promotes cell growth.

The research is significant in helping determine why tamoxifen and other synthetic estrogens are linked to increased rates of endometriosis and uterine cancer, and identifies a pathway that could be targeted in drug therapies for those diseases, researchers say.

Findings are published in the July 1, 2009 issue of "*Cancer Research*," the journal of the American Association for Cancer Research. The paper also can be found online at http://cancerres.aacrjournals.org/current.shtml.

The research found that when activated by estrogens, endometrial cells obtained from patients suffering from endometriosis or human uterine cancer cells initiate a previously unknown cascade of signals that leads to cellular replication and further estrogen production, the paper says.

The ensuing cycle leads to abnormal growth of the cells lining the uterus, or endometrium, which occurs in endometriosis and uterine cancer, according to senior author Holly A. Ingraham, PhD, a professor in the UCSF School of Medicine's Department of Cellular and Molecular Pharmacology.

"It turns out that displaced endometrial cells, such as those used in this

study, are estrogen factories," said Ingraham, who also is affiliated with the UCSF Helen Diller Family Comprehensive Cancer Center and the UCSF Center for Reproductive Sciences. "They pump out estrogen in a feed-forward pathway, so the more estrogen they produce, the more estrogen they're capable of producing."

While this pathway was previously unknown, Ingraham said a June 2009 paper led by researchers at the University of New Mexico and published in the journal "*Nature* Chemical Biology" showed that blocking the GPR30 receptor in this pathway decreases uterine proliferation in a mouse. The two together, she said, validate what researchers now think may be a key area in addressing both uterine cancer and endometriosis.

Uterine cancer is the fourth most common cancer in women, with more than 37,000 women being diagnosed each year in the United States alone, according to data from the Centers for Disease Control.

Endometriosis, in which endometrial cells grow in areas other than the uterus, is the most common gynecological disease and affects more than 5.5 million women in North America, according to the National Institutes of Health. The disease often causes severe pain and can lead to infertility.

Working in collaboration with clinicians at Northwestern University in Chicago, the UCSF team analyzed cells from women with ectopic endometriosis. By studying those patients' endometrial cells, the team was able to identify an unusual, circular pathway involving these cells, the transmembrane estrogen receptor GPR30 and the nuclear receptor SF-1.

The researchers propose that this pathway increases local concentrations of estrogen and, together with classic estrogen-receptor signaling, control the proliferative effects of these estrogens in promoting endometriosis

and endometrial cancers.

The UCSF team used a unique chemical biology approach, making use of a tamoxifen-like compound developed in the laboratory of co-author Thomas Scanlan, PhD, who is affiliated with both the UCSF Department of Pharmaceutical Chemistry and the Department of Chemical Biology at the Oregon Health Sciences University in Portland.

"Tamoxifen and other synthetic estrogens have been known to increase the risk of uterine cancer, but until now, we didn't know why that was on a cellular level," Ingraham said. "We think this pathway is going to be an important one in solving that mystery."

Source: University of California - San Francisco