Journal of Cardiovascular Diseases & Diagnosis
ISSN: 2329-9517

Chemaly et al., J Cardiovasc Dis Diagn 2013, 1:3
DOI: 10.4172/2329-9517.1000113

Review Article Open Access

Sarco (Endo) Plasmic Reticulum Calcium Atpases (SERCA) Isoforms in the Normal and Diseased Cardiac, Vascular and Skeletal Muscle

Elie R Chemaly[1], Regis Bobe[2], Serge Adnot[3], Roger J Hajjar[1] and Larissa Lipskaia[1,3]*

[1]*Cardiovascular Research Center, Icahn School of Medicine at Mount Sinai, New York, NY 10029-6574, USA*
[2]*INSERM U770, CHU Bicêtre, Le Kremlin-Bicêtre, 94276, France*
[3]*INSERM U955 and Département de Physiologie, Hôpital Henri Mondor, Université Paris-Est (UPEC), Créteil, 94110, France*

Abstract

Deregulated or enhanced calcium ion (Ca^{2+}) influx across an unstable sarcolemma has been proposed to directly affect cardiac hypertrophic remodelling, vascular proliferative diseases and degenerative muscle disorders. Aberrant intracellular handling is partly due to a defect in Sarcoplasmic Reticulum (SR) function. Decreased Ca^{2+} uptake in cardiac, vascular and skeletal myocytes is associated with a decrease in the expression and activity of the fast sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA2a or SERCA1a isoforms). SERCA2a gene transfer was successfully used in heart failure; this approach holds further therapeutic promises in vascular proliferative diseases and dystrophin-deficient muscular diseases. The growing family of human SERCA isoforms comprises at least 14 mRNA and proteins with different functional characteristics and cell-specific expression. This review focuses on the biological role and therapeutic potential of different isoforms of SERCA in the physiology and pathology of cardiac, vascular and skeletal muscle cells.

Keywords: Skeletal myocytes; Cell-specific expression; Sarcoplasmic reticulum

Introduction

Calcium ions are present in low concentrations in the cytosol ($[Ca^{2+}]i$ ~ 100 nM) compared to their high concentration in both extracellular medium (in the range of mM) and intracellular stores (mainly the Sarco/Endo/Plasmic Reticulum (SR/ER)). This gradient allows Ca^{2+} to be a ubiquitous second messenger for various cellular functions: metabolism, apoptosis, proliferation and/or hypertrophic growth. The Sarco/Endoplasmic Reticulum Ca^{2+}ATPase (SERCA) is the only active Ca^{2+} transporter in the SR, regulation of its function is a key mechanism of Ca^{2+} homeostasis and depends on the cell type and state of differentiation. Furthermore, in muscular cells, SERCA plays a dual role: it controls the SR Ca^{2+} store that can be mobilised during muscle contraction, and it decreases cytosolic Ca^{2+} concentration to allow muscle relaxation [1].

Impaired Ca^{2+} handling, leading to aberrant calcium signal transduction, is reported in numerous cardiovascular diseases and muscular dystrophies affecting all types of muscular cells, including cardiomyocytes, Vascular Smooth Muscle Cells (VSMC) diaphragm and skeletal muscle [1-3]. In failing cardiomyocytes, deficient SR Ca^{2+} uptake resulting in defective mechanical function is also associated with an increase of resting Ca^{2+} [1,4,5]. Deficient Ca^{2+} uptake, in turn, affects SR Ca^{2+} release channels (Ryanodin Receptor Calcium Channel, RyR) and plasma membrane Ca^{2+} influx channels (transient receptor potential channels (TRPC) and the Ca^{2+} pore forming units Orai1 () further worsening the abnormal Ca^{2+} distribution. Increased basal Ca^{2+} is essential for transcriptional activation of cytosolic Ca^{2+} regulated transcription factor NFAT (nuclear factor of activated T lymphocytes), the key regulator of hypertrophic remodeling in cardiomyocytes and proliferative remodeling in vascular smooth muscle cells [1,4,5]. Recently, similar Ca^{2+}-regulated pathological mechanisms were discovered is vascular and skeletal myocytes [2,6-8]. Cardiac, vascular and skeletal myocytes share similar mechanism of Store-Operated Channels (SOC) Ca^{2+}influx dependent on two essential players: the ER located Ca^{2+} sensor STIM1 (Stromal Interaction Molecule 1) and the Ca^{2+} pore forming units Orai1-3 [9-12].

SOC channels are activated upon a reduction in the ER/SR Ca^{2+} concentration. When $[Ca^{2+}]$ decreases in the reticulum, Ca^{2+} dissociates from STIM1 leading to its oligomerization and translocation to specialized cortical reticulum compartments adjacent to the plasma membrane to activate the Ca^{2+} channels of Orai family [13,14]. Furthermore, TRPC proteins have been shown to associate with Orai1 and STIM1 in a dynamic ternary complex regulated by the occupation of membrane receptors in several cell models, which might play an important role in the function of SOC [15].

As SOC induction is directly dependent on ER/SR Ca^{2+} stores, the third player in its regulation has to be SERCA, which pumps the Ca^{2+} back into these stores. We have demonstrated that in VSMC increasing SR Ca^{2+} load by SERCA2a gene transfer restored contractile type of Ca^{2+} cycling and inhibited SOC through disruption of ORAI1/STIM1 association [2]. In line with this, SERCA2a gene transfer prevents vascular remodelling and post-injury restenosis in animal and organ culture models [16-18].

