

REVIEW

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The SERCA–PLN–DWORF axis in cardiometabolic disease: mechanisms and therapeutic perspectives

Ok-Hee Kim^{1†}, Seung Wan Noh^{2†}, Jun-Su Choi², YunJae Jung^{3*} and Byung-Chul Oh^{1,2*}

Abstract

Intracellular calcium (Ca^{2+}) homeostasis is a central determinant of cardiometabolic physiology, integrating excitation–contraction coupling, metabolic signaling, and stress adaptation across multiple organs. The sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA), regulated by the micropeptides phospholamban (PLN) and dwarf open reading frame (DWORF), governs ER/SR Ca^{2+} reuptake and thereby shapes Ca^{2+} -dependent signaling dynamics. Dysregulation of the SERCA–PLN–DWORF axis is increasingly recognized as a shared pathogenic mechanism in type 2 diabetes–related complications, including diabetic cardiomyopathy and heart failure with preserved ejection fraction (HFpEF), where reduced SERCA2a activity prolongs diastolic Ca^{2+} clearance and promotes calcineurin–NFAT activation and mitochondrial Ca^{2+} overload. In the liver, loss of SERCA2b activity promotes chronic ER stress, Ca^{2+} –phosphoinositide complex formation, insulin resistance, and fibrotic activation, thereby linking Ca^{2+} dysregulation to progressive metabolic liver injury in metabolic dysfunction–associated fatty liver disease (MAFLD) and steatohepatitis (MASH). These observations position Ca^{2+} dysregulation as a unifying mechanism across the cardiometabolic disease continuum, spanning myocardial dysfunction, systemic insulin resistance, and progressive fatty liver disease. Therapeutic strategies targeting the SERCA–PLN–DWORF axis, including SERCA activators, PLN-directed antisense oligonucleotides, DWORF gene therapy, and CRISPR-based modulation, have demonstrated efficacy in preclinical models by improving Ca^{2+} handling and alleviating metabolic or contractile stress. Further studies are required to determine the translational feasibility, long-term safety, and optimal patient subsets for SERCA-targeted interventions in cardiometabolic disease.

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Introduction

Intracellular calcium (Ca^{2+}) is a universal second messenger that regulates diverse cellular processes, including contraction, secretion, gene expression, and metabolic regulation. Precise regulation of Ca^{2+} dynamics is essential for proper organ function, particularly in excitable tissues such as cardiac and skeletal muscle, and is increasingly recognized as critical in metabolically active non-excitable cells like hepatocytes [1, 2]. Central to this regulation is the sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA), which actively sequesters cytosolic Ca^{2+} into the endoplasmic or sarcoplasmic reticulum



(ER/SR), thereby terminating cytosolic Ca^{2+} signals and refilling luminal stores [3–8].

SERCA function is finely modulated by small transmembrane peptides, known as regulins, including phospholamban (PLN), and the recently discovered dwarf open reading frame (DWORF) [9–11]. These micropeptides modify SERCA's affinity for Ca^{2+} and its enzymatic kinetics in a context-dependent manner, enabling tissues to dynamically adjust Ca^{2+} reuptake in response to physiological demands or stress signals [12–15]. PLN, predominantly expressed in cardiac and slow-twitch skeletal muscle, binds and inhibits SERCA2a when dephosphorylated, while phosphorylation at serine 16 (Ser16) or threonine 17 (Thr17) relieves this inhibition during β -adrenergic stimulation [9, 12, 16, 17]. Conversely, DWORF acts as an endogenous activator by displacing PLN and stabilizing SERCA in its active conformation, enhancing Ca^{2+} transport independent of phosphorylation status [10, 14, 18].

Dysregulation of this micropeptide-mediated SERCA control is a shared pathogenic feature in multiple diseases. In heart failure, elevated PLN expression combined with reduced phosphorylation impairs SERCA2a function, leading to delayed cytosolic Ca^{2+} clearance, decreased contractility, and arrhythmogenesis. Concurrently, DWORF expression is downregulated, worsening this functional imbalance [13, 19–21]. In non-contractile tissues such as the liver, SERCA2b is the predominant isoform. Although PLN is minimally expressed under physiological conditions, recent studies implicate PLN and PLN-like peptides (such as endoregulin [ELN] and another-regulin [ALN]) in modulating ER Ca^{2+} handling in hepatic stellate cells and hepatocytes, particularly under metabolic stress and fibrotic remodeling [22–28].

Loss of SERCA2b expression or function in the liver leads to ER Ca^{2+} depletion, chronic unfolded protein response (UPR) activation, mitochondrial Ca^{2+} overload, and inflammatory signaling cascades, driving progression of metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis [3, 29–33]. Analogous defects in the cardiac SERCA2a and PLN balance are central to heart failure pathogenesis, where emerging gene therapies and small-molecule interventions targeting this axis show promising preclinical and early clinical results [34–38].

Given the conserved yet tissue-specific roles of the SERCA–PLN–DWORF system, a comprehensive understanding of its molecular architecture, regulatory dynamics, and pathophysiological consequences is essential. This review aimed to integrate mechanistic insights from muscle physiology, liver metabolism, and disease models to elucidate the central role of this axis in Ca^{2+} homeostasis. Furthermore, it aimed to discuss current and emerging therapeutic approaches—ranging from small-molecule activators and gene therapy to micropeptide

modulation—that harness this knowledge to restore Ca^{2+} balance and mitigate organ dysfunction in cardiometabolic disease.

Overview of intracellular Ca^{2+} signaling and regulatory networks

Intracellular Ca^{2+} signaling plays a fundamental role in regulating diverse physiological processes, including muscle contraction, neurotransmission, hormone secretion, metabolism, immune responses, and gene expression [5, 39, 40]. The steep gradient between extracellular (approximately 1–2 mM) and intracellular (approximately 50–100 nM) Ca^{2+} concentrations provides a rapid and tightly regulated signaling mechanism, enabling cells to respond to external stimuli with precision and temporal specificity [3, 41, 42]. This homeostasis is maintained by an elaborate network of Ca^{2+} transport systems distributed across the plasma membrane, ER, mitochondria, and Golgi apparatus [3, 4]. Key regulators include plasma membrane Ca^{2+} ATPases (PMCA), SERCAs, and the mitochondrial $\text{Na}^+/\text{Ca}^{2+}/\text{Li}^+$ exchanger (NCLX), which extrude Ca^{2+} from the cytosol to restore basal Ca^{2+} levels following activation [22, 39, 42, 43]. Within the ER, Ca^{2+} depletion is detected by stromal interaction molecules STIM1 and STIM2, which translocate to ER–plasma membrane junctions and activate ORAI1 channels and Transient Receptor Potential Canonical channels. This process mediates store-operated Ca^{2+} entry (SOCE), a key mechanism for replenishing ER Ca^{2+} stores (Fig. 1, schematic of intracellular Ca^{2+} signaling and inter-organellar communication) [44–47].

Intracellular Ca^{2+} signaling is typically initiated by the activation of G protein-coupled receptors (GPCRs) in response to hormones such as glucagon, epinephrine, or norepinephrine. Gq-coupled receptors primarily mediate Ca^{2+} release by activating phospholipase C (PLC), which hydrolyzes phosphatidylinositol 4,5-bisphosphate ($\text{PI}(4,5)\text{P}_2$) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). IP_3 then binds to IP_3 Rs on the ER membrane, triggering Ca^{2+} efflux into the cytosol [48]. In contrast, Gas signaling regulates cAMP/PKA pathways that indirectly modulate Ca^{2+} handling—for example, by phosphorylating Ca^{2+} channels or sensitizing downstream effectors—rather than serving as a primary IP_3 generator [40, 49, 50]. In addition, IP_3 can be sequentially phosphorylated into various inositol phosphates (IPs) and pyrophosphates (PP-IPs), which provide additional layers of metabolic and stress-related regulation, although their contribution to direct Ca^{2+} signaling is secondary [51]. The spatial and temporal patterns of Ca^{2+} signals—ranging from localized “puffs” to global cytosolic waves—are shaped by stimulus strength and the availability of phosphoinositide cofactors such as PIP_2 , which primarily regulate PLC activity and certain TRP channels, indirectly

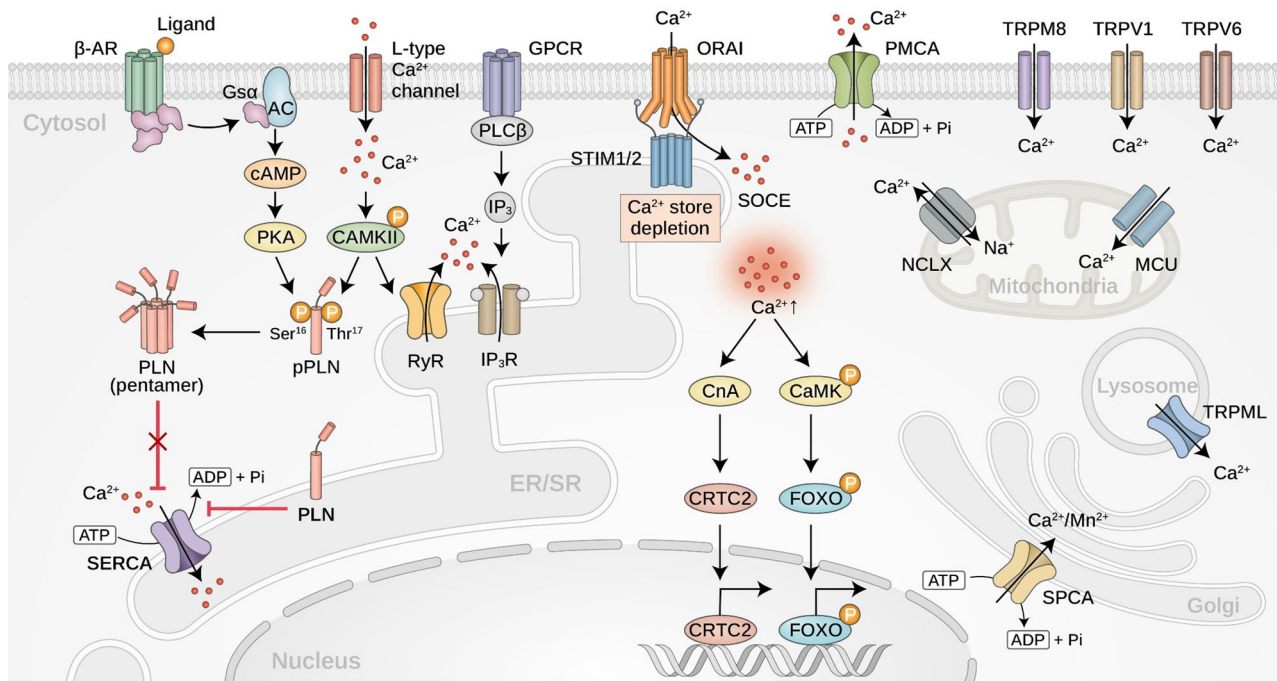


Fig. 1 Integrated Overview of Intracellular Ca^{2+} Handling and SERCA Regulation. This schematic representation summarizes the major pathways coordinating intracellular Ca^{2+} flux in excitable and non-excitable cells, emphasizing the β -adrenergic receptor (β -AR)–PLN–SERCA regulatory axis. β -AR activation stimulates Gs α –adenylyl cyclase signaling to elevate cAMP, which activates PKA and phosphorylates PLN at Ser¹⁶, relieving its inhibition of SERCA. Concurrently, Ca^{2+} influx through L-type Ca^{2+} channels triggers CaMKII-dependent phosphorylation of PLN at Thr¹⁷, further enhancing SERCA-mediated Ca^{2+} reuptake into the SR/ER. In its dephosphorylated state, PLN stabilizes SERCA in a low-affinity (E2) conformation, limiting Ca^{2+} sequestration, whereas phosphorylation or pentamerization inactivates PLN inhibition. Ca^{2+} release occurs through ryanodine (RyR) and IP₃ receptors, the latter activated via GPCR–PLC β –IP₃ signaling. ER Ca^{2+} depletion engages STIM1/2-mediated activation of ORAI channels, inducing store-operated Ca^{2+} entry (SOCE). Cytosolic Ca^{2+} is cleared by PMCA and buffered by mitochondria (via MCU/NCLX) and lysosomes (via TRPML channels), while Golgi Ca^{2+} /Mn²⁺-ATPases maintain secretory pathway stores. Elevated cytosolic Ca^{2+} activates calcineurin (CnA) and CaMK, which regulate transcriptional co-activators such as CRTC2 and FOXO to coordinate metabolic, stress-adaptive, and survival programs. Collectively, these integrated Ca^{2+} circuits ensure tight control of signaling amplitude and duration, with the PLN–SERCA module acting as a central determinant of Ca^{2+} clearance, excitation–contraction coupling, and organellar homeostasis across physiological and metabolic contexts

influencing Ca^{2+} signaling dynamics rather than directly modulating IP₃R sensitivity [52–54].

