

Disrupting an antioxidant pathway prevents heart disease caused by reductive stress

October 11 2013

University of Utah researchers have found that deficiency of an antioxidant response protein called nuclear erythroid-2 like factor-2 (Nrf2) delays or prevents hypertrophic cardiomyopathy, a type of a heart failure in which the heart muscle grows abnormally thick.

This new finding, published in the Oct. 1, 2013, issue of *Cardiovascular Research*, suggests that restoring the normal balance of reduction-oxidation [chemical reactions](#) in the body could prevent [heart disease](#) and other conditions caused by reductive stress.

Nuclear erythroid-2 like factor-2 (Nrf2) is a key regulatory protein in the signaling pathway that triggers the body's primary defense against oxidative stress, a condition where increased production of oxygen-containing free radicals causes cell damage. Many cardiac diseases, including hypertrophic cardiomyopathy, are linked to oxidative stress. However, in a previous study, University of Utah researchers demonstrated that reductive stress, the counterpart of oxidative stress, can also harm the heart due to excessive levels of an antioxidant called reduced glutathione.

"Heart muscle cells, like all cells, are sensitive to shifts in the chemical reactions occurring inside and around them," says Namakkal S. Rajasekaran, Ph.D., research assistant professor of internal medicine at the University of Utah and principal author on the study. "While antioxidants are widely considered an important defense against heart disease, an increasing body of evidence indicates that excessive

antioxidant activity can harm the body by creating a condition of reductive stress."

Rajasekaran and his colleagues studied laboratory mice with heart disease caused by mutations in alpha B-Crystallin, a protein that normally helps other proteins fold inside cells. These mice develop mutant protein aggregation cardiomyopathy (MPAC), a type of [heart failure](#) characterized by reductive stress and protein aggregation, the clumping together of misfolded proteins.

"From our earlier research, we know that Nrf2 is a critical regulator of antioxidant activity and sustained activation of Nrf2 causes reductive stress, which contributes to MPAC," says Rajasekaran. "In this study, we investigated whether disrupting Nrf2 can decrease the activity of antioxidant pathways and prevent the development of cardiac disease."

The researchers compared two strains of MPAC mice – one with normal Nrf2 and another with Nrf2 deficiency. They found that, while mice with normal Nrf2 developed [heart muscle](#) thickening and heart failure, mice that were deficient in Nrf2 did not. They also found that Nrf2 deficiency suppressed reductive stress, reduced cardiac protein aggregation and extended survival.

"Our study demonstrates that preventing excessive [antioxidant activity](#) and shifting away from a reductive environment is both necessary and sufficient to prevent harmful cardiac remodeling," says Rajasekaran.

The body's antioxidant response provides a natural defense against [oxidative stress](#), but not reductive stress. This new research reveals a novel mechanism for the development and prevention of reductive stress-induced [hypertrophic cardiomyopathy](#) and heart failure. Rajasekaran and his colleagues demonstrated that dampening the activity of Nrf-2 decreases chronic reductive stress and prevents improper protein

aggregation by restoring the equilibrium of chemical reactions inside heart muscle cells.

"While MPAC is a rare condition, our findings are broadly applicable to [heart](#) disease and other conditions caused by protein aggregation, such as Alzheimer's," says Rajasekaran. "What this means is that the antioxidant supplements many people take could actually be doing more harm than good, especially if they are taken in excess."

Provided by University of Utah Health Sciences

Citation: Disrupting an antioxidant pathway prevents heart disease caused by reductive stress (2013, October 11) retrieved 4 May 2024 from <https://medicalxpress.com/news/2013-10-disrupting-antioxidant-pathway-heart-disease.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--