Normalization of SERCA2a function has been shown to increase contractility in vitro in isolated cardiomyocytes and to improve cardiac function in animal models of HF (reviewed in and improves remodeling in chronic mitral regurgitation [19-21]. Over expression of SERCA2a by gene therapy in heart failure is progressing to a clinical trial in which an Adeno-Associated Virus (AAV) over expressing SERCA2a was administered to heart failure patients: the phase II of the Calcium

***Corresponding author:** Larissa Lipskaia, Cardiovascular Research Center, Icahn School of Medicine at Mount Sinai, Leon and Norma Hess Center for Science and Medicine, One Gustave L Levy Place, Box 1030, New York, NY 10029-6574, USA, Tel: 212-824-8904; Fax: 212-241-4080; E-mail: larissa.lipskaia@mssm.edu

Received May 28, 2013; **Accepted** July 11, 2013; **Published** July 16, 2013

Citation: Chemaly ER, Bobe R, Adnot S, Hajjar RJ, Lipskaia L (2013) Sarco (Endo) Plasmic Reticulum Calcium Atpases (SERCA) Isoforms in the Normal and Diseased Cardiac, Vascular and Skeletal Muscle. J Cardiovasc Dis Diagn 1: 113. doi:10.4172/2329-9517.1000113

Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID) study was recently published [22].

Clinical success of SERCA2a gene therapy in heart failure opens the perspective for the therapeutic use of this approach in other muscular diseases, particularly to correct vascular proliferative disorder as well as muscular and cardiac manifestations in patients with dystrophic myopaties. In support of this therapeutic perspective, we have recently reported that forced expression of SERCA reversed a defect in Ca^{2+} reuptake that characterizes dystrophic myofibers, reduced total cytosolic Ca^{2+}, and almost completely rescued the dystrophic phenotype in mouse models of muscular dystrophies [3].

This review focuses on the physiological role of different SERCA isoforms in cardiac, vascular and skeletal muscle cells in relationship with physiological and pathological conditions and discusses the potential interest of therapeutic SERCA gene transfer to various muscle cells.

SERCA Isoforms Family Members: Enzymatic Properties and Cell-Specific Expression

The sarco/endoplasmic Ca^{2+}ATPase (SERCA) belong to a family of P-type ion pumps [23]. The growing family of SERCA isoforms is coded by 3 ATP2A1-3 genes located on 3 different chromosomes, encoding for SERCA1, SERCA2 and SERCA3 isoforms respectively; further diversity is generated by alternative splicing [23,24]. At least 14 SERCA mRNAs have been identified with the corresponding proteins. Some of these isoforms are species specific; in particular, SERCA2c, SERCA3d, SERCA3e and SERCA3f are specific to humans [24]. Isoform expression is also specific of cell-type and developmental stage [23]. SERCA isoforms are highly conserved in structure, with 75% or more homology between proteins from the SERCA1, SERCA2 and SERCA3 families [23].

The SERCA1 gene encodes for 2 spliced mRNA variants mostly expressed in fast-twitch skeletal muscle; SERCA1a is expressed in adult fast-twitch skeletal muscle, while SERCA1b is expressed in fetal tissues evidence shows SERCA1a cardiac expression [23,25]. While there is no specific protein structure associated to the supplementary region (6 amino acids) of SERCA1b, SERCA1a is thought to play a central role in skeletal muscle development [26]. The Ca^{2+} uptake activity of the recombinant SERCA1a is similar to SERCA2a [27].

The SERCA2 gene gives rise to four species (a-d) through alternative splicing of the SERCA2 gene [24,28,29]. So-called "cardiac isoform" SERCA2a is expressed in cardiac muscle, slow-twitch skeletal muscle and smooth muscle cells while SERCA2b is a ubiquitous isoform of SERCA expressed in muscle and non-muscle cells [23]. SERCA2a and SERCA2b are produced by alternative splicing of the SERCA2 gene and differ only by an additional 49 amino acids in SERCA2b, by which SERCA2b has an additional transmembrane loop in the SR [30]. SERCA2c was first reported in cardiac [31]. The novel SERCA2c mRNA is mainly (but not only expressed in skeletal and cardiac muscles (like SERCA2a) and expresses a functional recombinant protein in HEK (Human Embryonic Kidney)-293 cells [24,28]. SERCA2d mRNA was very recently found in skeletal muscle [29]. However, evidence for functional and endogenous SERCA2d protein is still lacking.

SERCA3 has various 3'-end splice variants encoding species-specific isoforms, including 5 human (SERCA3b-f) 2 mouse (SERCA3b-c) and 1 rat (SERCA3b/c) proteins, in addition to the common SERCA3a isoform [32-35]. All recombinant proteins were found to be functional, and the endogenous proteins were expressed as well. SERCA3 isoforms (a total of 6) are mostly expressed in non-muscle cells, especially hematopoietic cells, with minor expression in muscle cells [23]. However, more recent evidence shows SERCA3d and SERCA3f to be expressed in the human heart [36].

