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Peptide being tested to treat atherosclerosis inhibits ovarian cancer growth

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A drug in testing to treat atherosclerosis significantly inhibited growth of ovarian cancer in both human cell lines and mouse models, the first such report of a peptide being used to fight malignancies, according to a study by researchers at UCLA's Jonsson Comprehensive Cancer Center.

The study follows previous discovery by the same group showing that a protein called apolipoprotein A-I (apoA-I) in patients may be used as a biomarker to diagnose early stage ovarian cancer, when it typically is asymptomatic and is much easier to treat. These earlier findings could be vital to improving early detection, as more than 85 percent of ovarian cancer cases present in the advanced stages, when the cancer has already spread and patients are more likely to have a recurrence after treatment, said Dr. Robin Farias-Eisner, chief of gynecologic oncology and co-senior author of the study with Dr. Srinu Reddy, a professor of medicine.

"The vast majority of ovarian cancer patients are diagnosed with advanced disease and the vast majority of those, after surgery and chemotherapy, will eventually become resistant to standard therapy," Farias-Eisner said. "That's the reason these patients die. Now, with this peptide as a potential therapy, and if successful in clinical trials, we may have a novel effective therapy for recurrent, chemotherapy-resistant ovarian cancer, without compromising the quality of life during treatment."

The study was published Nov. 1, 2010 in the early online edition of the

peer-reviewed journal Proceedings of the National Academy of Sciences .

In their previous work, Farias-Eisner, Reddy and their research teams identified three novel biomarkers that they used to diagnose early stage ovarian cancer. In September 2009, the U.S. Food and Drug Administration cleared the first laboratory test that can indicate the likelihood of ovarian cancer, OVA1TM Test, which includes the three biomarkers identified and validated by Farias-Eisner, Reddy and their research teams.

They observed that one of the markers, apoA-I, was decreased in patients with early stage disease. They wondered why the protein was decreased and set out to uncover the answer. They speculated that the protein might be protective, and may be preventing disease progression.

The protein, apoA-I, is the major component of HDL, the good cholesterol, and plays an important role in reverse cholesterol transport by extracting cholesterol and lipids from cells and transferring it to the liver for extraction. The protein also has anti-inflammatory and antioxidant properties. Because lipid transport, inflammation and oxidative stress are associated with the development and progression of cancer, Farias-Eisner and Reddy hypothesized that the reduced levels of apoA-I in ovarian cancer patients may be causal in disease progression.

Mice that were engineered to have many copies of human apoA-I gene showed very little cancer development when induced with ovarian cancer, while the mice without the extra copies of apoA-I showed much more disease. The mice with extra copies of the apoA-I gene also lived 30 to 50 percent longer than those who didn't receive it.

Farias-Eisner and Reddy wanted to treat the mice that had more cancer with the protein apoA-I, but it was too large to conveniently administer,

having 243 amino acids. The researchers then turned to apoA-I mimetic peptides - only 18 amino acids in length - that are being tested for cardiovascular diseases. That project had been ongoing for a number of years at UCLA, said Reddy, who is also a part of the cardiovascular research team led by Dr. Alan M. Fogelman, executive chair of the Department of Medicine.

"The smaller peptides mimic the larger apoA-I protein and provided us with agents we could give to the mouse to see if it was effective in fighting ovarian cancer," said Reddy. "One of the peptides was being tested as an experimental therapy for atherosclerosis, so we already have some information on how it's being tolerated in humans, which would be vital information to have if we progressed to human studies in ovarian cancer."

The peptide, thus far, has caused little to no side effects in atherosclerosis patients, Reddy said, a hopeful sign that it might be well tolerated in ovarian cancer patients.

The mice that were given the peptide by injection had about 60 percent less cancer than the mice that did not receive the peptide, Farias-Eisner said. The peptide also was given in drinking water or in mouse food and proved to be as effective when administered that way.

"It was an exciting result," Farias-Eisner said. "It looked like we had something that could be ingested or injected that might be very effective against ovarian cancer progression."

Farias-Eisner said the peptide avidly binds oxidized lipids, one of which is known to stimulate cancer cells to survive and multiply. In the mouse studies, the mice that received peptide had significantly lower levels of this cancer promoting lipid.

An early phase clinical trial is being planned testing the peptide in patients with aggressive ovarian cancers that are resistant to chemotherapy, a group of patients whose median survival is just 40 months. Farias-Eisner hopes the study will be started and completed within two years.

Provided by University of California - Los Angeles