Gene mapping reveals soy's dynamic, differing roles in breast cancer

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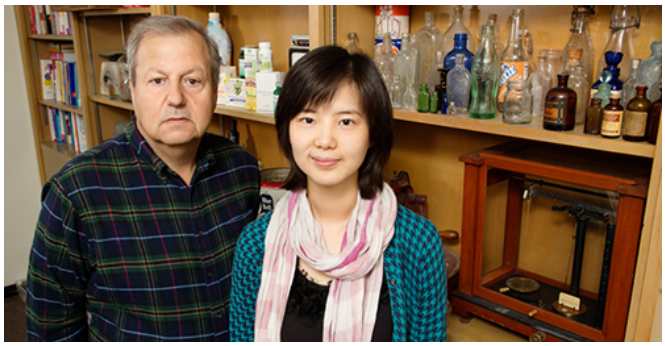

A study by nutrition professor William Helferich and graduate researcher Yunxian Liu at the University of Illinois suggests that while soy foods may protect against breast cancer, soy isoflavone supplements may fuel tumor growth in postmenopausal women. Credit: L. Brian Stauffer

Scientists have mapped the human genes triggered by the phytonutrients in soy, revealing the complex role the legume plays in both preventing and advancing breast cancer.

Researchers at the University of Illinois found that the compounds in minimally processed soy flour stimulate genes that suppress cancer, while purified soy isoflavones stimulate oncogenes that promote tumor growth. The paper, available online, was accepted for publication in the journal *Molecular Nutrition and Food Research*.

Yunxian (Fureya) Liu, a graduate researcher in the laboratory of nutrition professor William G. Helferich, investigated more than 22,680 gene expressions in tumors collected from mice. The mice were injected with MCF-7 human breast-cancer cells and fed one of four diets - including one based on soy flour that contained mixed isoflavones, and another diet based on a purified isoflavone mixture.

Each of these diets contained 750 parts per million of genistein equivalents, an amount comparable to that consumed by women eating a typical Asian diet. Genistein is the primary isoflavone in soy, and recent studies have raised concerns about its long-term effects and potential role in carcinogenesis.

Asian women's risks for breast cancer tend to be three to five times lower than those of women in the U.S., which some researchers have attributed to Asian women's consumption of soy-based whole foods, such as tofu and soy flour, across their lifespans. However, it's unclear whether post-menopausal women in the West achieve similar protective benefits by consuming purified isoflavone supplements later in life.

In the current study, the mice's ovaries had been removed to simulate post-menopausal women, and Liu found that the soy flour and purified isoflavone diets had differing effects on their cells' expression of genes associated with breast cancer.

The mice that consumed soy flour exhibited higher expression of the tumor-suppressing genes ATP2A3 and BLNK, each of which is associated with suppressed tumor growth. These mice also expressed lower levels of oncogenes MYB and MYC, which researchers have found to be critical to tumor growth during early stage breast cancer, and associated with the uncontrolled proliferation of cancer cells, respectively.

"Most important, we found that the soy flour strengthened the whole immune function, which probably explains why it does not stimulate tumor growth," said Liu, who is completing both a doctorate in human nutrition and a master's degree in statistics.

Conversely, the purified isoflavones stimulated tumor growth by activating oncogenes MYB and MYC, while suppressing both immune function and antigen processing, the body's natural process of

seeking out and destroying cancer cells.

Liu correlated the gene expression of the tumor cells with that of women with breast cancer. She found that the purified isoflavones promoted the expression of two kinesin family genes, KIF14 and KIF23, each of which has been associated with shorter survival rates - i.e., less than five years. Accordingly, the isoflavone diet also decreased expression of zinc finger protein gene 423, also called ZNF423, which has been linked with survival rates of five years or greater among breast cancer patients.

Liu's findings also support a hypothesis called the soy matrix effect, a theory that soy's cancer preventive properties are derived from the interactions of complex bioactive compounds - other than isoflavones - within whole foods, such as soy flour.

"There was a difference in the biological responses of mice that consumed the soy flour and those that consumed isoflavone supplements, although both diets contained the same amount of the phytoestrogen genistein," Liu said. "The findings suggest that it's advisable for women with breast cancer to get isoflavones from soy whole foods, rather than isoflavone supplements."

Helferich, a co-author on the paper, said purified isoflavones behave similarly to estrogens such as estradiol, which prior studies have linked with the growth and proliferation of breast cancer cells.

"The gene array data for the isoflavones look very similar to estradiol, which turns on many of the same genes, while the array data for the soy flour look somewhat like the negative control," said Helferich, who has been studying the effects of soy for more than 20 years. "When the estradiol is removed, the tumors regress and almost become non-detectable. But with the soy flour, the tumors don't grow or regress, so they're not exactly like the negative control."

In another new study at Illinois, researchers found that soy isoflavones enhanced the growth of bone micro-tumors in mice with estrogen-responsive breast cancer, causing the tumors to metastasize more aggressively from bone to lung. Xujuan Yang, an associate researcher in Helferich's laboratory, led that project.

The mice that consumed an isoflavones diet had triple the number of tumors - and had larger tumors - on their lungs, compared with their counterparts in the control groups, Yang found. A paper on the study was published in the April issue of Clinical and Experimental Metastasis.

"The main take-home message is, if you have breast cancer, isoflavone dietary supplements are not recommended," Helferich said. "However, consuming soy from a whole food - along with other legumes - is likely safe."

More information: *Molecular Nutrition and Food Research*, onlinelibrary.wiley.com/journal/10.1002/%28ISSN%291613-4133

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