SERCA isoforms are distinguished by affinity for calcium (2b> 2a> 1a> 2c> 3) and turnover rate (2b, c <2a <3a, b, c <1a) [37]. The SERCA2a isoform displays a lower affinity for Ca^{2+} (K0.5 = 0.985 μM) but has a higher turnovers rate (ATP hydrolysis 70 s-1) compared to SERCA2b (K0.5 = 0.508 μM; 35 s-1). The SERCA1a displayed an affinity similar to SERCA2a and an ATP hydrolysis rate similar to SERCA2b or -2c (K0.5 = 1.03 μM; 36s-1) [24]. The SERCA3 isoforms are characterized by a lower Ca^{2+} affinity (10 times lower than SERCA1a) and a rapid turnover (around 100 s-1) [38].

SERCA affinity for calcium is reduced by two intrinsic membrane proteins expressed in the sarco(endo)plasmic reticulum: Phospholamban (PLN) and Sarcolipin (SLN) [39]. SLN and PLN appear to bind to the same regulatory site in SERCA, however in a ternary complex, PLN occupies the regulatory site and SLN binds to the exposed side of PLN and to SERCA. Both SLN and PLN lower the apparent affinity for calcium of either SERCA1a or SERCA2a for Ca^{2+} [39]. Conversely, SERCA3 isoform lack PLN-binding domains and thus, the affinity of SERCA3 for calcium are not regulated by PLN [40].

SERCA Isoforms in the Normal and Diseased Cardiomyocytes: Pivotal Role for SERC2a in Contractile Function

Expression and localization of SERCA isoforms in cardiomyocytes

SERCA2a is the major cardiac isoform, while SERCA2b is a minor cardiac isoform [24,41]. SERCA2a is down-regulated during pathologic cardiac hypertrophy and heart failure and its down-regulation is associated with impaired calcium cycling, as previously reviewed in detail [4]. Restoration of SERCA2a expression by gene transfer improves various features of Heart Failure (HF) in preclinical models and in phase 1 and phase 2 clinical trials [1,5]. While the more advanced clinical trials are underway. Other isoforms were detected in the human heart, including SERCA1a, SERCA2c and several SERCA3 isoforms, but their physiological functions have not been established [24,31,36].

The SERCA2a, 2b and 2c isoforms are heterogeneous in terms of subcellular localisation in the cardiomyocyte [24]. SERCA2c protein was restricted to the subsarcolemmal compartment, in contrast with the more diffuse SR distribution of both SERCA2a and SERCA2b proteins, targeted to the same subcellular localizations (longitudinal SR) [24,30,42].

The level of SERCA1 mRNA expression in the heart is similar to the one observed in skeletal muscle [25]. However, it is not clear whether SERCA1 has a function in the cardiomyocytes. So far only one manuscript reported an up-regulation of SERCA1expression in the myocardium of dogs diagnosed with Dilated Cardiomyopathy (DCM) [43].

Weakly expressed SERCA3 isoforms are differently localized within human cardiomyocytes: SERCA3a is close to the T-tubules and intercalated disks, SERCA3d is perinuclear and SERCA3f subsarcolemmal [24,36].

Common and potentially distinct roles of SERCA2a, SERCA2b and SERCA1a in the cardiomyocyte: insight from transgenic animals and gene transfer studies

Numerous studies on transgenic mice investigated the effect of increased or decreased expression of SERCA isoforms, selectively in the cardiomyocyte [44].

Overexpression of SERCA2b in the cardiomyocytes of transgenic mice, led to an increased SR calcium transport through an increase in calcium pump affinity, and to an enhanced mechanical function (contractility and relaxation) without cardiac hypertrophy or fibrosis [30]. Interestingly, there was no secondary downregulation of the expression of endogenous SERCA2a, despite a dramatic overexpression of SERCA2b [30].

Alternatively, some studies have questioned whether SERCA2a and SERCA2b were interchangeable in cardiac function using transgenic mice in which the alternative splicing mechanism producing SERCA2a was disrupted [41,45,46]. The transgenic mice expressing mainly SERCA2b in the heart demonstrated increased embryonic and neonatal lethality and cardiac malformations (hypoplastic heart syndrome) [45]. Surviving mice had mild reductions in cardiac mechanical function (manifested in abnormal dP/dt) and concentric hypertrophy [45]. Interestingly, there was no left ventricular dilatation and no reduction in the fractional shortening in those mice [45]. The total level of SERCA2 was lower in SERCA2a-deficient homozygous mice, suggesting that cardiac hypertrophy could be attributed to the reduction of total SERCA2. However the fact that heterozygous mice with the similar reductions in SERCA2 expression but with functional copies of SERCA2a did not develop malformations or hypertrophy clearly indicate that the isoform switch is responsible for HF [45]. Indeed, in a subsequent study, increased expression of cardiac SERCA2b level in SERCA2a→2b isoform switch mice did not prevent cardiac hypertrophy [41].

Taken together, these studies suggest that SERCA2b per se is not detrimental to cardiac function when over expressed in addition to SERCA2a; however, it appears to be an inadequate substitute for SERCA2a [30,45].

