

Jefferson researchers provide genetic evidence that antioxidants can help treat cancer

EurekAlert

PHILADELPHIA?Researchers from Jefferson's Kimmel Cancer Center have genetic evidence suggesting the antioxidant drugs currently used to treat lung disease, malaria and even the common cold can also help prevent and treat cancers because they fight against mitochondrial oxidative stress?a culprit in driving tumor growth.

For the first time, the researchers show that loss of the tumor suppressor protein Caveolin-1 (Cav-1) induces mitochondrial oxidative stress in the stromal micro-environment, a process that fuels cancer cells in most common types of breast cancer.

"Now we have genetic proof that mitochondrial oxidative stress is important for driving tumor growth," said lead researcher Michael P. Lisanti, M.D., Ph.D., professor of cancer biology at Jefferson Medical College of Thomas Jefferson University and member of the Kimmel Cancer Center at Jefferson. "This means we need to make anti-cancer drugs that specially target this type of oxidative stress. And there are already antioxidant drugs out there on the market as dietary supplements, like N-acetyl cysteine."

These findings were published in the online February 15 issue of *Cancer Biology & Therapy*.

Lisanti's lab previously discovered Cav-1 as a biomarker that functions as a tumor suppressor and is the single strongest predictor of breast cancer patient outcome. For example, if a woman has triple negative breast cancer and is Cav-1 positive in the stroma, her survival is greater than 75 percent at 12 years, versus less than 10 percent at 5 years if she doesn't have the Cav-1 protein, according to Dr. Lisanti.

The researchers also established Cav-1's role in oxidative stress and tumor growth; however, where that stress originates and its mechanism(s) were unclear.

To determine this, Jefferson researchers applied a genetically tractable model for human cancer associated fibroblasts in this study using a targeted sh-RNA knock-down approach. Without the Cav-1 protein, researchers found that oxidative stress in cancer associated fibroblasts leads to mitochondrial dysfunction in stromal fibroblasts. In this context, oxidative stress and the resulting autophagy (producton of recycled nutrients) in the tumor-microenvironment function as metabolic energy or "food" to "fuel" tumor growth.

The researchers report that the loss of Cav-1 increases mitochondrial oxidative stress in the tumor stroma, increasing both tumor mass and tumor volume by four-

fold, without any increase in tumor angiogenesis.

"Antioxidants have been associated with cancer reducing effects?beta carotene, for example?but the mechanisms, the genetic evidence, has been lacking," Dr. Lisanti said. "This study provides the necessary genetic evidence that reducing oxidative stress in the body will decrease tumor growth."

Currently, anti-cancer drugs targeting oxidative stress are not used because is it commonly thought they will reduce the effectiveness of certain chemotherapies, which increase oxidative stress.

"We are not taking advantage of the available drugs that reduce oxidative stress and autophagy, including metformin, chloroquine and N-acetyl cysteine," Dr. Lisanti said. "Now that we have genetic proof that oxidative stress and resulting autophagy are important for driving tumor growth, we should re-consider using antioxidants and autophagy inhibitors as anti-cancer agents."

The diabetic drug metformin and chloroquine, which is used for the prevention and treatment of malaria, prevent a loss of Cav-1 in cancer associated fibroblasts (which is due to oxidative stress), functionally cutting off the fuel supply to cancer cells.

This research also has important implications for understanding the pathogenesis of triple negative and tamoxifen-resistance in ER-positive breast cancer patients, as well as other epithelial cancers, such as prostate cancers.

"Undoubtedly, this new genetically tractable system for cancer associated fibroblasts will help identify other key genetic 'factors' that can block tumor growth," Dr. Lisanti said.

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