Weighing in on Heart Failure: The Role of SERCA2a SUMOylation

Robert J. Schwartz, Edward T.H. Yeh

SUMO1-Dependent Modulation of SERCA2a in Heart Failure
Kho et al

Heart failure is a growing problem but a recent report in Nature provides new insights into the role of post-translational modification of SERCA2a by SUMOylation. The enhanced benefits of SUMOylation may provide new therapeutic venues for the treatment of heart failure.

Heart failure is a complex clinical syndrome resulting from structural changes in the myocardium that affects the ability of the ventricle to fill with or eject blood. It affects at least 5 million patients in the United States and consumes over 6% of our health care budget. Nearly half a million new patients are diagnosed to have heart failure each year and the incidence of new cases is increasing each year due to aging of the population and conversion of acute cardiac problems into chronic disorders. Coronary artery disease is the cause of heart failure in about two thirds of patients with left ventricular dysfunction. Without the ability for complete renewal, loss of functional cardiac myocytes due to MI or other causes will eventually lead to deterioration of myocardial function, resulting in heart failure.

Heart failure is characterized by the impaired efflux of cytosolic Ca2+ from the cell due to a sustained defect in SR Ca2+ reloading and release. A reduced expression and/or activity of the calcium-transporting ATPase ATP2A2, also known as SERCA2a, is responsible for Ca reuptake during excitation–contraction coupling. Over the last decade or more, defective Ca2+ uptake resulting from decreased expression and reduced activity of SERCA2a is recognized as a hallmark of heart failure. A recent study by Dr Roger Haijar and colleagues described as the “Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease” or CUPID showed that adenoviral restoration of SERCA2a expression improved cardiac function in heart failure patients. Also, their latest investigation revealed an important role for regulating the SERCA2a through SUMOylation.

The association of the small ubiquitin-related modifier (SUMO) conjugation pathway, an important posttranslational modification process, is a relatively new area and knowledge about the importance of the SUMO pathway for the development and maintenance of a normal cardiovascular system is just beginning to emerge (Reviewed in Wang and Schwartz). SUMO modification is accomplished by the reversible attachment of SUMO family members to the acceptor lysine residue(s) located in the target proteins, with the help of activating, conjugating, and ligating enzymes and by Sentrin/SUMO-specific proteases (SENP). The process of SUMOylation alters the functional activity of targets by regulating protein–protein interactions, nucleocytoplasmic translocalization, protein-DNA binding activity, and/or protein stability. Kho et al showed that SERCA2a was SUMOylated at lysine residues 480 and 585, which proved to be critical for maintenance of SERCA2a ATPase activity. Their study revealed increased stability of SUMOylated SERCA2a in mouse and human myocytes. Although decreased SERCA2a levels have been well-documented in heart failure, the study by Kho et al was the first to reveal SUMO1 and the SUMOylation of SERCA2a were greatly reduced in failing hearts. SUMO1 gene therapy with adeno-associated-virus-mediated delivery maintained the protein abundance of SERCA2a and markedly improved cardiac function in mice with heart failure. This effect was comparable to SERCA2A gene delivery. Moreover, SUMO1 overexpression in isolated cardiomyocytes augmented contractility and accelerated Ca2+ decay. Viral-mediated SUMO1 overexpression rescued cardiac dysfunction induced by pressure overload con-
comitantly with increased SERCA2a function. By contrast, downregulation of SUMO1 using small hairpin RNA (shRNA) accelerated pressure-overload-induced deterioration of cardiac function and was accompanied by decreased SERCA2a function.

Kho et al. performed additional experiments to determine whether the beneficial effect of SUMO-1 overexpression was indeed dependent on SERCA2a. They showed that knocking down SERCA2a prevented the helpful effect of SUMO-1 overexpression. On the surface, these experiments appear to prove that SUMO-1's beneficial effect is indeed dependent on SERCA2a. However, knocking down SERCA2a may have pleiotropic effects on other proteins that would not allow SUMO-1 to rescue. A more definitive set of experiments would prove the authors were correct, in which coexpression of shRNA-resistant wild type SERCA2a would allow SUMO-1 to rescue, whereas shRNA-resistant SERCA2a (SUMO mutant) would not. This experiment would provide definitive proof that SUMO-1’s beneficial effect is indeed exerted through SERCA2a.

SUMO-1 expression was reduced in heart failure samples and restoring SUMO-1 expression improved cardiac function. However, only a small sampling of human hearts was examined and larger numbers are needed to be more certain about SUMO1’s promising role. Also, SUMO1 rescue may not be directly attributed to SUMOylation of SERCA2a. SUMO-1 has multiple substrates in addition to SERCA2a.6,7 Thus, overexpression of SUMO-1 could have multiple effects depending on the modified substrates. They showed that GATA4 was not altered by SUMO-1 overexpression whereas the increase in SUMOylated serum response factor (SRF) may alter apoptotic signaling in heart failure. In fact, SUMOylated SRF is an important cardiac transcription factor, and cleavage of SRF by Caspase 3 in human end-staged failing hearts was dramatically reversed by left ventricle assist device.9 Could SUMO1 also reverse apoptosis, mimic cardiac unloading and increase SRF SUMOylation? Notably, 15 years ago SUMO-1 (Sentrin-1) overexpression was shown to block both tumor necrosis factor and TNF receptor superfamily member 6 or FAS-induced cell death.10 In addition, more experiments on the role of SUMO-1 overexpression in blocking the slow death of cardiac myocytes are needed to explain the positive effect of SUMO-1 overexpression in heart failure. Another important question is how SUMO-1 expression is regulated in heart failure. Is the reduction in SUMO-1 in heart failure due to transcriptional repression or decreased stability? Although Kho et al. did not see any changes in the expression of conjugating enzyme E2 (Ubc9) and deconjugating enzyme (SENP1) in their limited survey of heart failure patients, more information on the SUMO-activating enzyme (E1), ligating enzymes (E3), and other SENPs are needed to fully understand the implication of SUMO-1 in heart failure (Figure).6,7

Recently Wang et al. demonstrated that balanced sumoylation and desumoylation is required for normal cardiac development and can be a major factor in congenital heart disease. Their findings support the novel concept that a defective SUMO pathway as exemplified by SUMO-1 knockout mice, may contribute to the high prevalence of congenital cardiac defects. Reduction of SUMO-1 by only half was sufficient to elicit in ASD/VSDs in SUMO-1 haploid-insufficient mice. Wang et al. also noted that "whether environmental toxins, metabolites, and pharmaceuticals that may alter sumoylation gene activity cause heart disease. Any perturbation of signaling components and gene activity of SUMO conjugation pathway are the unknown intangibles that could tilt the balance of the SUMO conjugation pathway and potentially lead to cardiac disease.” Thus, the Kho et al. study opened up an exciting venue to explore the pathophysiology of heart failure in the context of defective SUMOylation.

Sources of Funding
Robert J. Schwartz and Edward T.H. Yeh are supported by State of Texas and NIH/NIHLBI research grants.

Disclosures
None.

References
Weighing in on Heart Failure: The Role of SERCA2a SUMOylation
Robert J. Schwartz and Edward T.H. Yeh

doi: 10.1161/RES.0b013e318246f187
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/110/2/198

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/