Evidence of adaptive SERCA isoform switch varies among studies. A decrease in SERCA2a after forced overexpression of SERCA1a was reported and a compensatory increase of SERCA2b in the setting of SERCA3 deficiency was also suggested [23,47]. As mentioned above, the over expression of SERCA2b in the cardiomyocytes did not lead to a decrease in SERCA2a and the reduced expression of total SERCA2 observed during the replacement of SERCA2a by SERCA2b did not lead to a compensatory increase in SERCA1 or SERCA3 [30,45]. On the contrary, it led to an increase in PLN expression, associated to its reduced phosphorylation [46]. Both changes reduce the affinity of SERCA for calcium [45]. One possible explanation is that the high affinity of SERCA2b for calcium might compensate the reduced expression of total SERCA2 in mice with a SERCA2a2b isoform switch [46]. The only abnormality of calcium uptake observed in those mice was delayed relaxation of calcium transient [48]. The detrimental effect of an excessively high affinity of SERCA for calcium in the heart was further investigated by the Wuytack laboratory [46]. In a double-knock-out mouse model where phospholamban knock-out was added to SERCA2a→2b isoform switch, ventricular hypertrophy was aggravated, features of higher ventricular stiffness with diastolic dysfunction were measured, and increased animal morbidity and mortality were observed [46].

Limited data are available on human failing cardiac tissue, in which only a significant increase in SERCA3f was recently demonstrated in addition to the well-established decrease in SERCA2a [24]. While the SR regulates excitation-contraction coupling due to its special ability to store calcium, the role of the ER in protein synthesis and processing, and the disruption of such processes in pathologic situations (known as ER stress) is of growing importance in the cardiomyocyte and in heart failure [23,24]. In that regard, an interesting connection can be made between (1) the increased expression of SERCA3f in human heart failure with a parallel increase in ER stress markers, (2) the ability of SERCA3f to induce ER stress and apoptosis in HEK-293 cells [24,36,49].

Cardiac overexpression of SERCA1a in transgenic mice resulted in enhanced calcium transport and cardiac function leading to suggestion that SERCA1a can substitute for SERCA2a [47]. Even so only one study using adenoviral SERCA1a gene transfer in cardiomyocytes showed a dose-dependent increase in calcium transport and a reduction in both time to peak shortening and relaxation time. However, myocyte fractional shortening and calcium transients failed to increase significantly at the higher doses [50].

In conclusion, the studies on transgenic animals point on the fact that SERCA isoforms are not interchangeable in their physiological function.

SERCA Isoform Expression in the Vascular Smooth Muscle Cell: SERCA2a/SERCA2b Switch as a Key Difference between the Contractile and Synthetic Phenotype

In vascular smooth muscle cells (VSMCs) two SERCA genes (ATP2A2 and ATP2A3) are simultaneously expressed [51]. While SERCA3, the lower Ca^{2+} affinity Ca^{2+} pump, remains a minor isoform, SERCA2a and SERCA2b isoforms seem to be widely expressed and to participate in the basal control of Ca^{2+} uptake [51]. The major VSMC SERCA2 isoform determining the type of agonist-induced Ca^{2+} transient can be either SERCA2a or SERCA2b, depending on the cell phenotype [51].

Within the mature blood vessel, VSMCs maintain a considerable plasticity throughout life, they also exhibit a diverse range of phenotypes [52,53]. The current classification of VSMC phenotypes distinguishes: synthetic/proliferating/migratory/inflammatoryphenotype *vs.* contractile/quiescent/differentiated ones. In mature vessels, most of the VSMCs exhibit a quiescent/contractile phenotype and control the vascular tone. In response to injury, transition of contractile VSMCs towards a synthetic phenotype plays a vital role in vascular repair mechanism but is also the primary pathophysiological mechanism leading to vascular remodelling during vascular proliferative diseases including atherosclerosis and post-angioplasty restenosis [52].

In contractile VSMC, expressing mainly SERCA2a isoform, an agonist-induced elevation of cytosolic Ca^{2+} triggers VSMC contraction [54,55].

Noteworthy, steady-state increase in cytosolic Ca^{2+} triggers tonic contraction, whereas oscillatory type of Ca^{2+} transient triggers phasic contraction, typical for coronary and low resistance arteries. The mode of Ca^{2+} transient in VSMCs depends solely on the SR Ca^{2+} ATPase function. Indeed, i) the oscillations are preserved in the absence of extracellular Ca^{2+} ii) blocking SERCA activity strongly inhibits the Ca^{2+} oscillations, demonstrating that they are caused by release of Ca^{2+}

from the SR [2,56,57]. iii) SERCA2a gene transfer to synthetic cultured VSMCs modifies the agonist-induced calcium transient from steady-state to oscillatory mode [2].

The synthetic status of VSMCs is characterized by a decrease of proteins associated with contractile response, specifically the fast isoform SERCA2a; cytosolic Ca^{2+} is weakly pumped by the slow Ca2+ pump SERCA2b [51]. In synthetic VSMCs, agonist binding leads to large cytosolic Ca^{2+} mobilization resulting in a long lasting increase of $[Ca^{2+}]i$ critical for the activation of proliferation-related transcription factor NFAT [58].

Restoring SERCA2a expression by gene transfer in synthetic cultured VSMCs inhibits proliferation and migration of these cells in the presence of serum via inhibition of transcription factor NFAT [2,16,18].

SERCA2a, the fast Ca^{2+} pump, specifically expressed in contractile VSMCs, can be responsible for the establishment of "cytosolic oscillator" thereby controlling phasic vs. tonic type of smooth muscle contraction [2,37,51]. Furthermore, by increasing SR Ca^{2+} upload and content, SERCA2a prevents cytosolic Ca^{2+} overload and, consequently, NFAT dependent proliferation and migration [2,16].

