New study shows antioxidants stimulate blood flow in tumors

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Vitamin C and other antioxidants stimulate the formation of new blood vessels in lung cancer tumors, a new study from Karolinska Institutet published in the *Journal of Clinical Investigation* shows. The discovery corroborates the idea that dietary supplements containing antioxidants

can accelerate tumor growth and metastasis.

"We've found that antioxidants activate a mechanism that causes cancer tumors to form new blood vessels, which is surprising, since it was previously thought that antioxidants have a protective effect," says study leader Martin Bergö, professor at the Department of Biosciences and Nutrition and vice president of Karolinska Institutet in Sweden. "The new blood vessels nourish the tumors and can help them grow and spread."

Antioxidants neutralize free oxygen radicals, which can damage the body, and are therefore commonly found in dietary supplements. But overly high doses can be harmful.

"There's no need to fear antioxidants in normal food but most people don't need additional amounts of them," says Professor Bergö. "In fact, it can be harmful for cancer patients and people with an elevated cancer risk."

Previously unknown mechanism

Professor Bergö's research group has previously shown that antioxidants like vitamin C and E accelerate the growth and spread of lung cancer by stabilizing a protein called BACH1.

BACH1 is activated when the level of free oxygen radicals drops, which happens, for example, when extra antioxidants are introduced via the diet or when spontaneous mutations in the tumor cells activate endogenous antioxidants. Now the researchers have been able to show that the activation of BACH1 induces the formation of new blood vessels (angiogenesis).

While low oxygen levels (hypoxia) are known to be required for

angiogenesis to occur in cancer tumors, the new mechanism identified by the researchers demonstrates that tumors can form new blood vessels in the presence of normal oxygen levels as well.

The study also shows that BACH1 is regulated in a similar way as the HIF-1α protein—a mechanism that was awarded the 2019 Nobel Prize in Physiology or Medicine and that allows cells to adapt to changes in oxygen levels. HIF-1α and BACH1 work together in the tumors, the new research shows.

Hoping for more effective drugs

"Many clinical trials have evaluated the efficacy of angiogenesis inhibitors, but the results have not been as successful as anticipated," says Ting Wang, doctoral student in Professor Bergö's group at Karolinska Institutet. "Our study opens the door to more effective ways of preventing angiogenesis in tumors; for example, patients whose tumors exhibit high levels of BACH1 might benefit more from anti-angiogensis therapy than patients with low BACH1 levels."

The researchers used a range of cell-biological methods and concentrated most of their work on lung cancer tumors by studying organoids—small cultivated microtumours from patients. But they also studied mice and samples of human breast and kidney tumors. Tumors in which BACH1 was activated, either via ingested antioxidants or by overexpression of the BACH1 gene, produced more new blood vessels and were highly sensitive to angiogenesis inhibitors.

"The next step is to examine in detail how levels of oxygen and free radicals can regulate the BACH1 protein, and we will continue to determine the clinical relevance of our results," says Ting Wang. "We'll also be doing similar studies in other cancer forms such as breast, kidney and skin cancer."

The study was conducted in close collaboration with KI researchers Susanne Schlisio, Staffan Strömblad and Eckardt Treuter and researchers at the First Affiliated Hospital of Zhengzhou University.

More information: Antioxidants stimulate BACH1-dependent tumor angiogenesis, *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI169671