Energy network within cells may be new target for cancer therapy

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Mitochondria, tiny structures within each cell that regulate metabolism and energy use, may be a promising new target for cancer therapy, according to a new study. Manipulation of two biochemical signals that regulate the numbers of mitochondria in cells could shrink human lung cancers transplanted into mice, a team of Chicago researchers report in the journal *FASEB*.

Within each cell, mitochondria are constantly splitting in two, a process called fission, and merging back into one, called fusion. Before a cell can divide, the mitochondria must increase their numbers through fission and separate into two piles, one for each cell.

By reversing an imbalance of the signals that regulate fusion and fission in rapidly dividing cancer cells, researchers were able to dramatically reduce cell division, thus preventing the rapid cell proliferation that is a hallmark of cancer growth. Increasing production of the signal that promotes mitochondrial fusion caused tumors to shrink to one-third of their original size. Treatment with a molecule that inhibits fission reduced tumor size by more than half.

"We found that human lung cancer cell lines have an imbalance of signals that tilts them towards mitochondrial fission," said Stephen L. Archer, MD, the Harold Hines Jr. Professor of Medicine at the University of Chicago Medicine and senior author of the study. "By boosting the fusion signal or blocking the fission signal we were able to tip the balance the other way, reducing cancer cell growth and increasing

cell death. We believe this provides a promising new approach to cancer treatment."

"This could be a potential new Achilles' heel for cancer cells," said the study's lead author, Jalees Rehman, MD, an associate professor of medicine and pharmacology at the University of Illinois at Chicago. "Many anticancer drugs target cell division. Our work shifts the focus to a distinct but necessary step: mitochondrial division. The cell division cycle comes to a halt if the mitochondria are prevented from dividing. This new therapy may be especially useful in cancers which become resistant to conventional chemotherapy that directly targets the cycle."

The researchers found that the mitochondrial networks within several different lung cancer cell lines were highly fragmented, compared to normal lung cells. Cancer cells had low levels of mitofusin-2 (Mfn-2), a protein that promotes fusion by tethering adjacent mitochondria, and high levels of dynamin-related protein (Drp-1), which initiates fission by encircling the organelle and squeezing it into two discrete fragments. The Drp-1 in cancer cells also tended to be in its most active form.

The researchers tested several ways to enhance fusion and restore the mitochondrial network, both in cell culture and in animal models. They used gene therapy to increase the expression of Mfn-2, injected a small molecule (mdivi-1) that inhibits Drp-1, and used genetic techniques to block the production of Drp-1. All three interventions markedly reduced mitochondrial fragmentation, increased networking and reduced cancer cell growth.

Although the authors identify mitochondrial fission and Drp-1 activation as a potential therapeutic target in lung cancer, "this is not a cure," Archer emphasized. The treatment drastically reduced tumor size but the tumors did not completely disappear. They continued to use high levels of glucose as fuel, a hallmark of cancer metabolism that can be seen on

PET scans. "This remnant could be either a central cluster of cancer stem cells," Archer said, "or an inflammatory response, the immune system infiltrating the tumor."

"Inhibiting mitochondrial fission", Archer said, "did not show any significant toxicity in mice or rats, so we are quite optimistic that our findings can lead to the development of novel, clinically feasible therapies."

The substances used to block fusion are commercially available for research purposes, but they have not been tested in humans. Mdivi-1 has been used in animals to prevent kidney injury.

Although the focus on mitochondria is fairly new to cancer biologists—despite a flurry of interest in the 1920s stimulated by the German Nobel Prize laureate Otto Warburg—this organelle has long been a central focus for physicians and scientists interested in muscle biology, especially cardiac muscle.

Archer, a cardiologist, specializes in pulmonary hypertension. In this disorder, as in cancer, excessive cellular growth causes disease. The death of his cousin and close friend from lung cancer made him start thinking about the connections. Rehman is a German scientist and became interested in studying mitochondria after reading some of the historical Warburg papers in German.

The fact that two cardiologists, Archer and Rehman, decided to study cancer and collaborated with a team of basic scientists, a cancer physician and a pathologist is "an indicator of how interconnected modern biomedical research has become," Rehman said.

Provided by University of Chicago Medical Center