Targeting EETs to treat cardiovascular disease may prove a double-edged sword

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A group of small molecules called EETs – currently under scrutiny as possible treatment targets for a host of cardiovascular diseases – may also drive the growth and spread of cancer, according to researchers at the Dana-Farber/Children's Hospital Cancer Center (DF/CHCC) and other institutions. Their findings also raise the possibility that drugs that block EETs could serve as a new avenue for cancer treatment.

This study, led by Dipak Panigrahy, MD, of DF/CHCC and the Vascular Biology Program at Children's Hospital Boston, appeared online December 19 in the Journal of Clinical Investigation.

EETs (or epoxyeicosatrienoic acids) are small fatty molecules, part of a larger family of lipids normally produced by the endothelial cells that line blood vessels to control inflammation and the response to injury. These molecules are also potent regulators of blood pressure, leading pharmaceutical companies to investigate compounds that raise EET levels for the treatment of nearly 20 cardiovascular diseases, including hypertension, stroke, and diabetes.

However, little work has been done to learn whether these molecules themselves might have some role to play in tumor growth or progression. This is despite evidence that enzymes that process EETs are associated with cancer, and that EETs can promote angiogenesis – the growth of blood vessels.

"EETs have primarily been studied in models of cardiovascular disease,"

said the study's lead author, Dipak Panigrahy, MD. "This is the first time that direct administration of exogenous EETs and of specific EET antagonists has been investigated in pre-clinical cancer models."

In order to determine the extent of the relationship between EETs and cancer, Panigrahy and his collaborators conducted a series of studies using animal models of EET activity developed in the laboratory of Darryl Zeldin, MD, at the National Institute of Environmental Health Sciences, part of the National Institutes of Health.

"NIEHS was pleased to work with such a distinguished international research team to address this important issue," Zeldin said.

With the models, the researchers were able to document that increasing the levels of EET levels – either by increasing their natural production or injecting them systemically – creates an environment conducive to tumor growth, even contributing to the transition of early tumors from a dormant state to active malignancy. They also found that EETs work in concert with VEGF, a potent stimulator of angiogenesis in both normal and cancerous tissues, to promote tumor metastasis, even in cancers that rarely spread to other organs.

"Many people have dormant tumors that may never become fully malignant," said Panigrahy. "The switch from a dormant to an active state is critically dependent on angiogenesis, as is metastasis, and so patients who have a high cancer risk could potentially increase that risk further by raising their EET levels."

The study team also found that compounds that block the activity of EETs, called EET antagonists, could reduce tumor growth and metastasis in the same animal models, suggesting that such compounds could have benefit as cancer treatments.

"Cardiovascular disease is a major cause of death in North America, and as such drugs that raise EET levels could provide significant benefit," says DF/CHCC's Mark Kieran, MD, PhD, one of the paper's senior authors. "We must be cautious, though, that in manipulating these molecules to regulate blood pressure we do not favor cancer growth and metastasis, another common cause of death.

"With these findings, though," Kieran continued, "we now have a better idea of how cancers drive themselves, opening up a new pathway for understanding and potentially treating cancer and metastasis that wasn't available to us before. At the same time, this data could potentially help inform the design of cardiovascular drugs that avoid raising cancer risk through this mechanism."

More information: Epoxyeicosanoids stimulate multiorgan metastasis and tumor dormancy escape in mice, *Journal of Clinical Investigation*.

Provided by Children's Hospital Boston