Elevated cytosolic Ca^{2+} levels activate various Ca^{2+} -sensitive signaling proteins, notably calmodulin (CaM), which undergoes conformational change upon Ca^{2+} binding to its EF-hand domains and subsequently activates a cascade of kinases and phosphatases [55, 56]. This includes Ca^{2+} /calmodulin-dependent kinases (CaMKs), protein kinase C (PKC), and the phosphatase calcineurin, each of which modulates specific transcriptional programs. As an example of tissue-specific Ca^{2+} -dependent feedback regulation, phospholamban (PLN) in cardiac muscle binds to the transmembrane domain of SERCA and inhibits its activity in the unphosphorylated state. This inhibition is relieved upon phosphorylation by PKA (Ser¹⁶) or Ca^{2+} /calmodulin-dependent kinase II (CaMKII; Thr¹⁷), thereby enhancing SERCA-mediated Ca^{2+} reuptake and promoting efficient cardiac contractility and relaxation during β -adrenergic stimulation [57–61]. For instance, CaMKs phosphorylate transcription factors such as Forkhead box O (FOXO), cAMP response

element-binding protein (CREB), p38 mitogen-activated protein kinase (p38 MAPK), nuclear factor kappa-light-chain-enhancer of activated B cells, and c-Jun N-terminal kinase to influence metabolic, inflammatory, and survival pathways [55, 62]. Simultaneously, calcineurin dephosphorylates transcription factors including CREB-regulated transcription coactivator 2 (CRTC2), myocyte enhancer factor-2 (MEF2), nuclear factor of activated T cells c, and transcription factor EB, enabling their nuclear translocation and activation of genes involved in metabolism, autophagy, lysosomal biogenesis, and immunity [63–65]. In addition, PKC activation is triggered by the concurrent rise in Ca^{2+} and DAG, which bind to its C2 and C1 domains, respectively, promoting translocation to the plasma membrane and subsequent phosphorylation of substrates, including MAPKs, I κ B, vitamin D receptor, and calpain [39, 66, 67]. Thus, intracellular Ca^{2+} functions as a versatile and highly integrated second messenger that governs numerous aspects of cellular physiology and inter-organellar communication. In this review, we focus specifically on the functional regulation and pathological

dysregulation of the SERCA–PLN–DWORF axis across tissues, highlighting its central role in Ca^{2+} reuptake and its therapeutic relevance in metabolic, cardiovascular, and fibrotic diseases.

Tissue-specific SERCA regulation

Three major isoforms of Ca^{2+} -ATPase (SERCA) are encoded by distinct genes (ATP2A1–3), and exhibit tissue-specific expression patterns critical for Ca^{2+} handling in diverse cellular contexts [68–73]. SERCA2a is the predominant isoform in cardiac muscle and slow-twitch skeletal fibers, optimized for rhythmic Ca^{2+} cycling required during contraction–relaxation. The ubiquitously expressed SERCA2b variant, derived from the same gene as SERCA2a but possessing a longer luminal C-terminal tail, is the principal isoform in non-excitable tissues such as liver, where it maintains ER Ca^{2+} levels critical for metabolic and secretory functions (Fig. 2A) [74, 75]. All SERCA isoforms share a conserved molecular structure comprising cytosolic nucleotide-binding, phosphorylation, and actuator domains linked to a transmembrane channel that mediates Ca^{2+} transport [9, 76, 77].

SERCA function is fine-tuned by small transmembrane micropeptides termed regulins, including PLN, and DWORF, which exhibit tissue- and isoform-specific expression patterns [78]. PLN, a 52-residue protein, is highly expressed in ventricular myocardium and slow oxidative skeletal fibers, where it regulates SERCA2a [28]. DWORF, a 35-residue muscle-specific peptide, is detectable in cardiac and slow skeletal muscle and functions as a direct SERCA activator. In cardiac tissue, PLN

is expressed at high levels, while DWORF is expressed at lower levels but may be upregulated under stress or via gene therapy [13, 79]. In non-excitable tissues like the liver, SERCA2b is the dominant isoform. PLN and DWORF are not robustly expressed under physiological conditions; however, PLN messenger RNA (mRNA) has been detected in hepatic stellate cells (HSCs), reported in some datasets but with functional significance remaining unclear [24], and DWORF expression is limited to trace transcriptomic signals without confirmed protein expression or functional relevance. Other SERCA-interacting regulins, such as ELN and ALN, have been identified in endothelial and epithelial cells and may functionally substitute for PLN in non-muscle tissues (Fig. 2A) [13, 22, 25, 78].

PLN modulates SERCA2a activity through direct interaction with its transmembrane domain, primarily M3. In its unphosphorylated state, PLN binds to SERCA and stabilizes the E2 conformation, reducing the pump's apparent affinity for Ca^{2+} and thereby slowing Ca^{2+} uptake into the SR [9, 80, 81]. X-ray crystallography and cryo-electron microscopy studies confirm that PLN binding traps SERCA in the Ca^{2+} -unbound state, effectively acting as a brake on cardiac relaxation (Fig. 2B) [10]. This inhibition is reversed upon phosphorylation of PLN at Ser16 [82] or Thr17 by CaMKII, [57, 58], which shifts PLN into a dynamic or dissociated conformation, freeing SERCA to bind and transport Ca^{2+} more efficiently [12, 16, 83]. This regulatory phosphorylation is integral to the β -adrenergic response, enhancing both inotropy and lusitropy during sympathetic stimulation.

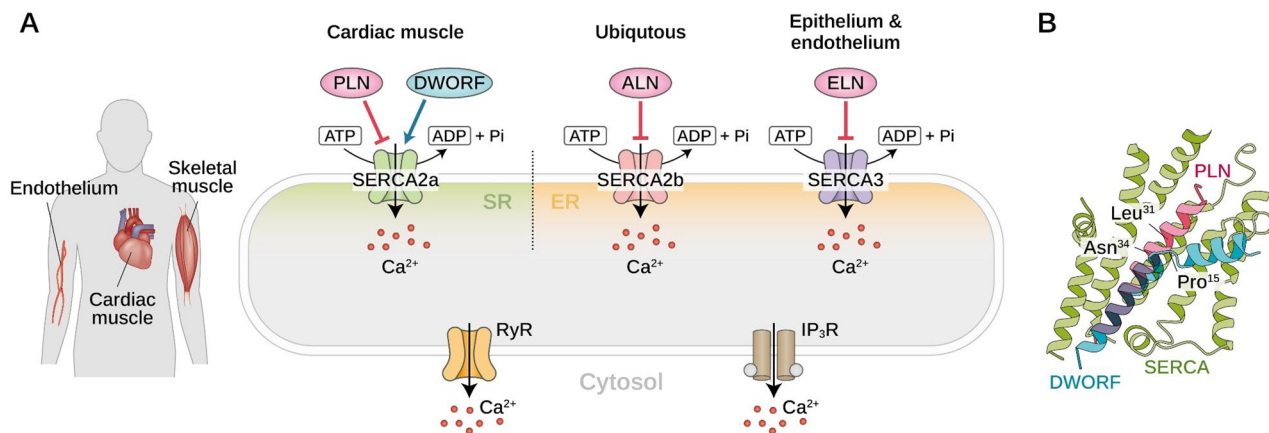


Fig. 2 Tissue-specific and structural regulation of SERCA by micropeptides. **A** Tissue-specific control of SERCA isoforms. Distinct SERCA isoforms exhibit specialized micropeptide regulation across tissues. In cardiac muscle, SERCA2a is repressed by phospholamban (PLN) and activated by DWORF, which competitively displaces PLN. In non-excitable cells, SERCA2b interacts with another-regulin (ALN), whereas SERCA3, expressed in epithelial and endothelial cells, is modulated by endoregulin (ELN). Each isoform drives ATP-dependent Ca^{2+} uptake into the SR or ER, counterbalanced by RyR or IP₃R-mediated Ca^{2+} release, ensuring precise, tissue-adapted control of Ca^{2+} cycling for contraction, secretion, and metabolic homeostasis. **B** Structural basis of PLN and DWORF regulation. SERCA's transmembrane helices (green) form a hydrophobic groove that binds PLN (pink), which inhibits Ca^{2+} transport via key residues Pro¹⁵, Leu³¹, and Asn³⁴. DWORF (blue) occupies the same binding pocket but acts antagonistically, displacing PLN and enhancing Ca^{2+} sequestration. This competitive interaction underscores the opposing regulatory roles of PLN and DWORF and identifies DWORF as a potential therapeutic activator of SERCA in muscle and metabolic disease

In contrast to these inhibitory peptides, DWORF acts as an endogenous activator of *SERCA* by occupying the same binding groove on the transmembrane domain and stabilizing the Ca^{2+} -bound E1 conformation [10, 13, 14, 84]. This single-pass α -helical peptide with a helix-linker-helix structure, stabilizes the Ca^{2+} -bound E1 conformation of *SERCA*, facilitating enhanced turnover and increased Ca^{2+} reuptake (Fig. 2A). DWORF not only displaces PLN from *SERCA* but also appears to exert allosteric effects that further enhance *SERCA* pump kinetics [10, 13]. Unlike its inhibitory counterparts, DWORF remains monomeric in the membrane and is the only known endogenous micropeptide that stimulates *SERCA* activity. DWORF is part of a growing family of small transmembrane peptides (collectively termed “regulins”) that modulate *SERCA*. Other members include MLN, ELN, and ALN, each predominantly expressed in specific tissues [13, 14, 27, 78, 85]. MLN, for instance, is expressed in skeletal muscle and acts as an inhibitor analogous to PLN, while ELN and ALN are found in non-muscle tissues (such as endothelial cells) and appear to have PLN-like functions. Uniquely, DWORF is the only known endogenous peptide that activates *SERCA* (Fig. 2A) [11, 14]. Its ability to enhance Ca^{2+} transport has made it a compelling target for therapeutic exploration.

The functional consequences of this regulatory balance are tissue-dependent and pathophysiologically relevant. In cardiac and skeletal muscle, phosphorylation of PLN or the presence of DWORF promotes rapid Ca^{2+} sequestration, enabling efficient relaxation and contractile performance [10, 12]. In contrast, excess PLN activity delays Ca^{2+} reuptake, predisposing to diastolic dysfunction, arrhythmogenic Ca^{2+} waves [13, 86]. In hepatocytes, high *SERCA2b* activity sustains luminal ER Ca^{2+} concentrations essential for protein folding and secretory capacity; its inhibition by PLN, ER stress, or lipotoxic conditions leads to UPR activation, mitochondrial Ca^{2+} overload, and hepatocellular injury [29, 87–90]. PKA signaling has been associated with reduced fibrogenic activation, potentially through Ca^{2+} -dependent mechanisms rather than direct PLN modulation [91, 92]. Overall, the balance between *SERCA* inhibition and activation, whether through PLN, SLN, DWORF, or other regulins, emerges as a central determinant of Ca^{2+} signaling fidelity and organ function, providing a framework for therapeutic targeting in metabolic, cardiovascular, and fibrotic diseases (Fig. 2B).

Dysregulation of the *SERCA2a*–PLN–DWORF signaling axis in heart failure (HF)

HF is a clinical syndrome of inadequate cardiac output due to impaired pump function, often following chronic stress such as hypertension, myocardial infarction, or genetic cardiomyopathies. A defining characteristic of

the failing myocardium is impaired intracellular Ca^{2+} handling, especially during excitation–contraction coupling, in contrast to the tightly regulated and efficient Ca^{2+} cycling observed in healthy myocardium (Fig. 3) [9, 12, 16, 86, 93]. In cardiomyocytes from failing hearts, studies have consistently found reduced *SERCA2a* expression and activity, along with elevated PLN levels or activity, shifting the balance toward suppressed Ca^{2+} reuptake [17, 37, 38, 43, 86, 94]. The result is a slower and incomplete removal of Ca^{2+} from the cytosol during diastole, leading to diastolic dysfunction (impaired relaxation) and a lower SR Ca^{2+} store for subsequent systoles, which contributes to reduced contractile force (systolic dysfunction) (Fig. 3B) [9].