SERCA Expression in the Skeletal Muscle: Implications in Muscular Dystrophy

In skeletal muscle all three SERCA genes are simultaneously expressed. The major adult fast-twitch specific isoform is SERCA1a, followed by SERCA2a, more specific for slow-twitch skeletal muscle [59]. Importantly, skeletal muscle tissue is almost the only missing the ubiquitous SERCA2b isoform, replaced by SERCA2c isoform [37].

Within SERCA3 family members, two ubiquitous isoforms SERCA3d and SERCA3f, were detected at mRNA level in adult human skeletal muscle; however their physiological role remains unknown [37].

Denervation of both slow-twitch and fast-twitch muscle leads to down regulation of either SERCA2a or SERCA1, respectively, with reduced total ATPase activity and impaired contraction [60].

Decreased SR Ca^{2+} uptake in skeletal muscle related to the reduction of SR ATPase activity causes a very rare inherited human muscle disease known as Brody's disease. The patients suffer from impaired muscle relaxation. Reduction of SR ATPase activity can be associated with a mutation of SERCA1 gene, lack of SERCA protein expression or reduced SR ATPase activity without modification of SERCA1a or SERCA2a expression [60].

Muscular dystrophies are another group of hereditary diseases characterized by muscle fiber necrosis and progressive muscle wasting and weakness [61]. In addition to progressive skeletal muscle wasting leading to respiratory failure, muscular dystrophies lead to progressive degradation of cardiac function with aging resulting in ventricular dilation, reduced fractional shortening, conduction defects, and fibrosis [61]. The genetic defects underlying these muscle diseases are not directly related to SERCA and other proteins of the calcium cycle, but excessive calcium influx into muscle fibres or disturbed intracellular calcium signalling are presumably involved in the pathomechanisms of muscle dystrophies [61]. Muscular dystrophy broadly encompasses a diverse group of genetic disorders that appear to affect the multi-protein sarcolemmal-spanning Dystrophin-Glycoprotein Complex (DGC), which is critical for maintaining integrity of the plasma membrane and the proper activity of signalling complexes and channels [62].

A disruption in the DGC is hypothesized to promote direct Ca^{2+} influx and/or abnormal cytosolic Ca^{2+} homeostasis, leading to increased vulnerability of myofibers to necrosis [63]. It has been recently demonstrated that, in dystrophic muscle, the direct Ca^{2+} influx is supported by abnormal store-dependent cation entry through Transient Receptor Potential Cannonical (TRPC) and Orai1 channels and activation of Stromal Interacting Molecule 1 (STIM1) [6-8].

Recently we have reported that forced expression of sarcoplasmic reticulum Ca^{2+} ATPase (SERCA1a or SERCA2a) reversed a defect in Ca^{2+} reuptake that characterizes dystrophic myofibers, reduced total cytosolic Ca^{2+}, and almost completely rescued the dystrophic phenotype in a mouse model [3]. Furthermore, SERCA2a gene transfer improved electrocardiographic abnormalities in a mouse muscular dystrophy model [61]. Although the benefit effect of SERCA1a or SERCA2a over expression in dystrophic cardiac and skeletal myocytes was reported, the molecular mechanism of this effect is unknown [3].

Calcium overload in dystrophin-deficient skeletal myotubes involves TRPC channels and STIM1 activation during repetitive calcium release [7]. This defect of plasma membrane function can be corrected by gene transfer of mini-dystrophin, providing a scaffold for assembling a multiprotein signalling complex modulating SOC activity [7]. However, using synthetic human vascular myocytes lacking dystrophin, we have demonstrated that increasing SR Ca^{2+} load by SERCA2a gene transfer restored oscillatory type of Ca^{2+} transient, specific for contractile phasic vascular smooth muscle cells and inhibited SOC through the disruption of ORAI1/STIM1 association [2,16]. Thus, in VSMC the velocity of SR internal store loading is critical to the modulation of the activity of PM channels. Although increased rates of cytosolic Ca^{2+} clearance appeared to be associated with increased membrane stability, it remains unclear whether the speed of SR Ca^{2+} refilling and SR Ca^{2+} content could control plasma membrane permeability in skeletal myocytes [2].

Conclusion

Based on recent evidence demonstrating that both amplitude and duration of the Ca^{2+} signal influence physiological cell function, SERCA, regulating the spatiotemporal pattern of Ca^{2+} transient, has emerged as a critical component of Ca^{2+} -dependent processes [2]. The data obtained in particular sets of experimental and pathological conditions suggest that the SERCA-mediated calcium transport is finely tuned, requiring simultaneous expression of multiple SERCA isoform with differential calcium affinity and pump activity to fall in a narrow interval depending on the cell type. It appears to be inadequate to substitute defective SERCA isoform by another one for therapeutic purposes [38,45,58,64]. Therefore, not only the variety but also the combination of SERCA isoforms achieves tight regulation of cellular functions.

Acknowledgments

This work is supported by Association Française Contre les Myopathies (AFM12595; AFM16442); RJH is supported by NIH grants HL088434, HL080498, HL100396 and NIH/NHLBI Contract HHSN268201000045C.

References

1. Lipskaia L, Chemaly ER, Hadri L, Lompre AM, Hajjar RJ (2010) Sarcoplasmic reticulum Ca(2+) ATPase as a therapeutic target for heart failure. Expert Opin Biol Ther 10: 29-41.

