MedicalXpress

Age-related decline in two sirtuin enzymes alters mitochondrial dynamics, weakens cardiac contractions

August 24 2021, by Anne Delotto Baier

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Sirtuins are a family of anti-aging proteins that help regulate cellular lifespan, metabolism, and resistance to stress. The potential protective

effect of these sirtuin enzymes in age-related diseases, including cardiovascular diseases, remains an area of intense investigation.

Now, a new preclinical study led by University of South Florida Health (USF Health) researchers has determined that sirtuin 1 (SIRT1) and sirtuin 3 (SIRT3) levels decline in aging hearts, disrupting the ability of cardiac muscle cells (cardiomyocytes) to contract in response to ischemia-reperfusion injury (also known as reperfusion injury). Furthermore, age-related SIRT1 and SIRT3 deficiency can impair cardiac function by altering mitochondrial dynamics, which play an important role in metabolic health and inflammatory response, the researchers report.

The findings were published online July 3 in *Aging Cell*.

"We discovered that age-related changes in mitochondrial dynamics are caused by SIRT1/SIRT3 deficiency, specifically in the cardiomyocytes," said principal investigator Ji Li, Ph.D., professor of surgery in the USF Health Morsani College of Medicine. "You need a strong presence of SIRT1 and SIRT3 to keep mitochondrial dynamics healthy in the heart. Otherwise, the heart's pumping function becomes weak."

Mitochondria produce the energy needed to drive nearly all processes in living cells. Cardiac muscle cells contain more mitochondria than any other cells, because the heart needs large amounts of energy to constantly pump blood throughout the body. Stabile mitochondrial dynamics maintain a healthy balance between the constant division (fission) and merging (fusion) of mitochondria and help ensure the quality of these specialized structures known as the "powerhouse" of the cell.

Reperfusion, a common treatment following acute heart attack, restores blood flow (and thus oxygen) to a region of the heart damaged by a blood clot blocking the coronary artery. Paradoxically, in some patients

this necessary revascularization procedure triggers further injury to heart muscle tissue surrounding the initial heart attack site. No effective therapies currently exist to prevent reperfusion injury.

To help analyze the response of cardiac mitochondria to ischemia-reperfusion stress, the USF Health researchers deleted SIRT1 or SIRT3 in cardiac muscle cells of mouse hearts, and examined the mitochondrial response to ischemic stress by restricted blood flow. The researchers found that the mitochondria in mouse hearts lacking cardiomyocyte SIRT3 were more vulnerable to reperfusion stress than the mouse hearts with SIRT3 intact. The cardiac mitochondrial dynamics (including shape, size, and structure of mitochondria) in these knockout mice physiologically resembled that of aged wildtype (normal) mice retaining cardiac SIRT3.

Furthermore, the young mice with SIRT1 or SIRT3 removed had measurably weaker cardiomyocyte contractions and exhibited aging-like heart dysfunction when ischemia-reperfusion stress was introduced. In essence, without SIRT1/SIRT3 the hearts of these otherwise healthy young mice looked and behaved like old hearts.

"We started this study trying to understand why older people have higher incidences of heart attacks than younger people, and why they die more often even if they receive maximum treatment. Younger people are much more likely to recover from heart attacks and less likely to suffer from ischemia-reperfusion injury," said Dr. Li, a member of the USF Health Heart Institute. "Our research suggests that one reason could be that both SIRT1 and SIRT3 are downregulated with aging. Younger people have higher levels of these proteins needed to make mitochondrial dynamics healthier."

The study also suggests that, before surgically opening blocked coronary arteries to restore blood flow in older patients, administering a treatment

to "rescue" (improve) their diminished SIRT1/ SIRT3 levels may increase tolerance to cardiac muscle reperfusion stress, thereby reducing heart attack complications and deaths, Dr. Li said. Such a cardioprotective treatment might apply a genetic approach to increase SIRT1/SIRT3 production, or an agonist (drug) to activate SIRT1/ SIRT3, he added.

If their mouse model findings translate to human hearts, Dr. Li's group wants to work with companies interested in developing and testing SIRT1/SIRT3 activators to mitigate heart attack-related reperfusion injury.

"Our ultimate goal is to identify ideal targets for the treatment of heart attack, especially in older patients," said Dr. Li, whose research is supported by grants from the National Heart, Lung, and Blood Institute, the National Institute on Aging, and the National Institute of General Medical Sciences.

More information: Jingwen Zhang et al, Alterations in mitochondrial dynamics with age-related Sirtuin1/Sirtuin3 deficiency impair cardiomyocyte contractility, *Aging Cell* (2021). DOI: 10.1111/acel.13419

Provided by University of South Florida