Mechanistically, in many forms of HF (especially non-ischemic or genetic cardiomyopathies), PLN remains in a largely dephosphorylated (active inhibitory) state under baseline conditions, because β -adrenergic signaling is blunted and phosphatase activity is often elevated [12, 95]. This means the inhibition of PLN on *SERCA2a* is not adequately released, even when the failing heart attempts to increase output. Supporting this, failing human hearts have shown not only a higher PLN/*SERCA* protein ratio but also lower PLN phosphorylation at Ser¹⁶ [12, 37, 38, 91]. The net effect is chronic depression of *SERCA2a* function, contributing to prolonged Ca^{2+} overload, secondary activation of $\text{Na}^+/\text{Ca}^{2+}$ exchanger (which can promote arrhythmias), and energetic inefficiency (Fig. 3B) [96]. A dramatic example of the pathological role of PLN is the hereditary PLN R14del mutation, which produces a mutant PLN that cannot be properly phosphorylated and tends to form toxic aggregates [19, 20, 34, 97, 98]. Patients with this mutation develop lethal dilated cardiomyopathy at a young age, underscoring how overactive PLN inhibition of *SERCA2a* (and associated ER stress from PLN aggregation) can alone drive HF. Mouse models of PLN R14del and other PLN overexpression similarly exhibit severe contractile dysfunction, arrhythmias, and ventricular dilation [19]. Conversely, partial reduction of PLN (haploinsufficiency) or PKA-mediated hyperphosphorylation of PLN can ameliorate contractile deficits in various HF models [16, 93].

DWORF's role in the heart has also gained attention. In healthy myocardium, DWORF modulates *SERCA2a* subtly under resting conditions. However, during heightened adrenergic drive (when PLN is phosphorylated), DWORF may bind *SERCA2a* and further accelerate Ca^{2+} uptake [28, 99, 100]. In HF, DWORF expression has been reported to be downregulated in several failing human heart samples and mouse HF models (Fig. 3B) [13, 21]. The loss of DWORF removes an important counterbalance to PLN. Reduced DWORF in HF may reflect aspects of fetal gene reprogramming (since DWORF is higher in adult heart and lower in fetal heart), which unfortunately

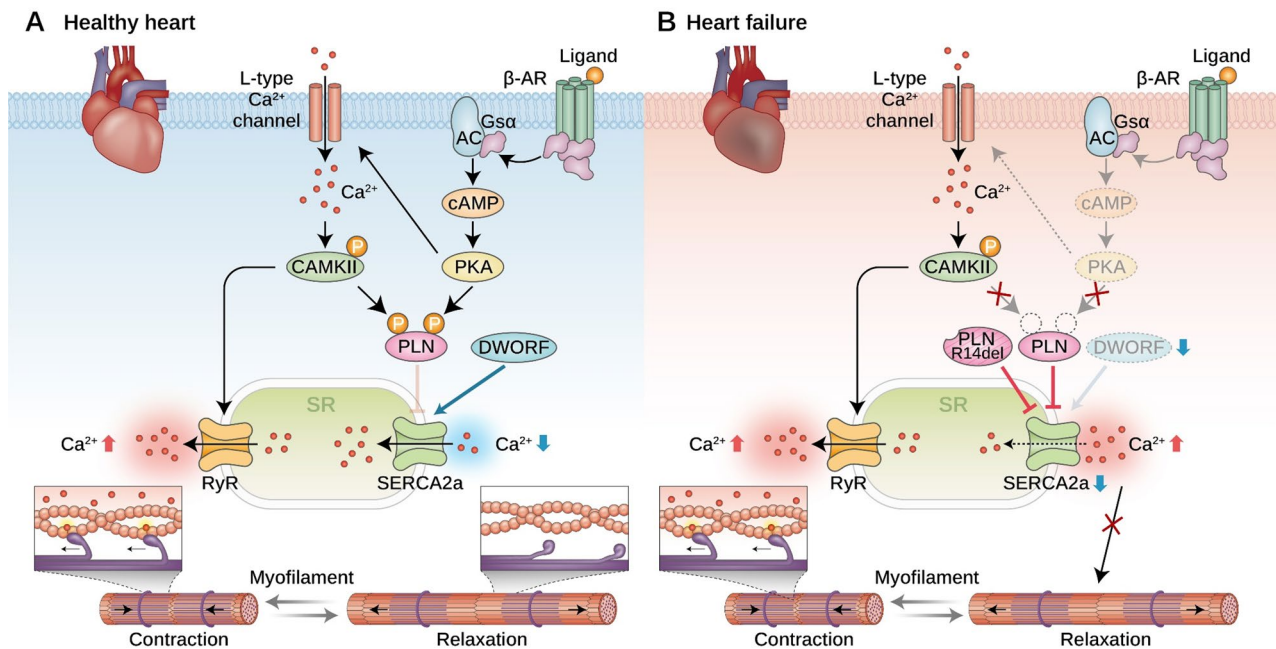


Fig. 3 Dysregulation of the SERCA2a–PLN–DWORF Axis in Heart Failure. **A** Healthy myocardium. β -adrenergic stimulation activates $G_{\alpha s}$ –AC–cAMP–PKA signaling, leading to PLN phosphorylation at Ser¹⁶ (by PKA) and Thr¹⁷ (by CaMKII). Phosphorylated PLN (pPLN) disengages from SERCA2a, enabling efficient Ca^{2+} reuptake into the SR and proper myofilament relaxation. DWORF further enhances SERCA2a activity by displacing PLN from its inhibitory site, maintaining balanced Ca^{2+} cycling between RyR-mediated release and SERCA2a-mediated sequestration. **B** Failing myocardium. Impaired β -adrenergic signaling reduces PKA activation and PLN phosphorylation, while pathogenic PLN variants (e.g., R14del) remain constitutively inhibitory. DWORF downregulation and SERCA2a suppression exacerbate SR Ca^{2+} reuptake failure, causing cytosolic Ca^{2+} overload and defective diastolic relaxation. RyR hyperactivity promotes persistent Ca^{2+} leak, driving contractile dysfunction and arrhythmogenesis characteristic of heart failure

leaves SERCA2a unopposed by inhibitors [13]. Indeed, transgenic DWORF overexpression in mice has been protective: when engineered mice with high cardiac DWORF were subjected to pressure overload or myocardial injury, they showed preserved ejection fraction and less hypertrophy/fibrosis compared to controls [11, 13]. DWORF presumably helped maintain SERCA activity in those stressed hearts, preventing the typical Ca^{2+} mis-handling and pathologic remodeling of HF.

Another contributor to Ca^{2+} dysregulation in HF is hyperactivation of kinases such as CaMKII, which can phosphorylate not only PLN (at Thr17) [57, 58] but also the ryanodine receptor (RyR2) [83, 101], leading to SR Ca^{2+} leak. In the context of HF, chronic hyperphosphorylation of RyR2 renders the channel leaky, leading to SR Ca^{2+} depletion even in the setting of impaired Ca^{2+} reuptake. This pathological state creates a vicious cycle wherein SERCA2a must function against two opposing forces: the inhibitory brake imposed by PLN and continuous Ca^{2+} leak through destabilized RyR2 channels (Fig. 3B). Experimental PLN ablation in knockout mice substantially enhances myocardial contractility, underscoring the critical role of PLN in limiting SERCA2a efficiency; however, in the absence of RyR2 stabilization, such interventions may provoke spontaneous Ca^{2+} waves and arrhythmias due to unrestrained SR Ca^{2+} release [20].

Therefore, successful therapeutic strategies must balance improvements in Ca^{2+} reuptake with stabilization of SR Ca^{2+} release. Nonetheless, the net effect in PLN knockout mice is improved cardiac performance, and remarkably, mice completely lacking PLN are viable and have supernormal cardiac function with no HF, although in humans, complete PLN deficiency has been linked to cardiomyopathy, suggesting species differences and possible compensatory mechanisms in mice [98, 102]. These findings underscore that SERCA regulation and micro-peptide function exhibit species-dependent variability, as rodents display higher Ca^{2+} cycling tolerance and compensatory reserve compared to humans. Therefore, translational extrapolation from murine to human systems requires careful validation using large-animal or humanized models. In summary, HF is fundamentally characterized by impaired intracellular Ca^{2+} cycling, driven by reduced SERCA2a expression or activity and excessive inhibition by PLN, particularly in its hypophosphorylated state. This dysfunction limits Ca^{2+} reuptake into the SR, resulting in depleted SR Ca^{2+} stores, weakened contractile force, and diastolic dysfunction. Moreover, insufficient SR Ca^{2+} buffering contributes to pro-arrhythmic spontaneous Ca^{2+} release events and activates pathological signaling cascades, including the calcineurin–nuclear factor of activated T cells (NFAT) axis and hypertrophic

transcriptional programs. A critical contributor to this pathological state is the imbalance within the SERCA2a–PLN–DWORF regulatory axis: elevated PLN activity inhibits SERCA2a, while the counter-regulatory action of DWORF is often reduced or insufficient to restore pump function. Accordingly, emerging preclinical strategies have focused on rebalancing this axis, either by silencing or inhibiting PLN or by augmenting DWORF expression or mimetics, to reactivate SERCA2a, improve SR Ca^{2+} sequestration, and normalize cardiac Ca^{2+} handling and contractility.

Hepatic SERCA2b–PLN signaling axis in health and disease

In healthy hepatocytes, SERCA2b is the predominant SERCA isoform and plays a central role in maintaining intracellular Ca^{2+} homeostasis by actively transporting Ca^{2+} from the cytosol into the ER lumen [30, 31, 103]. This process supports protein folding, lipid metabolism, and metabolic signaling by preserving luminal Ca^{2+} levels. Under basal physiological conditions, the expression of PLN, a well-known SERCA inhibitor in cardiac and slow-twitch skeletal muscle [9], is low in the liver [104]. Comparative protein analyses have revealed that hepatic PLN expression is approximately 100-fold lower than in cardiac muscle [104], and Northern blot confirmation of PLN mRNA in the liver remains limited. However, single-cell RNA sequencing has reported PLN transcripts in subsets of HSCs, but the functional significance of this expression remains unconfirmed [24]. HSCs, as liver-resident pericytes, regulate extracellular matrix production and contractility in response to injury, processes that are highly dependent on transient cytosolic Ca^{2+} elevations [105]. SERCA2b in these cells is thought to buffer cytosolic Ca^{2+} following G protein-coupled agonist stimulation (such as endothelin-1, angiotensin II) and may attenuate persistent activation. Although the regulatory function of PLN in liver cells remains unconfirmed, other SERCA-inhibiting micropeptides such as ELN and ALN have been identified in non-muscle cells [22, 23, 25, 106]. These peptides are believed to interact with SERCA2b to modulate ER Ca^{2+} reuptake, suggesting a conserved micropeptide-mediated regulatory system for ER Ca^{2+} pumps in epithelial cells, including hepatocytes and HSCs (Fig. 4A).

