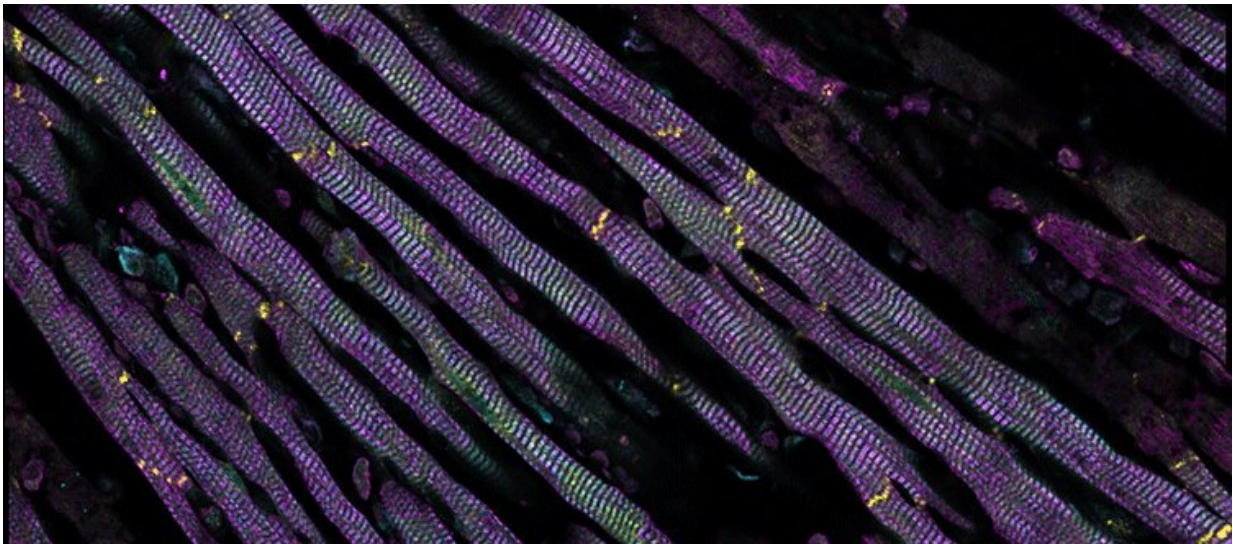


## Researchers reduce heart-attack-caused cardiac tissue damage by 30% in mice

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Immuno-staining of mouse heart cells under anoxia. Healthy striated heart muscle (lower left) gradually shows more and more signs of deterioration due to oxygen deprivation leading to fully necrotic cells (upper right). Credit: UNIGE

Each year, heart attacks kill almost 10 million people around the world, and more than 6 million die from stroke. A heart attack is caused by clots that block arterial blood flow. Tissues are deprived from blood-borne oxygen. Under these conditions, the affected tissues undergo a rapid necrosis. But why? Scientists at the University of Geneva (UNIGE), Switzerland, the University of Lyon and the Institut National de la Santé et de la Recherche Médicale (Inserm), France, have

discovered that the synthesis of a lipid called deoxydihydroceramide provokes necrosis. This lipid accumulates in the absence of oxygen and blocks cellular functions. By inhibiting its synthesis in a mouse suffering a heart attack, the biologists were able to reduce the tissue damage by 30 percent. These results, published in *Nature Metabolism*, suggest a new model of treatment for victims of heart attack or stroke.

"But what causes necrosis under these conditions?" asked Howard Riezman, professor in the Department of Biochemistry of the Faculty of Science at UNIGE and Director of the NCCR Chemical Biology. Not all animals are so sensitive to the absence of [oxygen](#)—worms can live three days without oxygen, some turtles can live several months, and certain bacteria indefinitely.

"That is why we sought to find the link between the lack of oxygen and [tissue](#) necrosis in mammals," said the scientist.

## **A lipid that inhibits normal cellular function**

The researchers saw that in worms, a particular species of ceramide, deoxydihydroceramide, accumulated to dangerous levels under anoxia, in which tissues were completely deprived of oxygen. "Ceramides are absolutely essential lipids for the body," says Thomas Hannich, a researcher at the Department of Biochemistry of the Faculty of Science at the UNIGE. "Without ceramides, several essential functions would be defective. For example, our skin would completely dry out."

Nevertheless, upon an infarct, the synthesis of deoxydihydroceramide increases and becomes toxic for cells. "Using [mass spectrometry](#), we observed that this ceramide blocks certain protein complexes and provokes defects in the cytoskeleton of cells and the proper function of mitochondria, causing tissue necrosis," continued Howard Riezman.

To confirm that deoxydihydroceramide was, indeed, responsible for tissue necrosis, the UNIGE team introduced a human mutation causing a [rare disease](#), HSAN type I, into the worms, raising the amount of deoxydihydroceramide. The worms became hypersensitive to the lack of oxygen, confirming the discovery.

## **Can clinicians reduce the impact of an infarct on the affected tissues?**

Based on these results, Michel Ovize and his team from the University of Lyon injected an inhibitor of ceramide synthesis in mice just before a heart infarct. They found that the mice that received the injection had 30 percent less tissue necrosis when compared to control mice that received an injection without the inhibitor. "This reduction is quite impressive," says Howard Riezman. This work opens new therapeutic perspectives for treatment of patients with vascular infraction.

This discovery could pave the way for a big advance in the development of treatments for heart attacks and stroke. The results obtained in mice are extremely encouraging, and the [ceramide](#) synthesis inhibitor is a well-known substance that has been tested in animal models.

"Nevertheless, this molecule inhibits the synthesis of all ceramides," says Thomas Hannich. So the researchers are now working on an inhibitor that will target more specifically deoxydihydroceramide, which is likely to have fewer side effects and maintain the normal body functions of ceramides.

**More information:** J. Thomas Hannich et al.

1-Deoxydihydroceramide causes anoxic death by impairing chaperonin-mediated protein folding, *Nature Metabolism* (2019). [DOI: 10.1038/s42255-019-0123-y](https://doi.org/10.1038/s42255-019-0123-y)

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