2. Bobe R, Hadri L, Lopez JJ, Sassi Y, Atassi F, et al. (2011) SERCA2a controls the mode of agonist-induced intracellular Ca2+ signal, transcription factor NFAT and proliferation in human vascular smooth muscle cells. J Mol Cell Cardiol 50: 621-633.

3. Goonasekera SA, Lam CK, Millay DP, Sargent MA, Hajjar RJ, et al. (2011) Mitigation of muscular dystrophy in mice by SERCA overexpression in skeletal muscle. J Clin Invest 121: 1044-1052.

4. Lompré AM, Hajjar RJ, Harding SE, Kranias EG, Lohse MJ, et al. (2010) Ca2+ cycling and new therapeutic approaches for heart failure. Circulation 121: 822-830.

5. Kairouz V, Lipskaia L, Hajjar RJ, Chemaly ER (2012) Molecular targets in heart failure gene therapy: current controversies and translational perspectives. Ann N Y Acad Sci 1254: 42-50.

6. Vandebrouck A, Sabourin J, Rivet J, Balghi H, Sebille S, et al. (2007) Regulation of capacitative calcium entries by alpha1-syntrophin: association of TRPC1 with dystrophin complex and the PDZ domain of alpha1-syntrophin. FASEB J 21: 608-617.

7. Sabourin J, Lamiche C, Vandebrouck A, Magaud C, Rivet J, et al. (2009) Regulation of TRPC1 and TRPC4 cation channels requires an alpha1-syntrophin-dependent complex in skeletal mouse myotubes. J Biol Chem 284: 36248-36261.

8. Sabourin J, Harisseh R, Harnois T, Magaud C, Bourmeyster N, et al. (2012) Dystrophin/Î±1-syntrophin scaffold regulated PLC/PKC-dependent store-operated calcium entry in myotubes. Cell Calcium 52: 445-456.

9. Liou J, Kim ML, Heo WD, Jones JT, Myers JW, et al. (2005) STIM is a Ca2+ sensor essential for Ca2+-store-depletion-triggered Ca2+ influx. Curr Biol 15: 1235-1241.

10. Roos J, DiGregorio PJ, Yeromin AV, Ohlsen K, Lioudyno M, et al. (2005) STIM1, an essential and conserved component of store-operated Ca2+ channel function. J Cell Biol 169: 435-445.

11. Peinelt C, Vig M, Koomoa DL, Beck A, Nadler MJ, et al. (2006) Amplification of CRAC current by STIM1 and CRACM1 (Orai1). Nat Cell Biol 8: 771-773.

12. Soboloff J, Spassova MA, Tang XD, Hewavitharana T, Xu W, et al. (2006) Orai1 and STIM reconstitute store-operated calcium channel function. J Biol Chem 281: 20661-20665.

13. Wu MM, Buchanan J, Luik RM, Lewis RS (2006) Ca2+ store depletion causes STIM1 to accumulate in ER regions closely associated with the plasma membrane. J Cell Biol 174: 803-813.

14. Shen WW, Demaurex N (2012) Morphological and functional aspects of STIM1-dependent assembly and disassembly of store-operated calcium entry complexes. Biochem Soc Trans 40: 112-118.

15. Salido GM, Jardín I, Rosado JA (2011) The TRPC ion channels: association with Orai1 and STIM1 proteins and participation in capacitative and non-capacitative calcium entry. Adv Exp Med Biol 704: 413-433.

16. Lipskaia L, del Monte F, Capiod T, Yacoubi S, Hadri L, et al. (2005) Sarco/endoplasmic reticulum Ca2+-ATPase gene transfer reduces vascular smooth muscle cell proliferation and neointima formation in the rat. Circ Res 97: 488-495.

17. Lipskaia L, Hadri L, Le Prince P, Esposito B, Atassi F, et al. (2013) SERCA2a gene transfer prevents intimal proliferation in an organ culture of human internal mammary artery. Gene Ther 20: 396-406.

18. Merlet E, Lipskaia L, Marchand A, Hadri L, Mougenot N, et al. (2013) A calcium-sensitive promoter construct for gene therapy. Gene Ther 20: 248-254.

19. del MonteF, Harding SE, Schmidt U, Matsui T, Kang ZB, et al. (1999) Restoration of contractile function in isolated cardiomyocytes from failing human hearts by gene transfer of SERCA2a. Circulation 100: 2308-2311.

20. Kawase Y, Ladage D, Hajjar RJ (2011) Rescuing the failing heart by targeted gene transfer. J Am Coll Cardiol 57: 1169-1180.

21. Beeri R, Chaput M, Guerrero JL, Kawase Y, Yosefy C, et al. (2010) Gene delivery of sarcoplasmic reticulum calcium ATPase inhibits ventricular remodeling in ischemic mitral regurgitation. Circ Heart Fail 3: 627-634.

22. Jessup M, Greenberg B, Mancini D, Cappola T, Pauly DF, et al. (2011) Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID): a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca2+-ATPase in patients with advanced heart failure. Circulation 124: 304-313.

23. Periasamy M, Kalyanasundaram A (2007) SERCA pump isoforms: their role in calcium transport and disease. Muscle Nerve 35: 430-442.

24. Dally S, Corvazier E, Bredoux R, Bobe R, Enouf J (2010) Multiple and diverse coexpression, location, and regulation of additional SERCA2 and SERCA3 isoforms in nonfailing and failing human heart. J Mol Cell Cardiol 48: 633-644.

