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In iron-dependent cell death, lysosome destabilization is key

Findings reveal a new avenue for cancer treatments

Fukuoka, Japan—The duplication and division of cells is critical to keeping all multicellular organisms alive. But the opposite process is equally important: cell death. Controlled death of cells, or programmed cell death, is also necessary for the proper development and function of the body. It has also been a focus of researchers developing treatments for cancer by finding ways to activate the cell death of cancer cells themselves.

Ferroptosis is a recently discovered form of programmed cell death and has been a promising target for the development of cancer treatments. It is mediated by iron molecules, with the cell dying through the degradation of the phospholipid bilayer by oxidation, a process called lipid peroxidation. However, recent studies have shown that certain cancer cells are less susceptible to ferroptosis, raising concerns that this resistance could pose a barrier to future therapeutics.

In a paper published in *Nature Communications*, researchers from Kyushu University, using cultured cells and mice, found that the lipid peroxidation of the lysosomes—the organelle responsible for degrading and recycling molecules in a cell—plays a critical role in the execution of ferroptosis. The team also showed that this process leads to iron leakage from the lysosome, which further promotes ferroptosis. Moreover, administration of chloroquine—a drug that promotes lysosomal membrane damage—facilitates ferroptosis in cancer cells that are less sensitive to this process.

"Previous studies of ferroptosis have shown that there are mechanisms that control lipid peroxidation and that the cell membrane is damaged in the final stages of cell death. However, the origin of this lipid peroxidation that causes ferroptosis has remained a topic of debate," explains Professor Ken-ichi Yamada of Kyushu University's Faculty of Pharmaceutical Sciences, who led the study. "We know that during ferroptosis, lipid peroxidation occurs at different sites within the cell. So, to identify where ferroptosis begins, our team developed a way to visualize lipid radicals in a cell."

The team discovered that peroxidation of lysosomes plays a key role in the execution of ferroptosis-mediated cell death. Additionally, they found that lysosomal lipid peroxidation causes the membrane to permeabilize, allowing iron molecules to leak out, which in turn promotes the spread of lipid peroxidation to other intracellular organelles.

"Interestingly, in cancer cells that are less susceptible to ferroptosis, lipid peroxidation occurred in the lysosomes, but this did not lead to lysosomal membrane damage," continues Yamada. "Upon further investigation, we found that administration of chloroquine, a drug that promotes lysosomal membrane damage, induced ferroptosis even in these less susceptible cancer cells."

The team hopes that their new findings can further the development of not only cancer treatments harnessing ferroptosis, but also other pathologies where ferroptosis could be a therapeutic target. They also plan to further investigate the mechanisms governing ferroptosis.

"Strategies to overcome ferroptosis-low-susceptibility have been proposed by simultaneously inhibiting multiple enzymes that suppress lipid peroxidation. However, the effects would differ between certain cell types. Here, we presented a new strategy that could overcome low ferroptosis sensitivity," concludes Yamada. "However, we still don't know the underlying mechanism as to why lysosomal membrane damage does not occur in ferroptosis-low-susceptible cells. Further investigation is needed."

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For more information about this research, see "Lysosomal lipid peroxidation contributes to ferroptosis induction via lysosomal membrane permeabilization," Yuma Saimoto, Daiki Kusakabe, Kazushi Morimoto, Yuta Matsuoka, Eisho Kozakura, Nao Kato, Kayoko Tsunematsu, Tomohiro Umeno, Tamiko Kiyotani, Shota Matsumoto, Mieko Tsuji, Tasuku Hirayama, Hideko Nagasawa, Koji Uchida, Satoru Karasawa, Mirinthorn Jutanom, and Ken-ichi Yamada, *Nature Communications* https://doi.org/10.1038/s41467-025-58909-w

About Kyushu University

Founded in 1911, Kyushu University is one of Japan's leading research-oriented institutes of higher education, consistently ranking as one of the top ten Japanese universities in the Times Higher Education World University Rankings and the QS World Rankings. The university is one of the seven national universities in Japan, located in Fukuoka, on the island of Kyushu—the most southwestern of Japan's four main islands with a population and land size slightly larger than Belgium. Kyushu U's multiple campuses—home to around 19,000 students and 8000 faculty and staff—are located around Fukuoka City, a coastal metropolis that is frequently ranked among the world's most livable cities and historically known as Japan's gateway to Asia. Through its VISION 2030, Kyushu U will "drive social change with integrative knowledge." By fusing the spectrum of knowledge, from the humanities and arts to engineering and medical sciences, Kyushu U will strengthen its research in the key areas of decarbonization, medicine and health, and environment and food, to tackle society's most pressing issues.

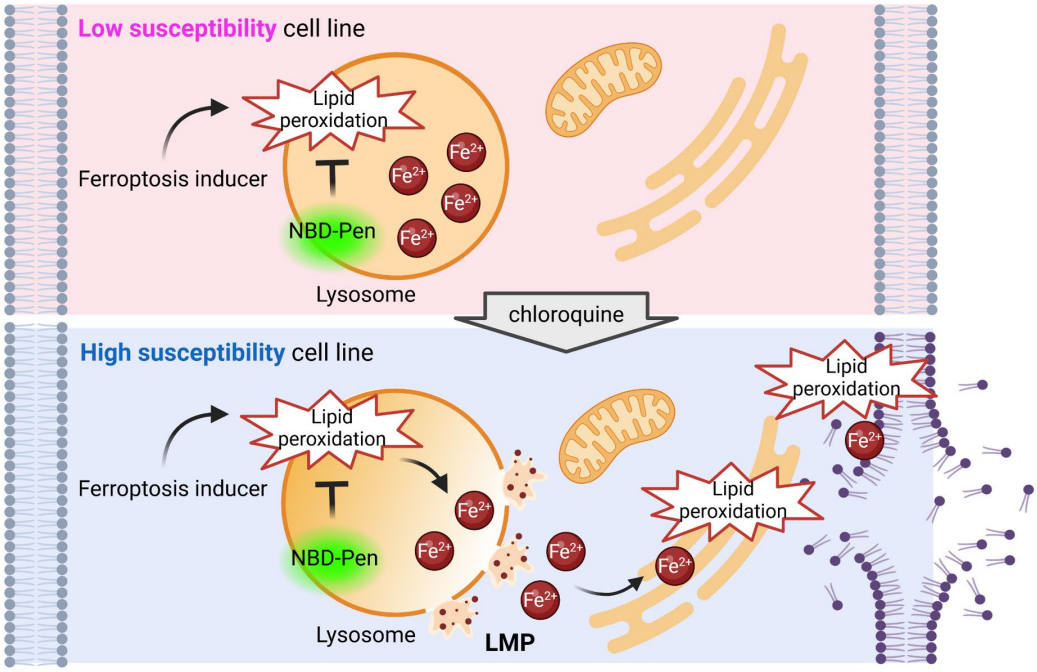

Fig. 1. Overview of the research. By detecting lipid oxidation, the research team found that lipid oxidation in lysosomes is the cause of ferroptosis, iron mediated cell death. This results to leakage of iron from lysosomes which contributes to the further induction of cell death. The team also found that treating low-ferroptosis-sensitivity cells with chloroquine promotes lysosomal iron leakage, making it possible to induce ferroptosis. (Yamada Lab/Kyushu

University. Created in BioRender. Yuma, S. (2025) https://BioRender.com/w81p034)

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