UT SOUTHWESTERN MEDICAL CENTER NEWS

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UT Southwestern researchers discover how estrogen can prevent vascular disease without increasing cancer risk

DALLAS – June 23, 2010 – Researchers at UT Southwestern Medical Center have pinpointed a set of biological mechanisms through which estrogen confers its beneficial effects on the cardiovascular system, independent of the hormone's actions on cancer. Their investigation suggests that drugs targeting a specific subpopulation of estrogen receptors found outside the cell nucleus might activate the cardiovascular benefits of estrogen without increasing cancer risk.

"Finding a way to get the beneficial effects of estrogen without increasing a woman's risk of cancer is something that could make a big difference to a lot of people," said Dr. Philip Shaul, professor of pediatrics.

Dr. Shaul and UT Southwestern colleagues created and tested in mice a synthetic molecule to determine the mechanisms by which estrogen promotes blood vessel health. Their findings are available online and in the July 1 issue of the *Journal of Clinical Investigation*.

Estrogen receptors – or molecular "docking points" for the hormone – usually are found in the cell nucleus. A small subpopulation is also found outside the nucleus of certain cells, including the endothelial cells that line arteries and veins.

Dr. Shaul, the senior author, said the new molecule is a unique selective estrogen recaptor modulator (SERM). Tamoxifen, a drug taken by millions of breast cancer patients, is also a SERM.

"We have discovered that the small population of estrogen receptors outside the nucleus of endothelial cells has a unique means to activate cell growth and migration, which are important to blood vessel maintenance and repair, and to regulate the production of nitric oxide, which is a protective molecule in the vascular system," he said. "Whereas all existing estrogen-related drugs change the function of the nuclear receptors which stimulate cancer cell growth, the synthetic molecule targets only the non-nuclear estrogen receptors. We're at the stage where we can start to think about how to translate these findings to humans."

Women generally have a low risk for heart disease until menopause, when their estrogen levels decline. The hormone has the potential to protect women from heart attack and stroke by maintaining healthy blood vessels, but it also can fuel tumor growth in reproductive tissues. Hormone replacement therapy, which usually includes estrogen, is often used to stave off osteoporosis and symptoms of menopause.

(MORE)

Decreasing estrogen's cancer risk – 2

. In the study, the researchers examined female mice with high cholesterol and injured carotid arteries, which become substantially blocked if the ovaries have been removed, mimicking diseased arteries in the heart and brain that cause heart attacks and strokes.

When researchers treated the injured mice with the new molecule, the arteries remained clear and unobstructed. Other studies showed that estrogen has the same effect.

"Cholesterol is extremely high in these mice, and the stage is set for them to have severe vascular disease, yet this molecule completely prevents that," Dr. Shaul said.

The team also wanted to determine if the mechanisms that promote blood vessel health are different from those that promote cancer. To do this, they studied how normal and cancerous uterine cells respond to the synthetic molecule. Whereas estrogen caused robust growth of both normal and cancerous uterine cells, the synthetic molecule did not. In addition, in experiments evaluating breast cancer tumor growth in mice, the tumors grew considerably with estrogen but not with the new SERM.

Dr. Shaul said the findings strongly suggest that the molecule helps maintain vascular health without adverse impact on cancer risk. He noted that this approach is likely applicable to both men and women and not limited to older individuals.

Although the molecule used in this study has been tested only in mice, Dr. Shaul and his colleagues are now creating and studying similar molecules for potential use in humans.

Other UT Southwestern researchers participating in the study were Dr. Ken Chambliss, co-lead author and senior research scientist in pediatrics; Dr. Qian Wu, co-lead author and postdoctoral researcher in pediatrics; Dr. Michihisa Umetani, instructor of pediatrics; Dr. Chieko Mineo, assistant professor of pediatrics; Ivan Yuhanna, senior research associate in pediatrics; Drs. Sean Dineen, Sarah Oltmann and Christina Roland, surgery residents; Dr. Rolf Brekken, associate professor of surgery; and Dr. Gail Thomas, former associate professor of internal medicine.

Researchers from the National Institute of Health and Safety; the University of Milan, the University of Illinois at Urbana-Champaign and the University of Cincinnati College of Medicine also contributed to the study, supported by the National Institute of Health, the American Heart Association, The Lowe Foundation and the Crystal Charity Ball Center for Pediatric Critical Care Research.

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