SUMO-1 Gene Transfer Improves Cardiac Function in a Large-Animal Model of Heart Failure

Tilemann et al


A small ubiquitin-like protein was shown to be beneficial to the failing heart through enhancing sarcoplasmic reticulum Ca\(^{2+}\) ATPase 2a (SERCA2a) stability and activity in a large animal model of heart failure.

Dysregulation of calcium cycling in cardiomyocytes has been recognized as a major molecular mechanism of heart failure. SERCA2a plays a pivotal role in regulating calcium homeostasis, and reduction of SERCA2a activity has been recognized as a hallmark of heart failure. Hajjar and his colleagues\(^1\) reported that the activity of SERCA2a is regulated by conjugation of small ubiquitin-like modifier-1 (SUMO-1) to SERCA2a. They also demonstrated that SUMO-1 gene delivery can restore SERCA2a expression and activity in the failing heart in a mouse model. Based on these findings, they postulated that SUMO modification (SUMOylation) is a critical regulator of SERCA2a function, which led to the design of SUMO-1 gene therapy in a swine ischemia–reperfusion heart failure model.\(^2\) The authors performed a temporary balloon occlusion of the proximal left anterior descending artery to create myocardial infarction. One month later, 31 survived pigs were randomized to receive via antegrade coronary infusion either saline or adeno-associated vector type 1 (AAV1) loaded with SUMO-1 (low and high dose), SERCA2a, or both. They showed that both SUMO-1 and SERCA2a levels were increased in the pigs that received AAV1.SUMO-1 with or without AAV1.SERCA2a 2 months later. However, the changes in left ventricular ejection fraction (EF) were not statistically significant in all treated groups. Statistically significant changes were demonstrated in the maximal rate of pressure rise ([dP/dt(max)]) in the groups that received high-dose SUMO-1, SERCA2a, or both. Furthermore, the treated groups have less left ventricular dilatation. The authors concluded that SUMO-1 gene either alone or in combination with SERCA2a is beneficial in a large animal model of heart failure and holds promise for the treatment of heart failure in humans.

SERCA2a is a calcium-ion pump that takes up calcium from the cytosol into the sarcoplasmic reticulum.\(^3\) The expression level and activity of SERCA2a were found to be diminished in the failing heart.\(^4\) In contrast to the well-known SERCA2a, SUMO is relatively unknown to the cardiovascular research community. SUMO belongs to a family of ubiquitin-like proteins that covalently attached to a large number of cellular proteins. SUMOylation is a versatile post-translational protein modification system that regulates a protein’s cellular localization, function, and stability.\(^5\) There are 3 different SUMOs: SUMO-1, SUMO-2, and SUMO-3 (Figure). SUMO-2 and SUMO-3 are closely related and are usually described as SUMO-3/2. SUMO-1 usually modifies its substrate as a monomer, whereas SUMO-2 or SUMO-3 can build up poly-SUMO chains. Similar to phosphorylation and dephosphorylation, SUMO modification can be removed by a family of Sentrin/SUMO-specific proteases. SUMOylation and de-SUMOylation have been shown to play critical roles in regulating protein stability and activity, as well as cell cycle, cell proliferation, and cell death.

The opinions expressed in this Commentary are not necessarily those of the editors or of the American Heart Association.

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Commentaries are edited by Anurit Bhattachar & Ali J. Marian.

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(Circ Res. 2014;114:1561-1563.)

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Circulation Research is available at http://circres.ahajournals.org

DOI: 10.1161/CIRCRESAHA.114.304125

Wrestling With Heart Failure
SUMO-1 to the Rescue

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Circulation Research

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DOI: 10.1161/CIRCRESAHA.114.304125
in cell biology, including development, DNA replication/repair, and the hypoxic response.6–8 Interestingly, several cardiac transcription factors are SUMOylated and their transcriptional activities are altered by SUMOylation.9

The authors first demonstrate that AAV1.SUMO-1 restores the expression of SUMO-1 and SERCA2a in the failing heart. This occurs at both the mRNA and protein levels. Furthermore, SUMOylated SERCA2a is markedly increased in the group that received both SUMO-1 and SERCA2a. This is because of the persistence of AAV1 in the cardiac tissues 2 months after gene delivery. Despite restoration of SUMO-1 and SERCA2a expression, changes in EF only showed a trend toward improvement in the high-dose SUMO-1 group as compared with control but did not reach statistically significance. The authors argued that the improvements on the molecular level may precede the functional benefits. One wonders whether a longer observation period could demonstrate a statistically significant improvement in the EF in the treated group.

Hajjar and his colleagues10 previously reported in a phase 1/2 human gene therapy trial using AAV1.SERCA2a that patients treated with high-dose SERCA2a have marked reduction in all-cause mortality. The number of cardiovascular events, such as myocardial infarction, worsening heart failure, ventricular assist device placement, cardiac transplantation, and death, was also reduced in the low- and mid-dose group as compared with placebo control. However, EF was not reported in the 3-year follow-up but was not statistically significant at 12-month follow up.10,11 Thus, EF improvement was not seen in the 3-year follow-up.10,11 Thus, EF improvement was not statistically significant at all-cause mortality. The number of cardiovascular events, have marked reduction SERCA2a 1/2 human gene therapy trial using AA V1. SUMOylation has been shown to inhibit the cleavage of SERCA2a.1 Thus, another potential therapeutic approach is to block SERCA2a degradation with a proteasome inhibitor. Indeed, proteasome inhibitors have been shown to exert a beneficial effect on the failing heart.15 The downside of the proteasome inhibitor approach is the lack of specificity and potential pleiotropic effects. If the goal is to increase SUMOylation of SERCA2a, one can reduce the expression and activity of Sentrin/SUMO-specific proteases that are specific for SERCA2a. Alternatively, one can increase the expression and activity of a SERCA2a-specific E3 ligase. In summary, Tilemann and his colleagues2 have introduced an innovative approach to treat heart failure. Although additional investigations are required, we are hopeful that SUMO-1 gene therapy or strategies to increase SUMO-1 level may provide new therapy for patients with heart failure in the future.

Disclosures

None.

References


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Circ Res. 2014;114:1561-1563
doi: 10.1161/CIRCRESAHA.114.304125
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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