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Fat cells in breast may connect social stress to triple-negative breast cancer

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Local chemical signals released by fat cells in the mammary gland appear to provide a crucial link between exposure to unrelenting social stressors early in life, and the subsequent development of breast cancer, researchers from the University of Chicago report in the July 2013 issue of the journal *Cancer Prevention Research*.

Some forms of stress exposure may be associated with an increased risk of certain types of aggressive breast cancer. But the mechanisms linking the biology of social stress to cancer have been hard to identify. To unravel that mechanism, the researchers looked for differences between mice raised in small groups and those that grow up in an isolated setting—an established model of chronic stress without social supports.

"We found that exposure to the stress of social isolation leads to reprogramming of genes in fat cells in the mammary glands," said study author Suzanne Conzen, MD, professor of medicine at the University of Chicago. "These fat cells then secrete substances that cause nearby pre-cancerous epithelial cells to proliferate more rapidly, accelerating the development of breast cancer. This local effect of fat cells in the breast was completely unanticipated."

The researchers used a genetically altered mouse model of "triple-negative" breast cancer—a form of the disease that lacks receptors for estrogen, progesterone and HER2, three important treatment targets in humans. Triple-negative cancer, representing about 15 percent of all breast cancers, appears to occur disproportionately in younger women. In

this mouse model, animals develop precancerous changes in mammary epithelial cells that later lead to cancer.

The mice tested—known as SV40-T antigen mice—all develop tumors by about 16 weeks of age. The researchers previously showed that female mice raised in isolation develop significantly larger, more aggressive, triple negative tumors, and wanted to understand the detailed biology underlying this observation.

Conzen worked closely with colleague Martha McClintock, PhD, professor of psychology at the University of Chicago, to carefully model chronic social stress exposure in female mice. In previous joint projects they showed that a measurable chronic stress response could reliably be induced in mice by raising them in isolation after weaning, rather than housing them in small groups.

In this study, Conzen also worked with colleague, Matthew Brady, PhD, associate professor of medicine and a specialist in fat cell biology, to decipher the effect of stress on the mammary fat.

"By separating fat cells in the breast from the other cell types, we were able to measure expression of genes involved in metabolism in those fat cells and not other fat cells or different cell types from the breast tissue," Brady said.

The researchers looked for differences in gene expression in multiple tissues and circulating hormones between group-housed and isolated mice. To their surprise, there were no significant differences in circulating hormones.

They found a dramatic change, however, in fat cells located within mammary glands. Measurements of those cells taken at 15 weeks of age showed that social isolation stimulated significant increases in the

expression of three genes—Hk2 (hexokinase), Acly (ATP citrate lyase) and Acaca (acetyl-CoA carboxykase).

All three are crucial to the uptake and metabolism of glucose, the primary source of cellular energy. Mammary fat cells in the stressed mice took up about twice as much glucose as the same fat cells from unstressed mice, indicating a significant increase in metabolic activity.

These cells use glucose to synthesize lipids—fatty substances, often used to convey biological signals. Increased fat cell metabolism was associated with increased local secretion of substances such as leptin, an important chemical messenger produced by fat cells. Leptin can stimulate proliferation of epithelial cells within the mammary gland. Although leptin levels in the blood stream did not change, fat cells from isolated mice churned out three times as much leptin as the same cells from group-raised mice.

When premalignant epithelial cells from the tumors were exposed to the substances secreted by mammary-gland fat from isolated mice, they began to proliferate more rapidly, suggesting that the isolated animals' fat could secrete substances that boost tumor growth.

There is growing recognition that "fat cells secrete substances that act on neighboring cell types and that the particular location of the fat in the body matters," Conzen said, "These various fat 'depots' function with highly tissue-specific roles. Different types of fat tissues respond differently to stress, diet and exercise."

The changes in fat cell gene expression were most pronounced at 15 weeks of age, just before a tumor mass could be easily detected in the mice. At this point, the tumors were classified as "carcinoma in situ," a precursor to an invasive malignancy. When a biopsy reveals carcinoma in situ, women are typically encouraged to have a lumpectomy.

"Because the change in fat cell behavior precedes malignancy, there may be ways to intervene and thereby slow or prevent the development of a subsequent more serious breast cancer," Conzen said. "We could use drugs to block the production or secretion of the fat signals to proliferate. There may even be ways, including diet and exercise, to manipulate breast fat metabolism."

Why is breast fat particularly sensitive to the effects of social isolation? Scientists don't yet understand how this response fits into the larger picture of the deleterious effects of stress on an organism, but "it will be an important avenue to pursue, particularly when so much human disease appears to be negatively impacted by social stressors, diet, and other factors causing metabolic derangement," Conzen said.

The mammary glands in both mice and humans include many cell types, but fat cells, the authors note, are "arguably the most neglected and the least well understood component of the breast."

Provided by University of Chicago Medical Center