25. Chami M, Gozuacik D, Lagorce D, Brini M, Falson P, et al. (2001) SERCA1 truncated proteins unable to pump calcium reduce the endoplasmic reticulum calcium concentration and induce apoptosis. J Cell Biol 153: 1301-1314.

26. Toyoshima C, Nakasako M, Nomura H, Ogawa H (2000) Crystal structure of the calcium pump of sarcoplasmic reticulum at 2.6 A resolution. Nature 405: 647-655.

27. Dode L, Andersen JP, Leslie N, Dhitavat J, Vilsen B, et al. (2003) Dissection of the functional differences between sarco(endo)plasmic reticulum Ca2+-ATPase (SERCA) 1 and 2 isoforms and characterization of Darier disease (SERCA2) mutants by steady-state and transient kinetic analyses. J Biol Chem 278: 47877-47889.

28. Gélébart P, Martin V, Enouf J, Papp B (2003) Identification of a new SERCA2 splice variant regulated during monocytic differentiation. Biochem Biophys Res Commun 303: 676-684.

29. Kimura T, Nakamori M, Lueck JD, Pouliquin P, Aoike F, et al. (2005) Altered mRNA splicing of the skeletal muscle ryanodine receptor and sarcoplasmic/endoplasmic reticulum Ca2+-ATPase in myotonic dystrophy type 1. Hum Mol Genet 14: 2189-2200.

30. Greene AL, Lalli MJ, Ji Y, Babu GJ, Grupp I, et al. (2000) Overexpression of SERCA2b in the heart leads to an increase in sarcoplasmic reticulum calcium transport function and increased cardiac contractility. cl, bob 275: 24722-24727.

31. Dally S, Bredoux R, Corvazier E, Andersen JP, Clausen JD, et al. (2006) Ca2+-ATPases in non-failing and failing heart: evidence for a novel cardiac sarco/endoplasmic reticulum Ca2+-ATPase 2 isoform (SERCA2c). Biochem J 395: 249-258.

32. Wuytack F, Papp B, Verboomen H, Raeymaekers L, Dode L, et al. (1994) A sarco/endoplasmic reticulum Ca(2+)-ATPase 3-type Ca2+ pump is expressed in platelets, in lymphoid cells, and in mast cells. J Biol Chem 269: 1410-1416.

33. Martin V, Bredoux R, Corvazier E, Van Gorp R, Kovacs T, et al. (2002) Three novel sarco/endoplasmic reticulum Ca2+-ATPase (SERCA) 3 isoforms. Expression, regulation, and function of the membranes of the SERCA3 family. J Biol Chem 277: 24442-24452.

34. Bobe R, Bredoux R, Corvazier E, Andersen JP, Clausen JD, et al. (2004) Identification, expression, function, and localization of a novel (sixth) isoform of the human sarco/endoplasmic reticulum Ca2+ATPase 3 gene. J Biol Chem 279: 24297-24306.

35. Borge PD Jr, Wolf BA (2003) Insulin receptor substrate 1 regulation of sarco-endoplasmic reticulum calcium ATPase 3 in insulin-secreting beta-cells. J Biol Chem 278: 11359-11368.

36. Dally S, Monceau V, Corvazier E, Bredoux R, Raies A, et al. (2009) Compartmentalized expression of three novel sarco/endoplasmic reticulum Ca2+ATPase 3 isoforms including the switch to ER stress, SERCA3f, in non-failing and failing human heart. Cell Calcium 45: 144-154.

37. Lipskaia L, Hadri L, Lopez JJ, Hajjar R, Bobe R. (2013b) Benefit of SERCA2a gene transfer to vascular endothelial and smooth muscle cells: a new aspect in therapy of cardiovascular diseases. Current vascular pharmacology in press.

38. Dode L, Vilsen B, Van Baelen K, Wuytack F, Clausen JD, et al. (2002) Dissection of the functional differences between sarco(endo)plasmic reticulum Ca2+-ATPase (SERCA) 1 and 3 isoforms by steady-state and transient kinetic analyses. J Biol Chem 277: 45579-45591.

39. MacLennan DH, Asahi M, Tupling AR (2003) The regulation of SERCA-type pumps by phospholamban and sarcolipin. Ann N Y Acad Sci 986: 472-480.

40. Tada M, Toyofuku T (1996) SR Ca(2+)-ATPase/phospholamban in cardiomyocyte function. J Card Fail 2: S77-85.

41. Vangheluwe P, Schuermans M, Raeymaekers L, Wuytack F (2007) Tight interplay between the Ca2+ affinity of the cardiac SERCA2 Ca2+ pump and the SERCA2 expression level. Cell Calcium 42: 281-289.

42. Vangheluwe P, Louch WE, Ver Heyen M, Sipido K, Raeymaekers L, et al. (2003) Ca2+ transport ATPase isoforms SERCA2a and SERCA2b are targeted to the same sites in the murine heart. Cell Calcium 34: 457-464.

43. Summerfield N, Peters ME, Hercock CA, Mobasheri A & Young IS. (2010) Immunohistochemical evidence for expression of fast-twitch type sarco(endo)

plasmic reticulum Ca2+ ATPase (SERCA1) in German shepherd dogs with dilated cardiomyopathy myocardium. J Vet Cardiol12: 17-23.

