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Mitochondria send death signal to cardiac cells, study shows

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Scientists have determined how cardiac cells die just as emergency treatments restore blood flow to a heart in distress, a paradox that has long puzzled doctors who are able to relieve pain in patients suffering from blocked arteries but can't stop the damage caused by the renewed rush of blood.

The discovery may lead to new ways to save that dying tissue.

It is the stoppage of blood flow and resulting loss of oxygen to the heart that causes chest pain during cardiac events. Clinicians' first order of business is restoring that flow with medicine or other noninvasive procedures, or even an invasive procedure, such as placement of a stent or balloon to open a blocked vessel.

But the rush of blood – and the oxygen it carries – that restores a heart's beat and relieves the pain can also damage tissue and weaken the heart's function because cardiac cells die in the process. And like brain cells, cardiac cells take a long time for the body to replace, so the damage is difficult to repair.

Researchers at Ohio State University Medical Center have traced this cell-death signal to the mitochondria, the principal energy source of cells, through a specialized technique. In experiments, cardiac cell mitochondria were isolated and subjected to ischemia and reperfusion – the blockage and restart of blood flow. The researchers hope that identifying the origin of the cell-death signal will improve the chances of

finding a way to stop the signal, reducing the damage associated with restored blood flow to the heart.

The results were published in the October issue of the *Journal of Molecular and Cellular Cardiology*.

“This form of cardiac cell death is a major medical and health issue. The patient has severe pain from the loss of blood flow and oxygen to the heart, so we cannot do anything other than clear that artery to restore the blood and oxygen. But when that is done, the patient loses cardiac cells. It's a paradox,” said senior study author Pedram Ghafourifar, associate professor of surgery and pharmacology and director of basic science research in the division of vascular surgery at Ohio State 's Medical Center.

“The mitochondria have been suspected in this process, but to date, we haven't known for sure.”

Ghafourifar's lab developed a technique allowing researchers to watch isolated mitochondria in real time during this process. Using chemical probes and a novel technique called dual-wavelengths excitation spectrophotofluorometry, they saw that after the mitochrondria were subjected to ischemia followed by reoxygenation, a boost of calcium occurred in the mitochondria.

“Calcium levels went up like never before, which is unusual, because mitochrondria typically are able to tightly maintain a low level of calcium,” said Ghafourifar, also an investigator in the Davis Heart and Lung Research Institute. That glut of calcium, in turn, triggered an enzyme to begin churning out toxic levels of the free radical nitric oxide – much more than the mitochondria could handle. And that excess of nitric oxide led to the release of a mitochondrial protein that sends the death signal to the cell.

The enzyme at work in this process is called mitochondrial nitric oxide synthase, discovered and reported by Ghafourifar's lab in 1997. Because researchers don't know the cause of the calcium increase during reoxygenation of the heart, Ghafourifar and his colleagues have focused on the enzyme as a therapeutic target to stop the production of nitric oxide that leads to cell death.

“The next immediate step is finding whether we can inhibit this enzyme so it doesn't generate excess nitric oxide during the reoxygenation phase,” Ghafourifar said. “We're trying to develop experimental drugs that can be delivered at the time of reperfusion or just before. Some seem to be successful at selectively inhibiting the enzyme.”

The experimental therapies will soon be tested in animal studies.

The identification of the enzyme as a target to stop cell death could influence a range of therapeutic options, Ghafourifar said, by applying to disease processes characterized by cell death, or, in the case of cancer, the refusal of cells to die when they should.

“Cell death is involved in a variety of diseases that don't seem to be related,” he said. “In cancer, cells do not die. In Parkinson's and Alzheimer's disease, cells die earlier than we want them to. If we figure out how cell death happens, we can put up a fight against a number of diseases.”

Source: Ohio State University