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Review article

Sarcolipin and phospholamban as regulators of cardiac sarcoplasmic reticulum Ca^{2+} ATPase

Poornima Bhupathy, Gopal J. Babu, Muthu Periasamy *

Department of Physiology and Cell Biology, and Davis Heart and Lung Research Institute, The Ohio State University, 304 Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210, USA

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Abstract

The cardiac sarcoplasmic reticulum calcium ATPase (SERCA2a) plays a critical role in maintaining the intracellular calcium homeostasis during cardiac contraction and relaxation. It has been well documented over the years that altered expression and activity of SERCA2a can lead to systolic and diastolic dysfunction. The activity of SERCA2a is regulated by two structurally similar proteins, phospholamban (PLB) and sarcolipin (SLN). Although, the relevance of PLB has been extensively studied over the years, the role SLN in cardiac physiology is an emerging field of study. This review focuses on the advances in the understanding of the regulation of SERCA2a by SLN and PLB. In particular, it highlights the similarities and differences between the two proteins and their roles in cardiac patho-physiology.

Keywords: SERCA2a; Sarcolipin; Phospholamban; Calcium; Regulation

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1. Introduction

The cardiac sarco(endo)plasmic reticulum (SR) Ca^{2+} ATPase (SERCA2a) is a pivotal molecule for maintaining a balanced concentration of intracellular Ca^{2+} during the cardiac contraction–relaxation cycle [1,2]. SERCA2a promotes muscle relaxation by lowering the cytosolic Ca^{2+} concentration through active Ca^{2+} transport into the SR and,

Abbreviations: SERCA2a, sarcoplasmic reticulum calcium ATPase; PLB, phospholamban; SLN, sarcolipin; SR, sarcoplasmic reticulum; Ca^{2+}, calcium; Val, valine; Leu, leucine; Ile, isoleucine; Thr, threonine; Trp, tryptophan; Cys, cysteine; Met, methionine; Ser, serine; ER, endoplasmic reticulum; MHC, myosin heavy chain; PKA, cyclic AMP-dependent protein kinase; CaMKII, calcium-calmodulin-dependent protein kinase; pp1, protein phosphatase 1.

* Corresponding author. Tel.: +1 614 292 2310; fax: +1 614 292 4888.
E-mail address: Periasamy.1@osu.edu (M. Periasamy).

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thereby, restores the intracellular Ca^{2+} needed for the next contraction cycle [1]. The expression and regulation of SERCA2a activity have been widely investigated, emphasizing its central role in the regulation of Ca^{2+} homeostasis during development and under a variety of patho-physiological conditions [3–6]. Studies from a variety of animal models of heart disease [7–9] and end-stage human heart failure [10,11] suggest that defects in SR Ca^{2+} uptake function are one of the major contributing factors for the progression of heart failure. Several studies have demonstrated the role of SERCA2a interacting proteins in modulating pump activity and in normal and failing hearts. It is well established that in the heart SERCA2a activity is regulated by a small phosphoprotein, phospholamban (PLB). Recent studies have suggested that another small molecular weight protein, sarcolipin (SLN) is also involved in the regulation of SR Ca^{2+} ATPase activity. Current data suggest that these two proteins play important roles in regulating SERCA2a activity and cardiac physiology, however much remains to be understood. The focus of this review is to compare the functional significance of SLN and PLB, in particular their roles in SERCA2a regulation and cardiac contractility, and in cardiac patho-physiology.

