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Steven Sollott & Dmitry Zorov talk with *ScienceWatch.com* and answer a few questions about this month's Fast Moving Fronts paper in the field of Agricultural Sciences.

Article: Mitochondrial ROS-induced ROS release: An update and review
Authors: **Zorov, DB**;Juhaszova, M;**Sollott, SJ**
Journal: BBA-BIOENERGETICS, 1757 (5-6): 509-517, MAY-JUN 2006
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SW: Why do you think your paper is highly cited?

Damage to the cells of critical organs such as the heart or brain (e.g., due to a heart attack or stroke, respectively) is the primary cause of morbidity and mortality in developed societies. Considerable scientific efforts are thus being aimed at better understanding the nature of this damage as well as investigating means of preventing or limiting it.

It has been increasingly recognized that the unwanted production of harmful levels of reactive oxygen species (ROS) mediates much of the cellular damage after a heart attack or stroke, and its source has become an area of intense interest.

We found that the main energy-producing organelles, mitochondria, can produce pathological levels of ROS inside injured cells that can spread between mitochondria as a damaging wave throughout the cell via the activation of a previously unrecognized positive-amplification cascade, which we named, ROS-induced ROS release. We proposed that this is a critical mechanism in certain forms of cell damage and death, an idea that has gained increasing acceptance.

SW: Does it describe a new discovery, methodology or synthesis of knowledge?

The paper describes and extends the original discovery of ROS-induced ROS release first published in an article entitled: "Reactive oxygen species (ROS)-induced ROS release: a new phenomenon

accompanying induction of the mitochondrial permeability transition in cardiac myocytes," (Zorov DB, *et al*., *J. Exp. Med.* 192[7]:1001-14, 2000).

SW: Would you summarize the significance of your paper in layman's terms?

Mitochondria are abundant organelles residing inside each of the body's cells that perform major functions, both in maintaining cellular health, and, under certain circumstances, regulating or even causing their death. They produce much of the energy needed to fuel vital cellular functions, but in so doing also produce modest levels of some potentially toxic byproducts, including highly reactive and potentially damaging forms of oxygen ("ROS") that in healthy cells are rendered harmless by chemical anti-oxidant mechanisms before they can cause any damage.

Lead author: Dmitry Zorov

However, under certain circumstances, such as during a heart attack or stroke, these mechanisms become very dysfunctional, so that the levels of the toxic ROS can achieve levels that produce widespread damage, including to the mitochondria themselves, rendering them unable to produce cellular energy.

In addition, these toxic ROS levels can cause certain channels and/or large pores in the mitochondrial membranes to open, resulting in an additional large burst and release of toxic ROS that can spread to, and induce the same destructive process in, the neighboring mitochondria, propagating like a chain-reaction.

We named this previously unrecognized mechanism, mitochondrial ROS-induced ROS release. This self-amplifying mechanism operates as a positive-feedback loop that can produce a wave of destructive ROS spreading throughout the cell, causing widespread damage and destruction of mitochondria and other sensitive targets which can ultimately kill the cell.

This damage to the cells, often irreversible and resulting in their death, is what causes the relatively permanent and serious dysfunction of the heart or brain after a heart attack or stroke, respectively. This mechanism has also been linked to arrhythmias of the heart, which together with loss of functional cells, can contribute to the significant morbidity and mortality of heart attacks.

Insights gained from understanding the nature of this mechanism can lead to more effective treatments to limit the damage due to diseases such as heart attacks and strokes.

SW: How did you become involved in this research and were any particular problems encountered along the way?

Mitochondria had been extensively studied for decades before our research, mainly using biochemical techniques. Our experiments required the use of advanced, laser-based confocal microscopy techniques together with probes of vital organelle function that would not have been available even a few years before we conducted our project.

Also, the mechanisms we were proposing required a certain revision to long-standing dogma about the ability of mitochondria to produce ROS under certain conditions, which we had to overcome.

In particular, in the case we were examining, under the circumstances when we found that the

mitochondria produce a ROS-burst, most of the world's mitochondrial experts would have predicted that ROS formation would be virtually absent, let alone demonstrating some kind of increase.

Our experimental interpretations were met with some initial skepticism, but soon our findings were reproduced by several independent laboratories in other parts of the world, and these ideas have been gaining increasing acceptance in the fields of mitochondrial and cell biology.

SW: Where do you see your research leading in the future?

We have found that the mechanisms we are examining are significantly affected during the aging process. Furthermore, heart attacks and strokes, while vastly more prevalent with age, are also more severe in the elderly.

We anticipate that this research might lead to understanding what are the critical variables involved in the aging process, and to be able to develop more effective treatments to limit the damage due to serious diseases of the elderly, such as heart attacks and strokes.

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