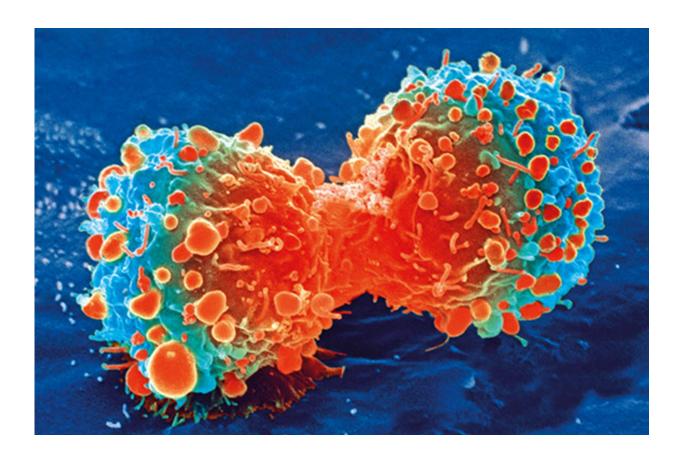


More evidence that cellular 'death by iron' could be promising avenue of cancer treatment

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Cancer cell during cell division. Credit: National Institutes of Health

If there is a silver lining in cancer's chaotic biology, it's that the same traits that give cancer cells a growth advantage often present



opportunities for sabotaging them.

That's the central idea behind a new research paper published November 23 in *Proceedings of the National Academy of Sciences (PNAS)* by Xuejun Jiang, a <u>cell biologist</u> in the Sloan Kettering Institute, and Craig Thompson, President and CEO of Memorial Sloan Kettering. They found that <u>cancer</u> cells often exhibit metabolic changes that make them vulnerable to a particular type of cell death called ferroptosis.

Ferroptosis—literally, death by iron—is often triggered by oxidative stress, the buildup in cells of free radicals and other corrosive chemicals that are byproducts of using oxygen to burn fuel for energy. But many cancer cells, which need abundant amounts of energy to grow and divide, have found a way around this problem.

"Genetic <u>mutations</u> that allow cancer cells to cope with oxidative stress make them more resistant to ferroptosis," Dr. Jiang says. "Another way to say this is that without the benefit of those mutations, cancer cells might be very, very sensitive to ferroptosis."

He and his colleagues, including postdoctoral fellows Junmei Yi and Jiajun Zhu, tested this idea by giving mice a combination of drugs—one that promotes ferroptosis and one that blocks the effect of the mutations. The results of this one-two punch were dramatic.

A Commonly Mutated Pathway

The particular mutations Dr. Jiang and colleagues studied affect a signalsending pathway called PI3K-AKT-mTOR, which controls metabolism. Mutations in this pathway are among the most common found in cancer. That likely reflects the fact that cancer cells have increased metabolic demands owing to how quickly they reproduce. Cancers with mutations in the PI3K-AKT-mTOR pathway are some of the most difficult to



treat.

The team found that <u>tumor cells</u> with these mutations demonstrated a hardy resistance to an experimental ferroptosis-inducing drug that was administered to cells growing in a dish. When the scientists added drugs that block the action of this metabolic pathway to the ferroptosisinducing drug, the cancer cells died.

Next, they tested whether this same effect would be seen in mouse models of breast and prostate cancers containing these mutations. Indeed, the drug combination resulted in near-complete tumor destruction in the mice.

"These were some of the most significant tumor regressions I've ever seen coming from experiments in my lab," Dr. Jiang says.

He and his collaborators further showed that the way the mutated PI3K-AKT-mTOR pathway protects <u>cancer cells</u> is by increasing the activity of a protein that is involved in making lipids for the cell's outer membrane. These extra lipids help to protect the cells against <u>oxidative</u> <u>stress</u>, and therefore ferroptosis. Blocking PI3K-AKT-mTOR prevents this lipid synthesis and re-sensitizes the cells to ferroptosis.

The new findings complement previous work from the Jiang lab, published in 2019 in the journal *Nature*. In that paper, Dr. Jiang found the some cancers have mutations that make them more sensitive to ferroptosis, even without administering metabolism-altering drugs. In a sense, the new results represent the flipside of the equation.

"The key point is that many cancers have genetic alterations that can be exploited to trigger ferroptosis and kill the <u>cells</u>. It's an exciting way to think about developing new cancer treatments."



The team has applied for a patent related to this work. Their next step is to test the <u>drug</u> combination in tumor samples obtained from patients being treated at MSK.

More information: Junmei Yi et al. Oncogenic activation of PI3K-AKT-mTOR signaling suppresses ferroptosis via SREBP-mediated lipogenesis, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.2017152117

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