44. Babu GJ, Periasamy M (2005) Transgenic mouse models for cardiac dysfunction by a specific gene manipulation. Methods Mol Med 112: 365-377.

45. Ver Heyen M, Heymans S, Antoons G, Reed T, Periasamy M, et al. (2001) Replacement of the muscle-specific sarcoplasmic reticulum Ca(2+)-ATPase isoform SERCA2a by the nonmuscle SERCA2b homologue causes mild concentric hypertrophy and impairs contraction-relaxation of the heart. Circ Res 89: 838-846.

46. Vangheluwe P, Tjwa M, Van Den Bergh A, Louch WE, Beullens M, et al. (2006) A SERCA2 pump with an increased Ca2+ affinity can lead to severe cardiac hypertrophy, stress intolerance and reduced life span. J Mol Cell Cardiol 41: 308-317.

47. Loukianov E, Ji Y, Grupp IL, Kirkpatrick DL, Baker DL, et al. (1998) Enhanced myocardial contractility and increased Ca2+ transport function in transgenic hearts expressing the fast-twitch skeletal muscle sarcoplasmic reticulum Ca2+-ATPase. Circ Res 83: 889-897.

48. Antoons G, Ver Heyen M, Raeymaekers L, Vangheluwe P, Wuytack F, et al. (2003) Ca2+ uptake by the sarcoplasmic reticulum in ventricular myocytes of the SERCA2b/b mouse is impaired at higher Ca2+ loads only. Circ Res 92: 881-887.

49. Chaâbane C, Corvazier E, Bredoux R, Dally S, Raïes A, et al. (2006) Sarco/endoplasmic reticulum Ca2+ATPase type 3 isoforms (SERCA3b and SERCA3f): distinct roles in cell adhesion and ER stress. Biochem Biophys Res Commun 345: 1377-1385.

50. Teucher N, Prestle J, Seidler T, Currie S, Elliott EB, et al. (2004) Excessive sarcoplasmic/endoplasmic reticulum Ca2+-ATPase expression causes increased sarcoplasmic reticulum Ca2+ uptake but decreases myocyte shortening. Circulation 110: 3553-3559.

51. Lipskaia L, Limon I, Bobe R, Hajjar R (2012) Calcium Cycling in Synthetic and Contractile Phasic or Tonic Vascular Smooth Muscle Cells. In Current Basic and Pathological Approaches to the Function of Muscle Cells and Tissues - From Molecules to Humans, ed. Sugi H. InTech.

52. Owens GK, Kumar MS, Wamhoff BR (2004) Molecular regulation of vascular smooth muscle cell differentiation in development and disease. Physiol Rev 84: 767-801.

53. Fisher SA (2010) Vascular smooth muscle phenotypic diversity and function. Physiol Genomics 42A: 169-187.

54. Aalkjaer C, Nilsson H (2005) Vasomotion: cellular background for the oscillator and for the synchronization of smooth muscle cells. Br J Pharmacol 144: 605-616.

55. Haddock RE, Hill CE (2005) Rhythmicity in arterial smooth muscle. J Physiol 566: 645-656.

56. Bartlett IS, Crane GJ, Neild TO, Segal SS (2000) Electrophysiological basis of arteriolar vasomotion in vivo. J Vasc Res 37: 568-575.

57. Haddock RE, Hill CE (2002) Differential activation of ion channels by inositol 1,4,5-trisphosphate (IP3)- and ryanodine-sensitive calcium stores in rat basilar artery vasomotion. J Physiol 545: 615-627.

58. Dolmetsch RE, Lewis RS, Goodnow CC, Healy JI (1997) Differential activation of transcription factors induced by Ca2+ response amplitude and duration. Nature 386: 855-858.

59. Berchtold MW, Brinkmeier H, Müntener M (2000) Calcium ion in skeletal muscle: its crucial role for muscle function, plasticity, and disease. Physiol Rev 80: 1215-1265.

60. Schulte L, Peters D, Taylor J, Navarro J, Kandarian S (1994) Sarcoplasmic reticulum Ca2+ pump expression in denervated skeletal muscle. Am J Physiol 267: C617-622.

61. Shin JH, Bostick B, Yue Y, Hajjar R, Duan D (2011) SERCA2a gene transfer improves electrocardiographic performance in aged mdx mice. J Transl Med 9: 132.

62. Kaplan JC (2009) Gene table of monogenic neuromuscular disorders (nuclear genome only) Vol 19. No 1 January 2009. Neuromuscul Disord 19: 77-98.

63. Allen DG, Gervasio OL, Yeung EW, Whitehead NP (2010) Calcium and the damage pathways in muscular dystrophy. Can J Physiol Pharmacol 88: 83-91.

64. Lompré AM, Hadri L, Merlet E, Keuylian Z, Mougenot N, et al. (2013) Efficient transduction of vascular smooth muscle cells with a translational AAV2.5 vector: a new perspective for in-stent restenosis gene therapy. Gene Ther.

Citation: Chemaly ER, Bobe R, Adnot S, Hajjar RJ, Lipskaia L (2013) Sarco (Endo) Plasmic Reticulum Calcium Atpases (SERCA) Isoforms in the Normal and Diseased Cardiac, Vascular and Skeletal Muscle. J Cardiovasc Dis Diagn 1: 113. doi:10.4172/2329-9517.1000113