Starving pancreatic cancer of cysteine may kill tumor cells

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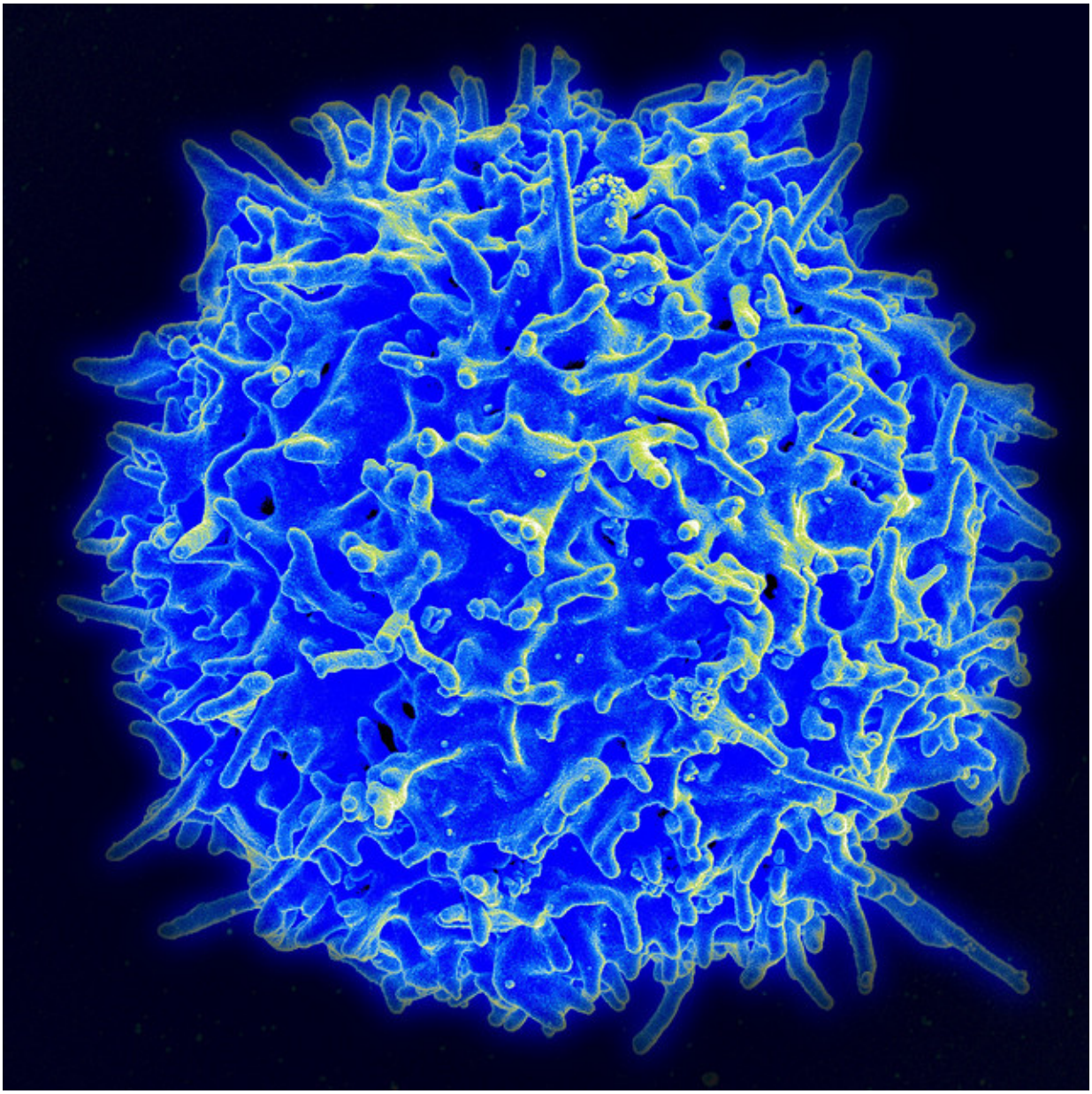

Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIAID

A new study from Columbia University Irving Medical Center and the Herbert Irving Comprehensive Cancer Center suggests a compound in development for a rare kidney stone disease may have potential against pancreatic cancer. The compound starves tumors of an amino acid, cysteine, which was found to be critical to the survival of pancreatic cancer cells.

The study, conducted in mice with pancreatic cancer, was published online today in the journal *Science*.

"We're very encouraged by these results," says Kenneth P. Olive, Ph.D., associate professor of medicine at Columbia University Vagelos College of Physicians and Surgeons, member of the HICCC, and senior author of the study. "Pancreatic cancer is a uniquely lethal disease, with an average survival rate of just six months after diagnosis. We're in desperate need of new treatments."

Most pancreatic tumors ramp up the production of oxidants that can kill many normal cells. Yet, pancreatic tumors thrive under these toxic conditions by importing large amounts of cysteine into their cells. All cells, including pancreatic tumor cells, use cysteine to manufacture molecules that detoxify oxidants.

"Since pancreatic tumors appear to depend on cysteine import for their survival, we hypothesized that it might be possible to slow tumor growth by selectively targeting this amino acid," Olive said.

That strategy of starving the pancreatic cancer cells of cysteine worked.

When the gene that controls cysteine import was knocked out in mice with pancreatic cancer closely resembling human tumors, cutting off the cancer's supply of cysteine, the tumors stopped growing and median survival time doubled.

The researchers achieved similar results when the mice were treated with cysteinase—an experimental drug that breaks down cysteine in blood. (Cysteinase is currently being developed by researchers at the University of Texas Southwestern Medical Center for the treatment of cystinuria, a rare genetic disorder in which high levels of cysteine concentrate in the urine, causing kidney and urinary tract stones.)

Human pancreatic cancer cells also appear to be dependent on cysteine, the researchers found. When cysteinase was added to human pancreatic cancer cells in tissue culture, cancer cells died.

Role of ferroptosis in pancreatic cancer

When starved of cysteine, the pancreatic cancers cells are killed by a process called ferroptosis, the researchers also found. Ferroptosis is a form of programmed cell death that results from oxidation damage to cell membranes. Recently discovered by Columbia University researcher Brent Stockwell, professor of biological sciences, a coauthor on the new paper, ferroptosis may also be harnessed against other types of cancer.

Olive's team also worked with a group from the University of Michigan, led by Dr. Costas Lyssiotis, and a group from the Salk Institute, led by Dr. Geoffrey Wahl, to explore the detailed cellular and molecular mechanisms of ferroptosis in pancreatic cancer, in hope that this understanding might lead to additional therapeutic approaches.

Olive's team is now planning to test whether the effect of cysteinase can be magnified by combining it with other treatments, including

immunotherapy.

"Though it is not yet known if pancreatic cancers in patients are also susceptible to ferroptosis from cysteine depletion," Olive says, "the clinical development of cysteinase for treatment of the metabolic disorder cystinuria may allow us to test the idea soon."

One of the most exciting aspects of the new study is that cysteine depletion did not appear to harm healthy, normal cells. "You might imagine that all the cells of your body need every amino acid equally, but we knew from prior studies that most normal cells need only very low levels of cysteine," says Olive. "Our whole goal in targeting this difference between normal cells and cancer cells is to develop a treatment that is toxic to cancer and gentle on the rest of the body."

The study is titled, "Cysteine depletion induces pancreatic tumor ferroptosis in mice."

More information: "Cysteine depletion induces pancreatic tumor ferroptosis in mice" *Science* (2020). science.sciencemag.org/cgi/doi …1126/science.aaw9872

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