Wrestling With Heart Failure
SUMO-1 to the Rescue

Pimprapa Vejpongsa, Edward T.H. Yeh

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 [\(\mathrm{dp/dt(max)}\)] 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-3/3. 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 protein function and stability. The SUMOylation reaction requires the activating enzyme (E1), conjugating enzyme (E2), and ligation enzyme (E3). SUMO/Sentrin-specific proteases (SENPs) deconjugate SUMO from SUMO-conjugated proteins. SENP1, SENP2, SENP3, and SENP5 are described as SUMO-2/3, SENP1, SENP2, and SENP6 remove SUMO-1, respectively.

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<th>Major SUMO Substrates in the Heart</th>
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<tr>
<td>GATA4</td>
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<td>Nkx2.5</td>
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<td>MEF2C</td>
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![Figure](http://circres.ahajournals.org/doi/pdf/10.1161/CIRCRESAHA.114.304125)

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Commentaries are edited by Aruni Bhatnagar & Ali J. Marian.

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increases the stability of SERCA2a directly and enhances its ATPase activity as shown by the authors’ previous report.1

SUMO-1 can modify many cellular proteins and could exert its beneficial effect in the failing heart in >1 way. The authors showed that the proform of caspase 3 is reduced in the treated group. One possible scenario is that SUMO-1 may exert an antiapoptotic effect on the dying cardiomyocytes. Interestingly, SUMO-1 was identified originally by us as Sentrin, a protein that protected cell from Fas ligand or tumor necrosis factor–mediated apoptosis.14 We showed that SUMO-1 binds to the death domains of both FAS and tumor necrosis factor receptor and prevents signaling leading to apoptosis. Thus, overexpression of SUMO-1 could protect the cardiomyocytes from cell death, which could reduce cardiac remodeling and preserve cardiac contractility.

An important question to be answered is why SUMO-1 expression is lowered in the failing heart. Additional research is necessary to identify the signaling pathway and transcription factors that are involved in the downregulation of the SUMO-1 gene transcription. It would be much easier to use a small molecule to increase the transcription of SUMO-1 in lieu of SUMO-1 gene therapy. The authors have shown previously that SUMOylation prevents the degradation 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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