SOUTHWESTERN NEWS

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Editor's Note: October is National Breast Cancer Awareness Month

RESEARCHERS DISCOVER POSSIBLE SOURCE OF ESTROGEN THAT STIMULATES BREAST TUMOR DEVELOPMENT

DALLAS — October 5, 1993 — Researchers at The University of Texas Southwestern Medical Center at Dallas believe they have pinpointed the source of estrogen that stimulates the development of estrogen-dependent breast cancer.

Dr. Evan Simpson, professor of obstetrics and gynecology and biochemistry at UT Southwestern, believes he and his colleagues have established that the estrogen is synthesized locally in fatty tissues in the breast. Their findings are published in the Sept. 15 issue of the *Journal of Biological Chemistry*.

Most scientists believe breast-tumor cells are dependent upon estrogen to grow in their early stages, but scientists have been uncertain as to the origin of the estrogen that stimulates tumor growth. Since breast cancer is common in elderly women — whose ovaries no longer produce estrogen — researchers surmised the estrogen was generated elsewhere in the body. Several years ago a team of researchers lead by Dr. Paul MacDonald, professor of obstetrics and gynecology, holder of the Cecil H. and Ida Green Distinguished Chair in Reproductive Biology Sciences and director of the Cecil H. and Ida Green Center for Reproductive Biology Sciences, showed that estrogens also are synthesized in the brain and adipose, or fatty tissues.

Simpson, who is associate director of the Green Center, and his colleagues have isolated the specific enzyme in the breast adipose tissue that is responsible for estrogen biosynthesis. The enzyme responsible is called aromatase. It is produced by a gene from the family known collectively as cytochrome P450, first discovered by Dr. Ronald Estabrook, professor of biochemistry at UT Southwestern and holder of the Cecil H. and Ida M. Green Chair in Biomedical Science and the Virginia Lazenby O'Hara Chair in Biochemistry.

Simpson has shown that aromatase resides primarily in the stromal cells, the connective tissue cells within the adipose, rather than the adipocytes, or fat cells, themselves. Simpson said that the close proximity in the breast of the stromal cells and epithelial cells, which line the mammary ducts and give

(More)

rise to most breast tumors, would allow any estrogen synthesized in the stromal cells to interact readily with the developing tumor cells.

In addition, Simpson said breast tumors produce growth factors, which not only stimulate the local stromal cells to produce more estrogen but also stimulate stromal cell growth and division, thus providing sites for further estrogen production. Such a positive feedback loop would allow for the continuous growth and development of the tumor.

"Looking at the way breast tumors grow, this scenario makes sense," Simpson said.

He said it appears that tumors develop in regions of the breast with the highest proportion of adipose stromal cells, since these synthesize the highest quantities of estrogen.

In studies of human breast tissue removed at the time of mastectomy, Simpson and his colleague Dr. Serdar Bulun, an assistant professor in the Department of Obstetrics and Gynecology, found that regions with the highest levels of aromatase expression are also the regions that bear tumors in more than 70 percent of the cases. Not surprisingly, these tend also to be the regions which contain more adipose stromal cells and fewer adipocytes.

At present the use of estrogen blockers like tamoxifen is the most common form of drug therapy for breast cancer. Increasingly, however, Simpson believes that inhibitors of aromatase activity will be tested as alternative forms of therapy in both young and old women. The disadvantage of this approach is that it may block estrogen supplies to the rest of the body, which could promote osteoporosis in older women.

Simpson and his colleagues hope to find a way to block expression of aromatase specifically in the breast.

"We've found that breast adipose appears to contain a unique tissue-specific promoter of the aromatase gene," said Simpson. "This promoter and its associated transcription factors could be targets for new therapies to specifically eliminate aromatase expression uniquely in the breast."

Simpson's research is funded by a merit award from the National Institute on Aging within the National Institutes of Health.

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