Fatty acid metabolite shows promise against cancer in mice

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A team of UC Davis scientists has found that a product resulting from a metabolized omega-3 fatty acid helps combat cancer by cutting off the supply of oxygen and nutrients that fuel tumor growth and spread of the disease.

The scientists report their discovery in the *Proceedings of the National Academy of Sciences* (*PNAS*). The groundbreaking study was a collaboration among multiple UC Davis laboratories and Harvard University.

The metabolite is epoxy docosapentaenoic acid (EDP), an endogenous compound produced by the human body from the omega-3 fatty acid named docosahexaenoic acid (DHA), which is found in fish oil and breast milk. In animal studies, the UC Davis scientists found that EDP inhibits angiogenesis, the formation of new blood vessels in the body.

Tumors grow and spread by hijacking the normal biological process of angiogenesis, which plays a role in wound repair as well in growth and development. The UC Davis researchers determined that by inhibiting angiogenesis, EDP reduces the growth and spread (metastasis) of tumors in mice. The research provides the first scientific evidence about EDP's potent anti-cancer, anti-metastatic effects.

EDP works by a different mechanism than many current anti-cancer drugs that block angiogenesis.

"Our investigation opens up a new understanding of the pathways by which omega-3 fatty acids exert their biologic effects," said Guodong Zhang, the lead author of the article and a postdoctoral researcher in the laboratory of Bruce Hammock in the Department of Entomology and the UC Davis Comprehensive Cancer Center.

The researchers said that future studies hopefully will determine that stabilized EDP can be safely and effectively combined with other current anti-angiogenesis drugs in the treatment of cancer.

"As far as we know, EDPs are the first signaling lipids that have been discovered to have such potent anti-cancer effects. Researchers may be able to use EDPs as structural targets to develop stable analogs that mimic their anti-cancer agents," Zhang said.

"The study by Zhang and colleagues has uncovered a previously unrecognized anti-cancer effect of omega-3 fatty acids, which are an important lipid component of diets that have been developed to prevent heart disease and cancer," said Jonathan R. Lindner, professor of medicine at Oregon Health & Sciences University.

"The authors have demonstrated that metabolites of these lipids can act to suppress the growth of new blood vessels that are necessary to feed tumor growth," added Lindner, who was not involved in the study. "By shutting off a tumor's blood supply, these compounds can act to dramatically slow tumor growth and prevent spread. The results from this study suggest that new drug strategies for fighting cancer could emerge from knowledge of how the body uses nutrition to promote health."

The EDPs are broken down in the body by inhibiting the enzyme soluble epoxide hydrolase (sHI). In previous research, Hammock's lab showed that inhibitors of the sEHI enzyme help to normalize physiological

activity. In the current study, UC Davis researchers determined that the addition of sEHI stabilized EDP in circulating blood thereby producing EDPs' anti-tumor effects. The anti-cancer drugs sorafenib and regorafenib are FDA-approved sEHIs.

"It may be possible to improve the efficacy of these anti-cancer drugs by combining them with a diet high in omega-3 and low in omega-6 fatty acids," Hammock said.

The researchers also found that a metabolite of arachidonic acid (ARA), an omega-6 fatty acid, has the opposite effect of EDP. The ARA metabolite, epoxyeicosatrienoic acids (EETs), slightly increases angiogenesis and tumor progression in mice.

"There is no free lunch," said Katherine W. Ferrara, professor in the UC Davis Department of Biomedical Engineering. "The EETs encourage wound healing, while the EDPs block the growth and metastasis of solid tumors.

"Our results designate EDPs and EETs as unique mediators of an angiogenic switch to regulate tumorigenesis," Ferrara said. "They also implicate a novel mechanistic linkage between omega-3 and omega-6 fatty acids and cancers."

UC Davis scientists determined that EDP starves tumors by inhibiting vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2)-induced angiogenesis in mice. In laboratory cultures, EDP also suppresses the endothelial cell migration needed for new blood vessels.

Thus, EDP-based angiogenesis inhibitors offer an advantage over angiogenesis inhibitors that target the VEGF-VEGFR2 pathway. The drugs that target the VEGF-VEFGFR2 pathway increase patients' risk

for high blood pressure.

Because EDPs widen the blood vessels, a medication based on the UC Davis researchers' discovery should not increase the patient's risk for high blood pressure.

Harvard researchers Mark Kieran and Dipak Panigrahy conducted the metastasis studies. The in vivo imaging work that allowed the scientists to monitor tumors in living mice was done in Ferrara's UC Davis laboratory.

More information:
www.pnas.org/content/early/2013/04/03/1304321110

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