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 cell signaling and protein localization.

**Figure.** SUMOylation and de-SUMOylation. SUMO modification is a dynamic process that regulates many biological functions. The conjugation of SUMO to the target proteins required the activating enzyme (E1), conjugating enzyme (E2), and ligating enzyme (E3). SUMO/Sentrin-specific proteases (SEPNs) deconjugate SUMO from SUMO-conjugated proteins. DRP1 indicates dynamin-related protein 1; ERK5, extracellular signal-regulated kinase 5; GATA4, GATA binding protein 4; MEF2C, myocyte enhancer factor 2C; NKX2.5, NK2 homeobox 5; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARγ, peroxisome proliferator-activated receptor gamma; SERCA2a, sarcoplasmic reticulum Ca\(^{2+}\) ATPase 2a; and SRF, serum response factor.

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

Commentaries serve as a forum in which experts highlight and discuss articles (published here and elsewhere) that the editors of Circulation Research feel are of particular significance to cardiovascular medicine.

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**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

_Sci Transl Med._ 2013;5:211ra159.
in cell biology, including development, DNA replication/re-
pair, 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 re-
stores the expression of SUMO-1 and SERCA2a in the fail-
ing 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 sig-
nificance. The authors argued that the improvements on the
molecular level may precede the functional benefits. One
wonders whether a longer observation period could demon-
strate 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 pa-
tients treated with high-dose SERCA2a have marked reduction
in all-cause mortality. The number of cardiovascular events,
such as myocardial infarction, worsening heart failure, ven-
tricular 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
either SERCA2a- or SUMO-1–based gene therapy in human. If
EF changes are not significant in both the animal model and
the human studies, how does SERCA2a or SUMO-1 gene therapy
benefits the failing heart? In this article, the authors showed
that there was a statistically significant improvement in cardiac
contractility as measured by dP/dt(max) and left ventricular
volume.2 Thus, the mechanism whereby SUMO-1 gene therapy
benefits the failing heart may be because of a beneficial effect
on cardiac remodeling. It is more difficult to explain why
improvement in contractility failed to translate into a better EF.
Perhaps, the number of the animals studied was too small to
reach that conclusion.

The authors provided limited analysis on the mechanisms
whereby SUMO-1 gene therapy exerted its beneficial effect.
They showed that specificity protein 1 (SP1), a transcrip-
tion factor for SERCA2a, is markedly increased in the saline
group but returned toward normal in the treated group, and
SUMOylated SP1 is increased in high-dose SUMO-1–treated
group. They suggested that the increase in SUMOylated SP1
is responsible for the increase in SERCA2a mRNA in the
treated groups. In contrast to the increase in the stability of
SUMOylated SERCA2a, SUMO-1–modified SP1 actually
leads to its degradation in a ubiquitin-dependent manner.12
SUMOylated SP1 was shown to be localized in the cytosol
and thus will not enhance transcription. In another study,
SUMOylation has been shown to inhibit the cleavage of
the SP1 N-terminal negative regulatory domain and SP1-
dependent transcription.13 Thus, the increase in SUMOylated
SP1 in the SUMO-1–treated group could not account for the
increase in SERCA2a mRNA. It is more likely that SUMO-1
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 first 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, overexpres-
sion 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 re-
search is necessary to identify the signaling pathway and
transcription factors that are involved in the downregula-
tion 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 protea-
some 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 prote-
ases that are specific for SERCA2a. Alternatively, one can
increase the expression and activity of a SERCA2a-specific
E3 ligase. In summary, Tilmann 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.

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