Study shows how vitamin E can help prevent cancer

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Researchers have identified an elusive anti-cancer property of vitamin E that has long been presumed to exist, but difficult to find.

Many animal studies have suggested that vitamin E could prevent cancer, but human clinical trials following up on those findings have not shown the same benefits.

In this new work, researchers showed in prostate cancer cells that one form of vitamin E inhibits the activation of an enzyme that is essential for cancer cell survival. The loss of the enzyme, called Akt, led to tumor cell death. The vitamin had no negative effect on normal cells.

"This is the first demonstration of a unique mechanism of how vitamin E can have some benefit in terms of cancer prevention and treatment," said lead author Ching-Shih Chen, professor of medicinal chemistry and pharmacognosy at The Ohio State University and an investigator in Ohio State's Comprehensive Cancer Center.

The study appears in the March 19, 2013, issue of the journal *Science Signaling*.

Chen cautioned that taking a typical vitamin E supplement won't offer this benefit for at least two reasons: The most affordable supplements are synthetic and based predominantly on a form of the vitamin that did not fight cancer as effectively in this study, and the human body can't absorb the high doses that appear to be required to achieve the anti-

cancer effect.

"Our goal is to develop a safe pill at the right dose that people could take every day for cancer prevention. It takes time to optimize the formulation and the dose," he said.

Chen has filed an invention disclosure with the university, and Ohio State has filed a patent application for the agent.

Vitamin E occurs in numerous forms based on their chemical structure, and the most commonly known form belongs to a variety called tocopherols. In this study, researchers showed that, of the tocopherols tested, the gamma form of tocopherol was the most potent anti-cancer form of the vitamin.

The scientists manipulated the structure of that vitamin E molecule and found that the effectiveness of this new agent they created was 20-fold higher than the vitamin itself in cells. In experiments in mice, this agent reduced the size of prostate cancer tumors.

These findings suggest that an agent based on the chemical structure of one form of vitamin E could help prevent and treat numerous types of cancer – particularly those associated with a mutation in the PTEN gene, a fairly common cancer-related genetic defect that keeps Akt active.

The researchers began the work with both alpha and gamma forms of the vitamin E molecule. Both inhibited the enzyme called Akt in very targeted ways, but the gamma structure emerged as the more powerful form of the vitamin.

In effect, the vitamin halted Akt activation by attracting Akt and another protein, called PHLPP1, to the same region of a cell where the vitamin was absorbed: the fat-rich cell membrane. PHLPP1, a tumor suppressor,

then launched a chemical reaction that inactivated Akt, rendering it unable to keep cancer cells alive.

"This is a new finding. We have been taking vitamin E for years but nobody really knew about this particular anti-cancer mechanism," Chen said.

The gamma form was most effective because its chemical shape allowed it to attach to Akt in the most precise way to shut off the enzyme.

Because of how the various molecules interacted on the cell membrane, the scientists predicted that shortening a string of chemical groups dangling from the main body, or head group, of the gamma-tocopherol molecule would make those relationships even stronger. They lopped off about 60 percent of this side chain and tested the effects of the new agent in the prostate cancer cells.

"By reducing two-thirds of the chain, the molecule had a 20 times more potent anti-tumor effect, while retaining the integrity of vitamin E's head group," Chen said. This manipulation enhanced the anti-tumor potency of the molecule by changing its interaction with the cell membrane, so that the head group was more accessible to Akt and PHLPP1.

When mice with tumors created by these two prostate cancer cell lines were injected with the agent, the treatment suppressed tumor growth when compared to a placebo, which had no effect on tumor size. Chemical analysis of the treated tumors showed that the Akt enzyme signal was suppressed, confirming the effects were the same in animals as they had been in cell cultures.

The animal study also suggested the experimental agent was not toxic. Chen's lab is continuing to work on improvements to the molecule.

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