In pathological conditions such as metabolic dysfunction-associated fatty liver disease (MAFLD) and its progressive inflammatory form, metabolic-associated steatohepatitis (MASH), disruption of hepatic ER Ca^{2+} homeostasis emerges as a central pathophysiological mechanism [87, 107, 108]. Across diverse experimental models—including ob/ob mice, high-fat/high-sugar diet-fed mice, and the methionine/choline-deficient (MCD) diet-induced steatohepatitis model—a consistent

and marked downregulation of SERCA2b expression and activity has been reported in hepatocytes [3, 31, 87, 109]. These alterations are accompanied by inactivation of key metabolic signaling pathways, particularly protein kinase B (AKT) and PKA, which are essential for insulin signaling and hepatic metabolic regulation [3, 4, 59, 109–111]. Catalucci et al. [112] demonstrated that Akt directly phosphorylates phospholamban (PLN) at Thr17, relieving its inhibition of SERCA2a and thereby enhancing Ca^{2+} reuptake and contractility. In transgenic mice expressing constitutively active Akt (Akt-E40K), improved Ca^{2+} handling occurred independently of CaMKII signaling, confirming a direct Akt–PLN interaction. This study provides key evidence linking insulin/IGF-1 signaling to SERCA2a-mediated Ca^{2+} cycling in the heart, supporting the concept that Akt inactivation may impair PLN phosphorylation and SERCA function in hepatocytes under lipotoxic stress. Catalucci et al. [112] demonstrated that Akt directly phosphorylates phospholamban (PLN) at Thr17, relieving its inhibition of SERCA2a and thereby enhancing Ca^{2+} reuptake and contractility. In transgenic mice expressing constitutively active Akt (Akt-E40K), improved Ca^{2+} handling occurred independently of CaMKII signaling, confirming a direct Akt–PLN interaction. This study provides key evidence linking insulin/IGF-1 signaling to SERCA2a-mediated Ca^{2+} cycling in the heart, supporting the concept that Akt inactivation may impair PLN phosphorylation and SERCA function in hepatocytes under lipotoxic stress.

Mechanistically, chronic cytosolic Ca^{2+} overload, a hallmark of SERCA2b dysfunction, has been proposed to induce direct interaction of Ca^{2+} with phosphorylated headgroups of phosphoinositides (PIPs) such as phosphatidylinositol 3,4-bisphosphate ($\text{PI}[3,4]\text{P}_2$), phosphatidylinositol 4,5-bisphosphate ($\text{PI}[4,5]\text{P}_2$), and phosphatidylinositol 3,4,5-trisphosphate ($\text{PI}[3,4,5]\text{P}_3$), resulting in the formation of stable Ca^{2+} –PIP complexes, a mechanism supported by experimental and modeling studies [110]. These complexes sequester PIPs into membrane microdomains and impair membrane recruitment of pleckstrin homology (PH) domain-containing proteins, including AKT, phospholipase C delta, and insulin receptor substrate 1, thereby disrupting PIP-dependent insulin signaling [4, 110]. This defect prevents the phosphorylation of PLN, allowing it to remain in its inhibitory state and chronically suppresses SERCA2b activity (Fig. 4B). The resulting impairment in ER Ca^{2+} reuptake leads to sustained cytosolic Ca^{2+} elevation and progressive ER Ca^{2+} depletion, disrupting intracellular Ca^{2+} dynamics and ER homeostasis [3, 4, 113].

As ER Ca^{2+} stores decline, the UPR is chronically activated, with upregulation of stress markers such as glucose-regulated protein 78/binding immunoglobulin protein (GRP78/BiP) and C/EBP homologous protein

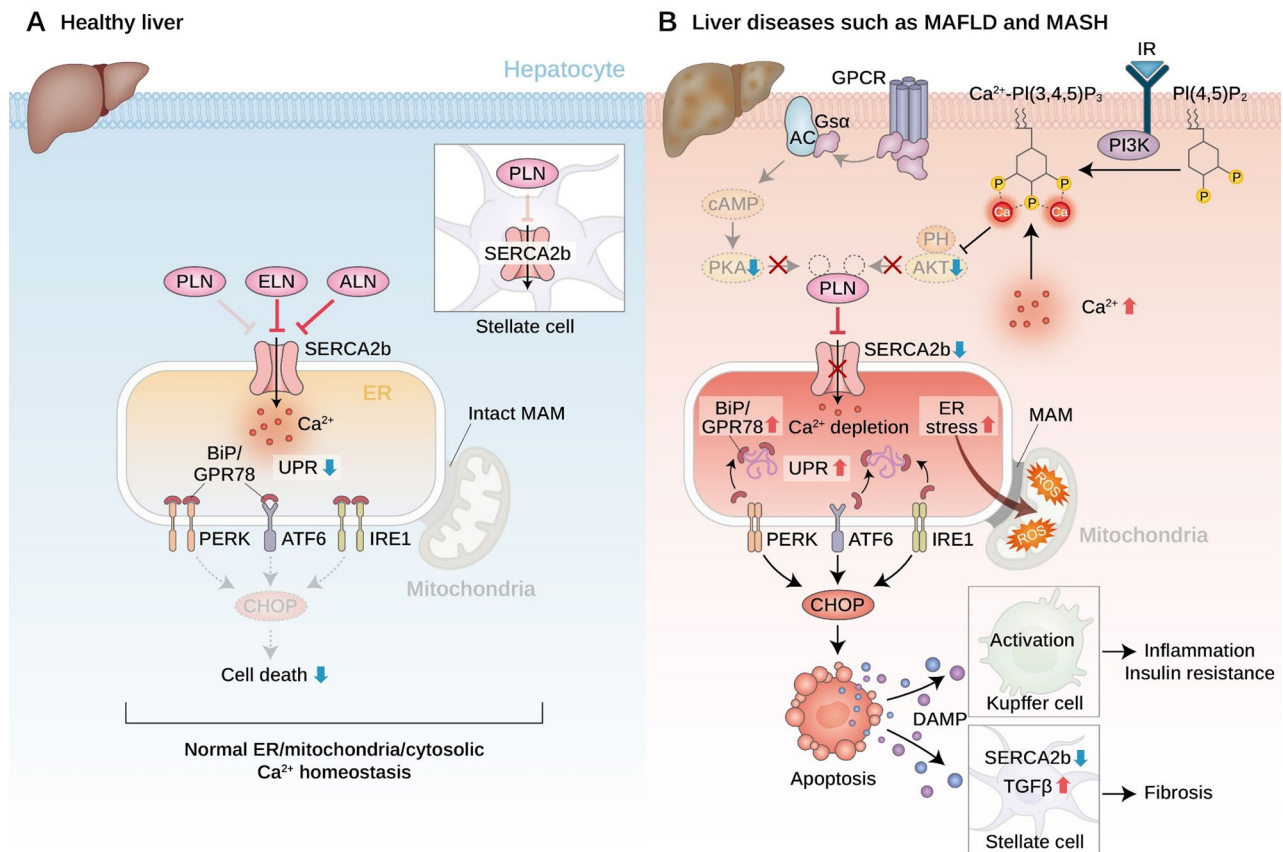


Fig. 4 Dysregulation of the SERCA2b–PLN Axis in Hepatic Ca^{2+} Homeostasis and Its Role in MAFLD/MASH Progression. **A** Healthy liver. In hepatocytes and stellate cells, SERCA2b maintains ER Ca^{2+} storage and cytosolic balance, while PLN inhibition is minimal. Alternative regulators such as ELN and ALN fine-tune SERCA2b activity to preserve ER–mitochondria coupling and suppress the unfolded protein response (UPR). Proper Ca^{2+} homeostasis sustains protein folding, redox balance, and mitochondrial integrity, preventing ER stress and supporting lipid metabolism and cell survival. **B** MAFLD and MASH. Impaired PI3K–AKT and $\text{Gs}\alpha$ –cAMP–PKA signaling keeps PLN unphosphorylated, suppressing SERCA2b activity. Resultant ER Ca^{2+} depletion and cytosolic Ca^{2+} overload trigger UPR activation (BiP, PERK, ATF6, IRE1) and formation of Ca^{2+} –PIP complexes, which sequester PIPs and block AKT membrane recruitment, worsening insulin resistance. Disrupted ER–mitochondrial Ca^{2+} coupling causes mitochondrial Ca^{2+} overload, ROS accumulation, and MAM destabilization, promoting apoptosis and release of DAMPs that activate Kupffer cells and inflammation. In stellate cells, reduced SERCA2b further enhances TGF- β –driven fibrogenesis, leading to collagen deposition and fibrosis. Collectively, these Ca^{2+} -dependent maladaptations drive hepatic apoptosis, inflammation, and fibrotic remodeling—key hallmarks of MAFLD/MASH pathogenesis

(CHOP), eventually triggering hepatocyte apoptosis and progressive hepatic injury [29, 30, 114, 115]. This maladaptive ER stress is particularly evident at mitochondria-associated ER membranes (MAMs), where SERCA2b levels are significantly reduced in fibrotic livers [29, 30, 116]. Loss of SERCA2b at MAMs disrupts ER–mitochondrial Ca^{2+} coupling, promotes mitochondrial Ca^{2+} overload, enhances reactive oxygen species production, and accelerates cell death (Fig. 4B) [31, 32, 117, 118]. In parallel, chronic activation of three UPR branches—protein kinase R–like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6)—shifts from adaptive to deleterious, amplifying hepatocellular dysfunction under sustained metabolic stress [119–121]. Damaged hepatocytes release damage-associated molecular patterns [122, 123], which activate Kupffer cells and recruit pro-inflammatory immune cells,

further exacerbating hepatic inflammation. Moreover, reduced ER luminal Ca^{2+} compromises lipid metabolic enzyme activity and impairs insulin signaling, thereby aggravating steatosis and promoting hepatic insulin resistance [3, 109, 110]. Thus, the sequential events triggered by SERCA2b dysfunction— Ca^{2+} –PIP complex formation, insulin signaling disruption, prolonged cytosolic Ca^{2+} elevation, and UPR-mediated cellular injury—represent a unified mechanism linking Ca^{2+} dysregulation to the pathogenesis of MAFLD and MASH, particularly at the interface of ER stress, lipid accumulation, and inflammation (Fig. 4B).

Upon liver injury or stimulation by pro-fibrotic agonists such as serotonin (5-HT), endothelin-1, angiotensin II, and platelet-derived growth factor, HSCs undergo rapid and sustained elevations in cytosolic Ca^{2+} concentration [124]. Although quiescent HSCs display only transient

and modest Ca^{2+} responses, activated HSCs, transdifferentiated into myofibroblast-like cells, acquire the capacity to generate prolonged Ca^{2+} transients essential for maintaining the fibrogenic phenotype. This transformation involves upregulation of Ca^{2+} signaling machinery, including GPCRs (such as 5-HT_{2A} and 5-HT_{2B}), ER IP₃Rs, SERCA isoforms for Ca^{2+} reuptake, and Ca^{2+} -binding chaperones such as calreticulin and calnexin [125, 126]. Elevated cytosolic Ca^{2+} acts as a central intracellular signal that both initiates and sustains expression of fibrogenic genes, including those encoding extracellular matrix (ECM) components such as collagen type I [125, 127]. This process is tightly linked to Ca^{2+} -dependent activation of the TGF- β signaling, particularly via SMAD-mediated transcription, which promotes pathological ECM deposition and liver fibrosis [128].

In this context, SERCA2b plays a critical role in terminating cytosolic Ca^{2+} signals by resequestering Ca^{2+} into the ER. However, its function is susceptible to inhibition by PLN. Although PLN expression in hepatocytes is negligible under physiological conditions [104], its possible expression in HSCs raises the hypothesis that PLN may theoretically inhibit SERCA2b and sustain cytosolic Ca^{2+} elevation, but this remains to be experimentally validated [125, 126]. Supporting this hypothesis, activation of the cAMP/PKA pathway has been shown to suppress HSC activation and fibrogenesis, potentially through mechanisms involving Ca^{2+} handling rather than direct PLN modulation (Fig. 4B) [91]. Further evidence comes from fibrotic liver models, where HSCs exhibit persistent SOCE and enhanced STIM1 activation, reflective of chronic ER Ca^{2+} depletion [129, 130]. Moreover, CSD2-deficient mice, lacking a SERCA2b-stabilizing factor, develop age-dependent non-alcoholic steatohepatitis (NASH) and liver fibrosis, underscoring the causal role of impaired SERCA2b function in hepatic fibrogenesis [131]. Notably, the consequences of hepatic Ca^{2+} dysregulation extend beyond the liver. In patients with cirrhosis, systemic manifestations such as cirrhotic cardiomyopathy are associated with abnormal myocardial PLN phosphorylation, suggesting a possible link whereby liver-derived inflammatory or endocrine mediators may influence SERCA–PLN signaling in the heart [132].

