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“Sorting” SERCA2a: A novel therapeutic strategy in heart failure?

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Calcium (Ca^{2+}) homeostasis is essential for maintaining proper electrophysiology and contractile properties of cardiomyocytes [1]. Ca^{2+} handling is tightly regulated through the coordination among multiple Ca^{2+} handling proteins in the cardiomyocytes. During systole, depolarization of the sarcolemma by a membrane potential activates the voltage-gated L-type Ca^{2+} channel (LTCC) located on the transverse-tubules. A small influx of Ca^{2+} enters the cytoplasm via LTCC, diffusing across a short distance to bind the type-2 ryanodine receptors (RyR2s) located on the sarcoplasmic reticulum (SR) and triggering a massive efflux of Ca^{2+} from the SR into the cytosol, a process known as the Ca^{2+} -induced- Ca^{2+} -release. This magnified Ca^{2+} transient culminates with Ca^{2+} -sensitive contractile proteins (troponin C) and stimulates actin-myosin cross-bridge linking which then use ATP to produce muscle contraction, a process called excitation-contraction coupling (EC coupling). During diastole, approximately 70% of the Ca^{2+} is actively sequestered back into the SR via the sarco/endoplasmic reticulum Ca^{2+} ATPase 2a (SERCA2a), or expelled from the cardiomyocytes by the Na^{+} - Ca^{2+} exchanger (NCX) pumps eventually leading to muscle relaxation. These tightly coordinated Ca^{2+} handling processes are pivotal for cardiomyocytes achieving effective contraction, and dysregulation of any of the above Ca^{2+} handling processes may result in heart failure (HF) and/or lethal cardiac arrhythmias [2]. Decreased SERCA2a levels and activity are proven to be one of the molecular determinants underlying the development of HF [3]. Decreased levels and/or activity of SERCA2a in cardiomyocytes can result in depleted SR Ca^{2+} stores and consequently less Ca^{2+} available for systolic release, leading to inefficient systolic contraction. On the other hand, there is an

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increase in end-diastolic cytosolic Ca^{2+} levels (known as Ca^{2+} overload) and prolongation of the Ca^{2+} transients during diastole, which can cause diastolic dysfunction. Moreover, abnormal Ca^{2+} handling can also cause the development of delayed after-depolarizations and early after-depolarizations, which can trigger arrhythmias [4]. Increased diastolic levels of Ca^{2+} in failing hearts, due to higher opening probability of RyR2s along with impaired diastolic clearance, may activate NCX, resulting in a transient inward current (I_{Ti}) that may depolarize the cell membrane, causing afterdepolarizations and cardiac arrhythmias. Thus, the contribution of dysregulated Ca^{2+} handling to systolic/diastolic dysfunction and arrhythmogenesis in HF identifies SERCA2a as an attractive therapeutic target. A number of animal studies have shown that overexpression of SERCA2a in transgenic mouse or ischemia/reperfusion (I/R) injury rat models improves myocyte contraction and relaxation and suppresses ventricular arrhythmias associated with the development of HF [5,6].

To date, a number of molecular mechanisms underlying the downregulation of SERCA2a or reduced SERCA2a activity in HF have been established, including reduced sumoylation, enhanced microRNA-25 mediated posttranscriptional regulation, and increased nitration and acetylation, etc. [7]. In this issue of *International Journal of Cardiology*, Zhao and colleagues demonstrated a novel mechanism - sorting nexin 17 (SNX17) mediated protein degradation of SERCA2a - could also contribute to the decreased SERCA2a protein levels in a rat model of myocardial infarction (MI) [2]. SNX17 is a member of large family of sorting nexins that function variously in pro-degradative sorting, internalization, endosomal recycling, or endosomal sorting [8]. SNX17 has been shown to mediate the internalization and recycling, and prevent the degradation of plasma membrane proteins [8]. In this study, Zhao et al. revealed that SNX17 and SERCA2a were co-localized in cytosol of cardiomyocytes, and the level of SNX17 was reduced in the MI model. The downregulation of SNX17 was associated with increased intracellular Ca^{2+} level, ventricular arrhythmias including premature ventricular contractions and ventricular tachycardia, and impaired ventricular systolic function. Similarly, silencing of SNX17 in the cardiomyocytes using small interfering RNA led to reduced protein level of SERCA2a and intracellular Ca^{2+} overload. On the contrary, overexpression of SNX17 in the MI rats using an adenovirus vector decreased the frequency of ventricular arrhythmias and preserved the ventricular systolic function [2]. This is the first evidence that sorting protein is involved in regulating SERCA2a protein homeostasis and Ca^{2+} handling in cardiomyocytes. In addition, the authors also revealed that SNX17 co-immunoprecipitates with SERCA2a, of which the interaction is mediated via the highly conserved phox-homology (PX) domain [9]. Identification of the interaction region between SNX17 and SERCA2a may be beneficial for design of compounds that can facilitate the binding between SNX17 and SERCA2a, thereby enhancing the stability of SERCA2a and normalizing SR Ca^{2+} release in HF.

Because of the important role of SERCA2a in maintaining Ca^{2+} homeostasis and proper contractility of cardiomyocyte, a number of clinical trials utilizing adeno-associated viral vectors (AAVs) to correct the SERCA2a levels in myocardium were conducted in patients with HF [10]. However, all three clinical trials (CUPID2, Agent-HF, SERCA-LVAD) failed to demonstrate improvement in survival and/or were terminated prior to sufficient data collection [10]. While the reasons for failure of these clinical trials are unclear, a potential explanation is the limited targeting of SERCA2a. Therefore, targeting of a downstream

molecule that modulates multiple other targets in addition to SERCA2a is needed to derive a clinical benefit. In this respect, SNX17 targeting may provide some hope. Speculatively, SNX17 may direct the trafficking and degradation of multiple proteins with desirable roles in myocardial contractility/relaxation and Ca^{2+} cycling. The role of SNX17 in modulation of expression levels of other proteins has not been investigated in this work. Additional research is needed to determine whether the observed desirable effects of SNX17 are solely derived from protection of SERCA2a from lysosomal degradation. Moreover, the current study has not determined whether other adaptor proteins are involved in the trafficking of SERCA2a in cardiomyocytes and whether these interactions are altered and partly responsible for Ca^{2+} dysregulation in association with the pathogenesis of HF. Despite these limitations, the findings from this study provide new opportunity for normalizing SERCA2a homeostasis by establishing proper sorting, which may become a new anti-HF and anti-arrhythmic strategy.

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