2. Sarcolipin is structurally similar to PLB

Structural similarities between the *PLB* and *SLN* gene as well as the homology between their protein sequences (Fig. 1), suggest that both PLB and SLN belong to the same family of proteins [12,13]. The 52 amino acids of PLB are organized into three domains. The cytoplasmic domain IA, consisting of residues 1–20, of which the first 16 are likely in an α-helical conformation, cytoplasmic domain IB consisting of residues 21–30 and domain II with residues 31–52 is the hydrophobic transmembrane domain which is probably in an α-helical conformation [13,27,81]. On the other hand, SLN is a 31-amino-acid SR membrane protein and shows a distribution pattern similar to SERCA2a and PLB [12,16]. Similar to PLB, the amino acids in SLN are organized into three domains; cytoplasmic domain, transmembrane and lumenal domains. The first 7 amino acids in SLN are hydrophilic and are cytoplasmic, the next 19 hydrophobic amino acids form a single transmembrane α-helix, and the last 5 hydrophilic amino acids are lumenal [12,17]. Amino acid sequence comparison and modeling studies have shown that the transmembrane helices of SLN and PLB share considerable homology [12,14,18,19]. In 19 transmembrane amino acids of SLN, 8 are identical, 7 share Val, Leu, or Ile, 3 share Thr, Trp, or Cys and one is Met for Ile substitution [12,19,20]. Amino acid conservation in the transmembrane domains of SLN and PLB suggests that both proteins interact in a similar way with SERCA [21,22]. There is substantial similarity between the N-terminal part of the transmembrane domain of SLN and domain Ib of PLB [19]. Domain Ib of PLB is proposed to be important for the dynamic protein–protein interaction which is regulated by the phosphorylation–dephosphorylation of Ser16 and Thr17, which modulates PLB function [19,56,57]. Although, the N-terminal cytoplasmic domain of

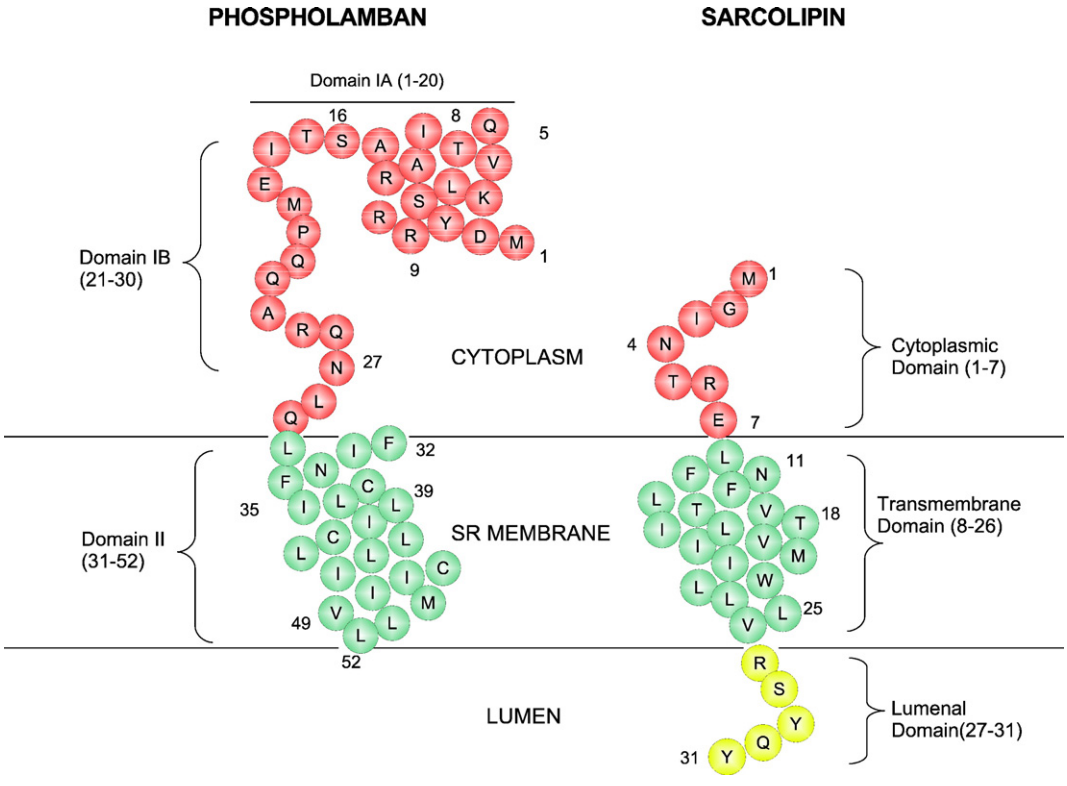

Fig. 1. Schematic representation of homology between the PLB and SLN protein sequence. Horizontal lines denote the membrane boundaries and amino acids are shown in circles using their one letter code (see main text for detailed description).