Disruption of ER Ca^{2+} homeostasis is also implicated in drug-induced liver injury. Pharmacological agents such as sorafenib, acetaminophen, and volatile anesthetics can impair ER Ca^{2+} balance either by directly inhibiting SERCA2b or inducing Ca^{2+} leakage, contributing to hepatocellular stress and death [133]. Similarly, herbal compounds like saikosaponins, known SERCA inhibitors, have been linked to hepatotoxicity and cardiotoxicity [30]. Importantly, restoring or enhancing SERCA2b function shows therapeutic potential. In MCD diet-fed mice, the augmenter of liver regeneration restored SERCA2b

expression, preserved ER Ca^{2+} stores, and mitigated hepatic steatosis and apoptosis [30]. Likewise, the natural compound matrine increased SERCA2b expression in palmitate-challenged hepatocytes, reducing cytosolic Ca^{2+} overload and UPR activation [134]. Conversely, hepatic Serca2b knockdown in healthy mice induced steatosis, glucose intolerance, and ER stress, highlighting its essential role in hepatic metabolic integrity [135]. Sustained cytosolic Ca^{2+} overload in HSCs—driven by receptor activation, ER Ca^{2+} leakage, and SERCA2b inhibition—thus represents a central mechanism promoting HSC activation, ECM production, and fibrosis. SERCA2b dysfunction, whether through direct inhibition, regulatory suppression by PLN, or loss of stabilizing factors like CSD2, integrates ER stress, mitochondrial dysfunction, and pro-fibrotic signaling. Therefore, restoring SERCA2b expression or activity, potentially alongside inhibition of negative regulators such as PLN, offers a compelling therapeutic strategy against fibrogenesis and progression of metabolic liver disease.

Targeting SERCA regulation: pharmacologic activation, PLN suppression, and gene-based upregulation

Therapeutic interventions targeting the PLN–SERCA–DWORF axis focus on restoring Ca^{2+} homeostasis through three principal strategies: direct pharmacologic activation of SERCA, suppression of PLN-mediated inhibition, and upregulation of SERCA expression (Fig. 5). Small-molecule SERCA activators, such as CDN1163, have demonstrated efficacy in hepatic models of fatty liver disease by restoring SERCA2b function, reducing ER stress, improving redox balance, and ameliorating systemic metabolic dysfunction [74, 87]. In the cardiac setting, istaroxime has shown similar benefit by directly activating SERCA2a independent of PLN phosphorylation, improving diastolic relaxation and cardiac output in patients with acute HF without inducing arrhythmias [36, 136]. Indirect pharmacological approaches, including atractylenolide II, have been reported to upregulate SERCA2b transcription via FXR activation, thereby reducing hepatic steatosis [29]. Complementing these therapeutic strategies, PLN inhibition has emerged as an effective approach to relieve SERCA2a suppression, particularly in hereditary cardiomyopathies caused by the pathogenic R14del mutation. The R14del variant results in the deletion of a conserved arginine residue adjacent to the cytoplasmic phosphorylation sites of PLN, abolishing its ability to be phosphorylated at Ser¹⁶ and Thr¹⁷. This renders PLN constitutively inhibitory toward SERCA2a and promotes the formation of aberrant pentamers and toxic oligomeric aggregates within the SR membrane, which exert dominant-negative effects on Ca^{2+} handling and protein homeostasis [19, 20]. Antisense oligonucleotides

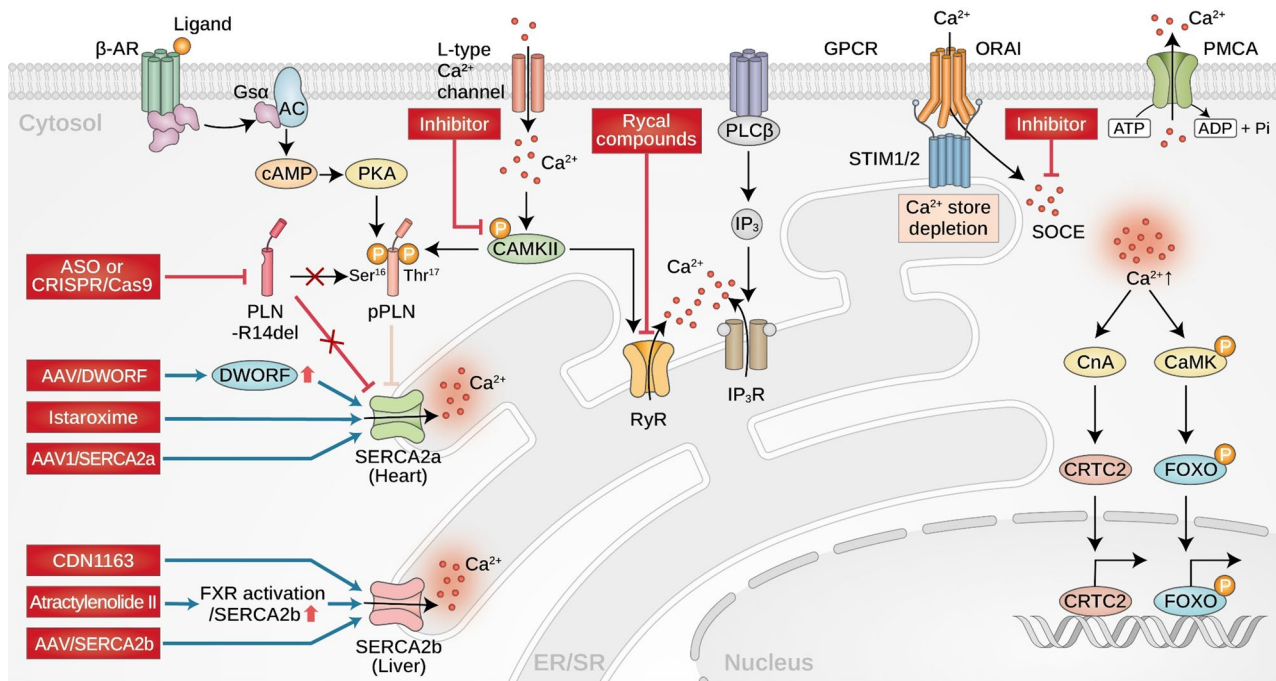


Fig. 5 Therapeutic modulation of the SERCA–PLN–DWORF axis in cardiac and hepatic Ca^{2+} Homeostasis. This schematic illustration summarizes major therapeutic strategies targeting the PLN–SERCA–DWORF regulatory network and Ca^{2+} signaling pathways. In the heart, β -adrenergic activation increases cAMP and PKA-mediated phosphorylation of PLN (Ser¹⁶/Thr¹⁷), relieving its inhibition on SERCA2a and promoting Ca^{2+} reuptake. In PLN-R14del cardiomyopathy, mutant PLN resists phosphorylation and forms toxic oligomers; ASO or CRISPR/Cas9 approaches silence or correct the mutant allele, while AAV-DWORF gene delivery restores SERCA2a function by competitively displacing PLN. Additional interventions include istaroxime (direct SERCA2a activator) and AAV1-SERCA2a therapy, both improving contractile Ca^{2+} cycling. Ryocal compounds stabilize RyR to prevent SR Ca^{2+} leak, and CaMKII inhibitors protect against hyperphosphorylation-induced dysfunction. In the liver, SERCA2b supports ER Ca^{2+} homeostasis and can be therapeutically enhanced by CDN1163, atractylenolide II (via FXR activation), or AAV-SERCA2b expression. Restoration of ER Ca^{2+} levels alleviates stress signaling and preserves mitochondrial–ER coupling. Pharmacologic SOCE inhibitors targeting STIM1/Orai further prevent cytosolic Ca^{2+} overload. Downstream, Ca^{2+} -activated calcineurin (CnA) and CaMK pathways modulate transcriptional regulators CRTC2 and FOXO, linking Ca^{2+} homeostasis to metabolic and stress adaptation. Together, these interventions underscore the therapeutic potential of SERCA activation, PLN inhibition, and DWORF augmentation as convergent strategies to normalize intracellular Ca^{2+} cycling in cardiac and hepatic diseases

(ASOs) targeting PLN mRNA reduce the expression of both wild-type and mutant PLN, thereby resolving toxic aggregates, alleviating SERCA2a inhibition, and restoring physiological Ca^{2+} cycling—collectively leading to improved cardiac function and survival in preclinical mouse models of PLN-R14del cardiomyopathy. In parallel, CRISPR/Cas9-mediated allele-specific editing of the mutant PLN offers a conceptually curative genomic strategy that has shown efficacy in preclinical systems but has not yet reached clinical translation (Fig. 5) [34]. Additional methods—such as phosphomimetic PLN peptides [93], PP1 inhibition to sustain PLN phosphorylation, and monoclonal antibodies or intrabodies to disrupt SERCA–PLN binding—are also under development. Although gene therapy with AAV1/SERCA2a in the CUPID trial demonstrated safety and suggested potential benefit rather than definitive efficacy due to vector delivery limitations, it confirmed the feasibility of SERCA overexpression in human HF [35]. In parallel, hepatic overexpression of SERCA2b has proven effective in alleviating ER stress and metabolic derangements in MAFLD

models [30, 31], supporting the feasibility of liver-targeted SERCA gene therapy.

In contrast to strategies that activate or disinherit SERCA, augmentation of DWORF represents a novel and mechanistically distinct approach. As a micro-peptide that competes with PLN for SERCA binding, DWORF overexpression has been shown in cardiac models to enhance contractile function, suppress ventricular remodeling, and provide protection against HF progression in settings such as dilated cardiomyopathy and Duchenne muscular dystrophy [13, 84]. Its action is independent of β -adrenergic or kinase signaling, making it particularly attractive for end-stage or genetic cardiomyopathies where upstream signaling is compromised. Although DWORF therapy has not yet been explored in hepatic models, it remains a hypothetical approach that requires experimental validation; AAV-mediated DWORF delivery could conceivably enhance SERCA2b function and attenuate hepatic fibrosis if proven feasible. Peptide-based delivery remains technically challenging due to the transmembrane structure of DWORF;

however, mRNA–lipid nanoparticle formulations are under investigation to enable transient, titratable expression. Importantly, DWORF overexpression *in vivo* has exhibited minimal off-target or pro-arrhythmic effects [34] (Fig. 5).

To complement the direct targeting of the SERCA–PLN–DWORF axis, several adjunctive strategies have been developed to further stabilize intracellular Ca^{2+} handling. Stabilization of RyR2 with rycal compounds reduces pathological SR Ca^{2+} leak and preserves SR Ca^{2+} stores, thereby potentiating the effects of SERCA activators. Other strategies, such as administration of exogenous Ca^{2+} buffers like parvalbumin or upregulation of endogenous chaperones including calreticulin, aim to reduce cytosolic Ca^{2+} overload, though they must be carefully balanced to avoid disrupting physiological signaling [20]. In hepatic stellate cells, blockade of SOCE via STIM1 or ORAI1 inhibition reduces Ca^{2+} influx and attenuates fibrogenic activation [131]. Particularly in HF, chronic overactivation of CaMKII leads to excessive phosphorylation of PLN at Thr¹⁷ and RyR2 at Ser²⁸¹⁴, driving SR Ca^{2+} leak, reduced Ca^{2+} content, and impaired relaxation. Targeted inhibition of CaMKII—either genetically or pharmacologically—ameliorates these maladaptive changes by decreasing pathological phosphorylation events and stabilizing Ca^{2+} homeostasis (Fig. 5) [59, 101, 137]. Together, these convergent strategies offer a multifaceted therapeutic framework to restore efficient Ca^{2+} cycling and protect against metabolic and contractile dysfunction across multiple organ systems.

