Dietary intervention primes triple-negative breast cancer for targeted therapy

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A diet that starves triple-negative breast cancer cells of an essential nutrient primes the cancer cells to be more easily killed by a targeted antibody treatment, UW Carbone Cancer Center scientists report in a recent publication.

The study's senior author, Vincent Cryns, professor of medicine at the University of Wisconsin School of Medicine and Public Health, says the study lays the foundation for a clinical trial to see if a low-methionine diet will help improve outcomes in women with "triple-negative" breast cancer.

Methionine is an essential amino acid that is present in low concentrations in some vegan diets.

Patients with triple-negative breast cancer have limited treatment options because their tumor cells lack the three receptors—estrogen, progesterone and human epidermal growth factor receptor 2 (HER-2)—commonly targeted in hormone or chemotherapy.

The journal *Clinical Cancer Research* chose the paper as a highlighted study in its June 15 edition.

Scientists have known for decades that methionine deficiency can block the growth of many types of cancer, but the underlying mechanisms have puzzled researchers.

"We've shown that removing methionine can have a specific effect on a molecular pathway that regulates cell death to increase the vulnerability of cancer cells to treatments that target this pathway," Cryns says. "What's particularly exciting about our findings is that they suggest that a dietary intervention can increase the effectiveness of a targeted cancer therapy."

Specifically, the researchers showed that when triple-negative breast cancer cells were deprived of methionine—an essential nutrient abundant in meat, fish, some legumes and nuts, but low in fruits and vegetables—the stressed cancer cells responded by increasing the amount of a receptor on the cell's surface called TRAIL-R2.

This resulted in the breast cancer cells becoming very sensitive to an antibody that binds to TRAIL-R2 on the surface of the cancer cells and triggers them to die.

"What we didn't anticipate is that the normal, non-cancer cells didn't upregulate the receptor under methionine stress the way the tumor cells did," Cryns says. "This shows that diet can help expose a targetable defect in cancer cells."

Lead author Elena Strekalova, a scientist in the Cryns lab, and the research team fed mice with triple-negative breast tumors a diet lacking methionine and treated them with an antibody that binds to the TRAIL-R2 receptor. Mice, like humans, can tolerate a methionine-free diet for a short period of time. The combination of diet and antibody was more effective at shrinking the breast tumors and preventing metastasis to the lungs than either treatment alone.

The University of Wisconsin team believes that their laboratory studies may pave the way for a clinical trial in breast cancer patients to examine the effectiveness of a low-methionine diet in combination with a TRAIL-

R2 monoclonal antibody. When used alone, TRAIL-R2 antibodies have not been effective in patients with metastatic solid tumors.

Cryns hopes that brief exposure to a low methionine diet will boost the effectiveness of TRAIL-R2 antibodies in patients, as it did in mice. "We still have much to learn," Cryns indicates, "but we believe that uncovering the molecular effects of specific nutritional interventions like a low methionine diet will open up new treatment options for cancer."

Provided by University of Wisconsin-Madison