Experimental models and translational evidence

A wide array of experimental systems has delineated the physiological and pathological roles of the SERCA–PLN–DWORF axis and its translational potential. *In vitro* cellular models, such as rodent and human induced pluripotent stem cell-derived cardiomyocytes, have reveal that PLN knockdown or DWORF overexpression enhances SERCA activity and Ca^{2+} reuptake into the SR, improving contractile function, though the magnitude of effect in human cells remains modest and requires further validation [13]. Hepatocyte cultures exposed to fatty acids (such as palmitate) replicate MAFLD-like stress responses, where SERCA2b overexpression or treatment with activators such as CDN1163 restores ER Ca^{2+} homeostasis and reduces UPR markers and cell death [29]. LX-2 stellate cells, while not yet tested for PLN/DWORF expression, exhibit reduced collagen output upon SERCA modulation independent of confirmed PLN/DWORF expression [91]. *In vivo*, transgenic and knockout mice have confirmed the protective roles of DWORF and the detrimental consequences of PLN overexpression in cardiac models of stress and HF [9, 138]. In the liver, dietary models such as HFD, MCD,

and Western Diet consistently show decreased Serca2b levels and increased ER stress, which are ameliorated by SERCA activators, ALR overexpression, or in C1SD2-deficient models that spontaneously develop liver injury [3, 30, 74, 87, 131]. Organ-level assays, such as Langendorff-perfused hearts and isolated liver perfusions, have provided mechanistic insights into how SERCA modulation alters Ca^{2+} dynamics and function under hormonal or pharmacological stimuli [139]. MAM assays in NASH liver models have revealed aberrant ER-mitochondria Ca^{2+} flux, normalized by SERCA reactivation [30]. Human biopsy studies, reported in several datasets, support these findings: failing hearts display reduced SERCA2a and DWORF mRNA with increased PLN levels [13, 86], and NASH liver tissue exhibits ER stress consistent with impaired Ca^{2+} sequestration. Safety studies using large animals (such as PLN knockout pigs or planned/early-stage AAV-DWORF studies in primates) and off-target screening for SERCA activators are essential for clinical translation, as SERCA shares structural homology with other P-type ATPases. Collectively, these integrated models validate the SERCA–PLN–DWORF axis as a modifiable regulator of Ca^{2+} -dependent pathology and provide a rational basis for ongoing therapeutic development.

Clinical translation of the SERCA–PLN–DWORF signaling axis: opportunities, challenges, and future directions in cardiometabolic disease

The PLN–SERCA–DWORF signaling axis has emerged as a central regulator of intracellular Ca^{2+} homeostasis, with direct implications for cardiac, hepatic, and skeletal muscle pathophysiology. Preclinical studies have established its relevance in disease contexts characterized by SR/ER Ca^{2+} dysregulation, including HF, MASH, and muscle-based metabolic disorders. Translating these insights into clinical therapies is now an active frontier, particularly in cardiology, with expanding potential in hepatology and skeletal muscle disease.

In cardiovascular medicine, the most advanced clinical efforts focus on SERCA2a gene therapy, particularly in the context of HF with reduced ejection fraction (HFrEF). Human trials such as CUPID [140] and MUSIC-HFrEF (ClinicalTrials.gov ID NCT04703842) have established proof-of-concept for AAV1-SERCA2a delivery, with ongoing refinements in vector design, targeted myocardial delivery, and patient stratification based on baseline SERCA activity [35]. Despite promising preclinical efficacy, significant translational challenges remain, including immune responses to viral vectors, limited transduction efficiency in diseased tissue, and potential off-target Ca^{2+} modulation. Long-term safety and dosage optimization will therefore be critical before clinical implementation. For HF with preserved ejection fraction

(HFpEF), characterized by diastolic dysfunction, SERCA2a augmentation may enhance active relaxation and improve compliance. Parallel to this, DWORF gene therapy (AAV9-DWORF), designed to displace PLN from SERCA2a, has shown promising preclinical efficacy and is nearing first-in-human testing, with considerations for optimal dosing, cardiac-specific expression, and re-dosing potential [13, 21]. In addition to gene therapy, pharmacologic agents targeting the SERCA axis are in development. Istaroxime, a dual Na^+/K^+ -ATPase inhibitor and SERCA2a activator, has demonstrated hemodynamic improvement in acute HF and may be reformulated for chronic use [36]. In genetic cardiomyopathies such as those caused by the PLN-R14del mutation, ASOs and CRISPR-derived base editing technologies offer the potential to specifically silence pathogenic PLN variants, restore SERCA function, and reverse disease phenotypes (Fig. 6) [34].

In hepatology, while direct clinical application remains in its early stages, a growing body of mechanistic

evidence supports SERCA2b as a therapeutic target. FXR agonists [141, 142], such as obeticholic acid, developed for NASH, have been shown to upregulate SERCA2b expression and reduce ER stress. GLP-1 analogs and emerging antifibrotics may indirectly support SERCA2b function by alleviating lipotoxicity and fibrogenic signaling. Notably, SERCA activators such as CDN1163 could be integrated into combination regimens with metabolic or anti-inflammatory agents to enhance efficacy in NASH [87, 143]. Although liver-targeted SERCA gene therapy [144] has not yet reached the clinic, it is technically feasible due to the hepatotropic properties of AAV serotypes, raising the possibility of AAV-SERCA2b or AAV-DWORF delivery for conditions such as acute liver failure, ER stress-driven hepatic injury, or Ca^{2+} dysregulation syndromes. Biomarker-based patient selection, using serum indicators (such as BiP and FGF21) or biopsy-derived ER stress markers (such as CHOP), may enable precision targeting in future trials (Fig. 6). Beyond the PLN–SERCA–DWORF axis itself, genetic and functional

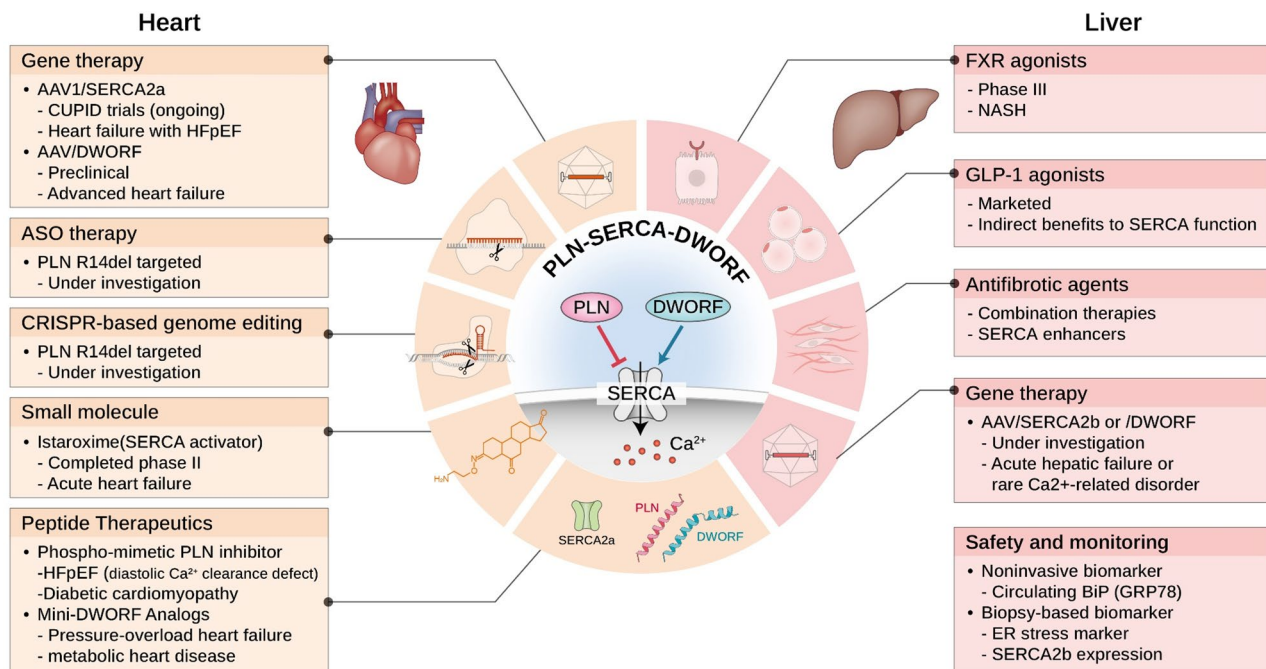


Fig. 6 Translational and Clinical Landscape of SERCA–PLN–DWORF-Targeted Therapies in Heart and Liver. This figure summarizes the current and emerging therapeutic strategies targeting the PLN–SERCA–DWORF axis across major organ systems. In the heart, AAV1-mediated SERCA2a gene therapy (CUPID trials) has established clinical proof-of-concept and is being extended to HFpEF. DWORF gene therapy remains in preclinical development for advanced heart failure, while PLN-R14del cardiomyopathies are under investigation for ASO and CRISPR-based correction to relieve SERCA inhibition. The small-molecule activator istaroxime has completed phase II trials, showing benefits in acute heart failure. In addition, peptide-based therapeutics are emerging as a versatile modality for direct modulation of SERCA regulatory proteins. Phospho-mimetic PLN inhibitors alleviate diastolic Ca^{2+} clearance defects in HFpEF and diabetic cardiomyopathy, while engineered mini-DWORF analogs competitively displace PLN to enhance SERCA activity in pressure-overload and metabolic heart disease. These peptides provide a protein-level strategy to restore cardiomyocyte Ca^{2+} homeostasis and complement existing gene- and small-molecule approaches. In the liver, FXR agonists (Phase III for NASH) and GLP-1 receptor agonists indirectly enhance SERCA2b activity, alleviating ER stress and metabolic dysfunction. Antifibrotic agents and AAV-based SERCA2b or DWORF gene therapies are being explored for hepatic Ca^{2+} disorders and fibrosis. Safety monitoring includes circulating BiP (GRP78) and biopsy-based ER stress and SERCA2b markers. Collectively, these strategies underscore a multi-organ therapeutic framework centered on restoring Ca^{2+} homeostasis via SERCA activation, PLN suppression, and DWORF augmentation—offering a unified pathway for treating cardiometabolic and fibrotic diseases

Table 1 Pathogenic SERCA (ATP2A) gene variants, associated diseases, and functional consequences

SERCA isoform (Gene)	Disease/syndrome	Mutation/expression	Functional consequence	References
<i>SERCA1</i> (<i>ATP2A1</i>)	Brody disease (autosomal recessive myopathy)	Missense (e.g., E918K, G211V)	Reduced Ca ²⁺ transport in skeletal muscle → impaired relaxation and exercise-induced stiffness	[145–147]
<i>SERCA2</i> (<i>ATP2A2</i>)	Darier disease (keratosis follicularis); Acrokeratosis verruciformis	Missense/nonsense (e.g., L565P, G769R)	ER Ca ²⁺ depletion → abnormal keratinocyte adhesion, ER stress; certain variants linked to cardiac arrhythmia	[71, 148–150]
<i>SERCA2a/ SERCA2b</i> (<i>ATP2A2</i>)	Heart failure (HF), MAFLD/MASH, ER stress-linked metabolic disorders	Reduced expression/activity (non-mutational)	Decreased SERCA2a/2b function → impaired Ca ²⁺ reuptake, ER stress, mitochondrial Ca ²⁺ overload, insulin resistance	[151–153]
<i>SERCA3</i> (<i>ATP2A3</i>)	Type 2 diabetes, endocrine dysfunction (pancreatic β-cells)	Downregulated expression rather than mutation	Impaired ER Ca ²⁺ uptake → defective insulin secretion, oxidative stress, altered glucose homeostasis	[154, 155]

abnormalities in *SERCA* isoforms have been directly linked to human diseases, underscoring the translational importance of Ca²⁺ pump regulation. Pathogenic mutations in *ATP2A1* (*SERCA1*) cause Brody disease [145–147], an autosomal recessive myopathy; *ATP2A2* (*SERCA2*) mutations underlie Darier disease [71, 148–150]; and reduced *ATP2A2/ATP2A3* expression has been implicated in heart failure [151–153], MAFLD/MASH, and type 2 diabetes [154, 155]. These findings collectively demonstrate that both genetic and acquired *SERCA* dysfunctions contribute to the pathogenesis of cardiometabolic disorders (Table 1).

However, the lack of tissue-specific delivery systems remains a barrier, especially given the risk of off-target cardiac effects, including arrhythmias from excessive *SERCA* activation in the heart. Given the multifaceted roles of this axis, combination therapies are expected to be necessary. In HF, *SERCA*-based interventions may complement β-blockers, renin–angiotensin system inhibitors, or sodium–glucose co-transporter 2 inhibitors, though care must be taken with β-agonist co-administration due to possible pro-arrhythmic synergy. In MASH, concurrent use of GLP-1 receptor agonists, PPAR agonists, or FXR modulators may optimize metabolic and anti-inflammatory outcomes. Patient stratification will be critical: individuals with high PLN expression, low *SERCA2a* activity, or impaired SR Ca²⁺ cycling may be ideal candidates for cardiac applications, while those with elevated ER stress markers in hepatic tissue (such as CHOP) may benefit most in the MASH setting (Fig. 6). Collectively, modulation of the *SERCA*–PLN–DWORF axis represents a paradigm shift in cardiometabolic therapy, offering disease-modifying potential by restoring intracellular Ca²⁺ homeostasis. Future success will depend on the development of tissue-specific delivery platforms, rigorous safety profiling, and precision medicine strategies integrating biomarkers, combination regimens, and patient-tailored intervention protocols.

Conclusion and perspectives

The discovery and functional elucidation of the *SERCA*–PLN–DWORF axis has substantially advanced our understanding of how intracellular Ca²⁺ homeostasis is precisely regulated across diverse tissue types. At the core of this system, *SERCA* pumps act as key effectors of Ca²⁺ sequestration into the ER/SR, maintaining Ca²⁺ gradients essential for muscle contractility, metabolic flux, and protein folding. Micropeptides such as PLN and DWORF are highly specialized regulators that fine-tune *SERCA* activity in response to physiological stimuli, developmental stages, and pathophysiological stressors [12–14].

In cardiac tissue, the balance between PLN-mediated inhibition and DWORF-driven activation of *SERCA2a* dictates the amplitude and timing of Ca²⁺ cycling critical for contractile performance. HF exemplifies how disruption of this balance—marked by increased PLN activity and diminished DWORF expression—leads to defective relaxation, Ca²⁺ overload, and contractile dysfunction [19, 20]. Emerging evidence indicates that *SERCA2b* and its micropeptide regulators in hepatocytes and hepatic stellate cells play similarly important roles in maintaining ER Ca²⁺ homeostasis, suppressing ER stress, and preventing fibrotic remodeling under metabolic or inflammatory stress [3, 4, 24, 30]. Although the cardiac, skeletal muscle, and hepatic systems exhibit distinct *SERCA* isoforms and micropeptide profiles, they share a conserved regulatory logic based on phosphorylation dynamics, Ca²⁺-dependent feedback, and stress-induced remodeling. This cross-organ comparison highlights the *SERCA*–PLN–DWORF axis as a unifying Ca²⁺ control module with context-specific adaptations.

Targeting the *SERCA*–PLN–DWORF axis is being explored as a potential strategy for treating Ca²⁺-dependent diseases. *SERCA* activators (such as CDN1163, istaroxime), PLN inhibitors (antisense oligonucleotides, CRISPR-based editing), and DWORF overexpression have demonstrated encouraging preclinical effects in preclinical studies in improving contractile function, reducing ER stress, and restoring metabolic balance in models of HF, MAFLD/MASH, and skeletal muscle dysfunction

[13, 34, 87]. However, several challenges remain for clinical translation. The tissue-specific expression and isoform diversity of SERCA and its regulators necessitate precision-targeted delivery to avoid off-target effects, particularly in excitable tissues. Moreover, the long-term safety and dosage optimization of SERCA activators and gene therapies must be rigorously evaluated, especially in chronic disease contexts where prolonged Ca^{2+} modulation could inadvertently trigger maladaptive signaling or arrhythmias.

Parallel to this, DWORF gene therapy (AAV9-DWORF), designed to displace PLN from SERCA2a, has shown preclinical efficacy and early translational potential, with considerations for optimal dosing, cardiac-specific expression, and re-dosing potential. Human trials such as CUPID and MUSIC-HFrEF have demonstrated safety and suggested modest benefit for AAV1-SERCA2a delivery, with ongoing refinements in vector design, targeted myocardial delivery, and patient stratification based on baseline SERCA activity. In genetic cardiomyopathies such as those caused by the PLN-R14del mutation, ASOs and CRISPR-derived base editing technologies have shown preliminary potential to specifically silence pathogenic PLN variants, restore SERCA function, and reverse disease phenotypes in preclinical models. Although liver-targeted SERCA gene therapy has not yet reached the clinic, it is technically feasible due to the hepatotropic properties of AAV serotypes, though immunogenicity and dosing remain significant challenges for clinical translation. Collectively, these translational efforts underscore the therapeutic potential of SERCA activation and PLN suppression in cardiometabolic contexts while highlighting the need for precision targeting and long-term safety validation before human applications.

Future research should focus on three major directions. First, expanding the characterization of novel regulins across tissue types—including hypothesized micropeptides in the liver and pancreas predicted by transcriptomic studies—to determine whether tissue-specific brakes on SERCA exist and can be therapeutically modulated. Second, structural and kinetic studies of SERCA and its micropeptide complexes are critical for designing selective small molecules and peptides that enhance SERCA activity without disrupting physiological regulation. Third, developing integrative therapeutic strategies combining SERCA modulation with other metabolic or anti-inflammatory agents (such as GLP-1 receptor agonists or FXR modulators) represents a promising but largely unexplored approach, particularly in complex diseases like NASH or HFrEF.

Although the present review consolidates the current mechanistic and translational knowledge of the SERCA–PLN–DWORF axis, several limitations must be acknowledged. First, much of the evidence is derived

from preclinical and animal models, and interspecies variability in SERCA isoform expression, PLN phosphorylation dynamics, and DWORF regulation limits direct extrapolation to humans. Second, the lack of comprehensive quantitative data on hepatic and skeletal muscle micropeptide interactions precludes definitive cross-organ comparisons. Third, therapeutic studies remain largely proof-of-concept, with long-term safety, delivery efficiency, and off-target Ca^{2+} modulation remaining unresolved. Finally, as this study is a narrative review rather than a meta-analysis, potential publication bias and incomplete inclusion of negative findings cannot be excluded. These limitations should be considered when interpreting the translational potential of SERCA-targeted interventions.

In conclusion, the SERCA–PLN–DWORF axis represents a key regulatory system for Ca^{2+} homeostasis across excitable and metabolic tissues. Modulating this axis may help improve Ca^{2+} handling and mitigate cellular stress responses relevant to cardiometabolic disease, but further validation in human models is needed to clarify its therapeutic feasibility and long-term safety.

Author contributions

Ok-Hee Kim wrote, edited the manuscript, and created the manuscript figures; Seung Wan Noh wrote the manuscript; Jun Su Choi contributed to manuscript writing; YunJae Jung wrote, edited, and revised the manuscript; Byung-Chul Oh wrote, edited, and revised the manuscript, and created figures for the manuscript. All authors have read and approved the final version of the article.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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References

1. Sanganalath SK, Dubey S, Veeranki S, Narisetty K, Krishnamurthy P. The interplay of inflammation, exosomes and Ca^{2+} dynamics in diabetic cardiomyopathy. *Cardiovasc Diabetol*. 2023;22(1):37.
2. Zhao S-M, Wang Y-L, Guo C-Y, Chen J-L, Wu Y-Q. Progressive decay of Ca^{2+} homeostasis in the development of diabetic cardiomyopathy. *Cardiovasc Diabetol*. 2014;13(1):75.
3. Arruda A, Hotamisligil Gökhan S. Calcium homeostasis and organ-elle function in the pathogenesis of obesity and diabetes. *Cell Metab*. 2015;22(3):381–97.
4. Oh BC. Phosphoinositides and intracellular calcium signaling: novel insights into phosphoinositides and calcium coupling as negative regulators of cellular signaling. *Exp Mol Med*. 2023;55(8):1702–12.
5. Clapham DE. Calcium signaling. *Cell*. 2007;131(6):1047–58.

6. Humbert A, Lefebvre R, Nawrot M, Caussy C, Rieusset J. Calcium signalling in hepatic metabolism: health and diseases. *Cell Calcium*. 2023;114:102780.
7. Makio T, Chen J, Simmen T. ER stress as a sentinel mechanism for ER Ca^{2+} homeostasis. *Cell Calcium*. 2024;124:102961.
8. Dahl R, Bezprozvanny I. SERCA pump as a novel therapeutic target for treating neurodegenerative disorders. *Biochem Biophys Res Commun*. 2024;734:150748.
9. MacLennan DH, Kranias EG. Phospholamban: a crucial regulator of cardiac contractility. *Nat Rev Mol Cell Biol*. 2003;4(7):566–77.
10. Fisher MLE, Bovo E, Aguayo-Ortiz R, Cho EE, Pribadi MP, Dalton MP, et al. Dwarf open reading frame (DWORF) is a direct activator of the sarcoplasmic reticulum calcium pump SERCA. *Elife*. 2021;10:e65545.
11. Li A, Yuen SL, Stroik DR, Kleinboehl E, Cornea RL, Thomas DD. The transmembrane peptide DWORF activates SERCA2a via dual mechanisms. *J Biol Chem*. 2024;296:100412.
12. Kranias EG, Hajjar RJ. Modulation of cardiac contractility by the phospholamban/SERCA2a regulatome. *Circ Res*. 2012;110(12):1646–60.
13. Makarewicz CA, Munir AZ, Schiattarella GG, Bezprozvannaya S, Raguimova ON, Cho EE, et al. The DWORF micropeptide enhances contractility and prevents heart failure in a mouse model of dilated cardiomyopathy. *Elife*. 2018. <https://doi.org/10.7554/eLife.38319>.
14. Nelson BR, Makarewicz CA, Anderson DM, Winders BR, Troupes CD, Wu F, et al. A peptide encoded by a transcript annotated as long noncoding RNA enhances SERCA activity in muscle. *Science*. 2016;351(6270):271–5.
15. Viskupicova J, Espinoza-Fonseca LM. Allosteric modulation of SERCA pumps in health and disease: structural dynamics, posttranslational modifications, and therapeutic potential. *J Mol Biol*. 2025. <https://doi.org/10.1016/j.jmb.2025.169200>.
16. Funk F, Kronenbitter A, Hackert K, Oebbecke M, Klebe G, Barth M, et al. Phospholamban pentamerization increases sensitivity and dynamic range of cardiac relaxation. *Cardiovasc Res*. 2023;119(7):1568–82.
17. Lai P, Hille SS, Subramanian H, Wiegmann R, Roser P, Muller OJ, et al. Remodeling of cAMP dynamics within the SERCA2a microdomain in heart failure with preserved ejection fraction caused by obesity and type 2 diabetes. *Cardiovasc Res*. 2024;120(3):273–85.
18. Garriga F, Martinez-Hernandez J, Parra-Balaguer A, Llanvera M, Yeste M. The sarcoplasmic/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) is present in pig sperm and modulates their physiology over liquid preservation. *Sci Rep*. 2025;15(1):4184.
19. Stege NM, Eijgenraam TR, Oliveira Nunes Teixeira V, Feringa AM, Schouten EM, Kuster DWD, et al. DWORF extends life span in a PLN-R14del cardiomyopathy mouse model by reducing abnormal sarcoplasmic reticulum clusters. *Circ Res*. 2023;133(12):1006–21.
20. Vafiadaki E, Glijnis PC, Doevendans PA, Kranias EG, Sanoudou D. Phospholamban R14del disease: the past, the present and the future. *Front Cardiovasc Med*. 2023;10:1162205.
21. Gibson AM, Pan X, Brito-Estrada O, Teixeira JA, Carl LK, Yue Y, et al. DWORF expression is reduced in a large animal model of Duchenne muscular dystrophy. *Dis Model Mech*. 2025;18(6):dmm052285.
22. Anderson DM, Makarewicz CA, Anderson KM, Shelton JM, Bezprozvannaya S, Bassel-Duby R, et al. Widespread control of calcium signaling by a family of SERCA-inhibiting micropeptides. *Sci Signal*. 2016;9(457):ra119.
23. Berta B, Tordai H, Lukács GL, Papp B, Enyedi Á, Padányi R, et al. SARS-CoV-2 envelope protein alters calcium signaling via SERCA interactions. *Sci Rep*. 2024;14(1):21200.
24. Oliva-Vilarnau N, Hankeova S, Vorrink SU, Mkrtchian S, Andersson ER, Lauschke VM. Calcium signaling in liver injury and regeneration. *Front Med (Lausanne)*. 2018;5:192.
25. Singh DR, Dalton MP, Cho EE, Pribadi MP, Zak TJ, Šeflová J, et al. Newly discovered micropeptide regulators of SERCA form oligomers but bind to the pump as monomers. *J Mol Biol*. 2019;431(22):4429–43.
26. Hassel KR, Gibson AM, Šeflova J, Cho EE, Blair NS, Van Raamsdonk CD, et al. Another-regulin regulates cardiomyocyte calcium handling via integration of neuroendocrine signaling with SERCA2a activity. *J Mol Cell Cardiol*. 2024;197:45–58.
27. Phillips TA, Hauck GT, Pribadi MP, Cho EE, Cleary SR, Robia SL. Micropeptide hetero-oligomerization adds complexity to the calcium pump regulatory network. *Biophys J*. 2023;122(2):301–9.
28. Rathod N, Bak JJ, Primeau JO, Fisher ME, Espinoza-Fonseca LM, Lemieux MJ, et al. Nothing regular about the regulins: distinct functional properties of SERCA transmembrane peptide regulatory subunits. *Int J Mol Sci*. 2021. <https://doi.org/10.3390/ijms22168891>.
29. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. *Nat Med*. 2015;21(7):677–87.
30. Xiao F, Zhang J, Zhang C, An W. Hepatic stimulator substance inhibits calcium overflow through the mitochondria-associated membrane compartment during nonalcoholic steatohepatitis. *Lab Invest*. 2017;97(3):289–301.
31. Park SW, Zhou Y, Lee J, Lee J, Ozcan U. Sarco(endo)plasmic reticulum Ca^{2+} -ATPase 2b is a major regulator of endoplasmic reticulum stress and glucose homeostasis in obesity. *Proc Natl Acad Sci USA*. 2010;107(45):19320–5.
32. Wires ES, Trychta KA, Bäck S, Sulima A, Rice KC, Harvey BK. High fat diet disrupts endoplasmic reticulum calcium homeostasis in the rat liver. *J Hepatol*. 2017;67(5):1009–17.
33. Rutkowski DT. Liver function and dysfunction – a unique window into the physiological reach of ER stress and the unfolded protein response. *FEBS J*. 2019;286(2):356–78.
34. Dave J, Raad N, Mittal N, Zhang L, Fargnoli A, Oh JG, et al. Gene editing reverses arrhythmia susceptibility in humanized PLN-R14del mice: modeling a European cardiomyopathy with global impact. *Cardiovasc Res*. 2022;118(15):3140–50.
35. Lyon AR, Babalis D, Morley-Smith AC, Hedger M, Suarez Barrientos A, Foldes G, et al. Investigation of the safety and feasibility of AAV1/SERCA2a gene transfer in patients with chronic heart failure supported with a left ventricular assist device – the SERCA-LVAD TRIAL. *Gene Ther*. 2020;27(12):579–90.
36. Metra M, Chioncel O, Cotter G, Davison B, Filippatos G, Mebazaa A, et al. Safety and efficacy of isatroxime in patients with acute heart failure-related pre-cardiogenic shock – a multicentre, randomized, double-blind, placebo-controlled, parallel group study (SEISMIC). *Eur J Heart Fail*. 2022;24(10):1967–77.
37. Shoosharian AK, O’Gallagher K, Shah AM, Zhang M. SERCA2a dysfunction in the pathophysiology of heart failure with preserved ejection fraction: a direct role is yet to be established. *Heart Fail Rev*. 2025;30(3):545–64.
38. Zhihao L, Jingyu N, Lan L, Michael S, Rui G, Xiyun B, et al. SERCA2a: a key protein in the Ca^{2+} cycle of the heart failure. *Heart Fail Rev*. 2020;25(3):523–35.
39. Trebak M, Kinet JP. Calcium signalling in T cells. *Nat Rev Immunol*. 2019;19(3):154–69.
40. Bugrim AE. Regulation of Ca^{2+} release by cAMP-dependent protein kinase. A mechanism for agonist-specific calcium signaling? *Cell Calcium*. 1999;25(3):219–26.
41. Guerrero-Hernandez A, Verkhatsky A. Calcium signalling in diabetes. *Cell Calcium*. 2014;56(5):297–301.
42. Cahalan MD, Chandy KG. The functional network of ion channels in T lymphocytes. *Immunol Rev*. 2009;231(1):59–87.
43. Lipskaia L, Chemaly ER, Hadri L, Lompre AM, Hajjar RJ. Sarcoplasmic reticulum Ca^{2+} ATPase as a therapeutic target for heart failure. *Expert Opin Biol Ther*. 2010;10(1):29–41.
44. Brandman O, Liou J, Park WS, Meyer T. STIM2 is a feedback regulator that stabilizes basal cytosolic and endoplasmic reticulum Ca^{2+} levels. *Cell*. 2007;131(7):1327–39.
45. Carrasco S, Meyer T. STIM proteins and the endoplasmic reticulum-plasma membrane junctions. *Annu Rev Biochem*. 2011;80:973–1000.
46. Son GY, Subedi KP, Ong HL, Noyer L, Saadi H, Zheng C, et al. STIM2 targets Orai1/STIM1 to the AKAP79 signaling complex and confers coupling of Ca^{2+} entry with NFAT1 activation. *Proc Natl Acad Sci USA*. 2020;117(28):16638–48.
47. Subedi KP, Ong HL, Son G-Y, Liu X, Ambudkar IS. STIM2 induces activated conformation of STIM1 to control Orai1 function in ER-PM junctions. *Cell Rep*. 2018;23(2):522–34.
48. Foskett JK, White C, Cheung KH, Mak DO. Inositol trisphosphate receptor Ca^{2+} release channels. *Physiol Rev*. 2007;87(2):593–658.
49. Mikoshiba K. IP3 receptor/ Ca^{2+} channel: from discovery to new signaling concepts. *J Neurochem*. 2007;102(5):1426–46.
50. Taylor CW. Regulation of IP₃ receptors by cyclic AMP. *Cell Calcium*. 2017;63:48–52.
51. Kim SH, Park SY, Kim ST, Jeon SJ. Analysis of short-term prestress losses in post-tensioned structures using smart strands. *Int J Concr Struct Mater*. 2022. <https://doi.org/10.1186/s40069-021-00488-3>.
52. Ivanova A, Atakpa-Adaji P, Rao S, Marti-Solano M, Taylor CW. Dual regulation of IP₃ receptors by IP₃ and PIP₂ controls the transition from local to global Ca^{2+} signals. *Mol Cell*. 2024;84(20):3997–4015.e3997.
53. Lock JT, Alzayady KJ, Yule DI, Parker I. All three IP₃ receptor isoforms generate Ca^{2+} puffs that display similar characteristics. *Sci Signal*. 2018;11(561):eaau0344.

54. Thillaiappan NB, Chavda AP, Tovey SC, Prole DL, Taylor CW. Ca^{2+} signals initiate at immobile IP_3 receptors adjacent to ER-plasma membrane junctions. *Nat Commun.* 2017;8(1):1505.
55. Zhang M, Tanaka T, Ikura M. Calcium-induced conformational transition revealed by the solution structure of apo calmodulin. *Nat Struct Biol.* 1995;2(9):758–67.
56. Park H-S, Lee SC, Cardenas ME, Heitman J. Calcium-calmodulin-calcineurin signaling: a globally conserved virulence cascade in eukaryotic microbial pathogens. *Cell Host Microbe.* 2019;26(4):453–62.
57. Mattiazzi A, Mundiña-Weilenmann C, Guoxiang C, Vittone L, Kranias E. Role of phospholamban phosphorylation on Thr¹⁷ in cardiac physiological and pathological conditions. *Cardiovasc Res.* 2005;68(3):366–75.
58. Zhao W, Uehara Y, Chu G, Song Q, Qian J, Young K, et al. Threonine-17 phosphorylation of phospholamban: a key determinant of frequency-dependent increase of cardiac contractility. *J Mol Cell Cardiol.* 2004;37(2):607–12.
59. Mattiazzi A, Kranias E. The role of CaMKII regulation of phospholamban activity in heart disease. *Front Pharmacol.* 2014; 5.
60. Wehrens XH, Lehnart SE, Reiken SR, Marks AR. Ca^{2+} /calmodulin-dependent protein kinase II phosphorylation regulates the cardiac ryanodine receptor. *Circ Res.* 2004;94(6):e61–70.
61. Bers DM. Cardiac excitation-contraction coupling. *Nature.* 2002;415(6868):198–205.
62. Han Z, Benlagha K, Lee P, Park CS, Filatov A, Byazrova MG, et al. The function of serine/threonine-specific protein kinases in B cells. *Front Immunol.* 2024;15:1459527.
63. Choi MS, Brines RD, Holman MJ, Klaus GG. Induction of NF-AT in normal B lymphocytes by anti-immunoglobulin or CD40 ligand in conjunction with IL-4. *Immunity.* 1994;1(3):179–87.
64. Hogan PG, Chen L, Nardone J, Rao A. Transcriptional regulation by calcium, calcineurin, and NFAT. *Genes Dev.* 2003;17(18):2205–32.
65. Settembre C, Di Malta C, Polito VA, Garcia Arencibia M, Vetrini F, Erdin S, et al. TFEB links autophagy to lysosomal biogenesis. *Science.* 2011;332(6036):1429–33.
66. Schmitz-Peiffer C, Biden TJ. Protein kinase C function in muscle, liver, and beta-cells and its therapeutic implications for type 2 diabetes. *Diabetes.* 2008;57(7):1774–83.
67. Lipp P, Reither G. Protein kinase C: the “masters” of calcium and lipid. *Cold Spring Harb Perspect Biol.* 2011. <https://doi.org/10.1101/cshperspect.a004556>.
68. Periasamy M, Kalyanasundaram A. SERCA pump isoforms: their role in calcium transport and disease. *Muscle Nerve.* 2007;35(4):430–42.
69. Xu H, Van Remmen H. The SarcoEndoplasmic reticulum calcium ATPase (SERCA) pump: a potential target for intervention in aging and skeletal muscle pathologies. *Skelet Muscle.* 2021;11(1):25.
70. Periasamy M, Maurya SK, Sahoo SK, Singh S, Sahoo SK, Reis FCG, et al. Role of SERCA pump in muscle thermogenesis and metabolism. *Compr Physiol.* 2017;7(3):879–90.
71. Dode L, Andersen JP, Leslie N, Dhitavat J, Vilsen B, Hovnanian A. Dissection of the functional differences between sarco(endo)plasmic reticulum Ca^{2+} -ATPase (SERCA) 1 and 2 isoforms and characterization of drier disease (SERCA2) mutants by steady-state and transient kinetic analyses. *J Biol Chem.* 2003;278(48):47877–89.
72. Lipskaia L, Keuylian Z, Bilirando K, Mougenot N, Jacquet A, Rouxel C, et al. Expression of sarco (endo) plasmic reticulum calcium ATPase (SERCA) system in normal mouse cardiovascular tissues, heart failure and atherosclerosis. *Biochim Biophys Acta.* 2014;1843(11):2705–18.
73. Martin V, Bredoux R, Corvazier E, van Gorp R, Kovács T, Gélébart P, et al. Three novel sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) 3 isoforms: expression, regulation, and function of the members of the (SERCA)3 family. *J Biol Chem.* 2002;277(27):24442–52.
74. Kang S, Dahl R, Hsieh W, Shin A, Zsebo KM, Buettner C, et al. Small molecular allosteric activator of the sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) attenuates diabetes and metabolic disorders. *J Biol Chem.* 2016;291(10):5185–98.
75. Tong X, Kono T, Anderson-Baucum EK, Yamamoto W, Gilon P, Lebeche D, et al. SERCA2 deficiency impairs pancreatic β -cell function in response to diet-induced obesity. *Diabetes.* 2016;65(10):3039–52.
76. Bublitz M, Musgaard M, Poulsen H, Thøgersen L, Olesen C, Schiøtt B, et al. Ion pathways in the sarcoplasmic reticulum Ca^{2+} -ATPase. *J Biol Chem.* 2013;288(15):10759–65.
77. Winters DL, Autry JM, Svensson B, Thomas DD. Interdomain fluorescence resonance energy transfer in SERCA probed by cyan-fluorescent protein fused to the actuator domain. *Biochemistry.* 2008;47(14):4246–56.
78. Anderson DM, Anderson KM, Chang CL, Makarewich CA, Nelson BR, McAnally JR, et al. A micropeptide encoded by a putative long noncoding RNA regulates muscle performance. *Cell.* 2015;160(4):595–606.
79. Cunningham JD, Phillips TA, Seflova J, Cho EE, Robia SL. Rapid quantification of intracellular calcium stores reveals effects of membrane micropeptides on SERCA function. *Cell Calcium.* 2025;126:103000.
80. Asahi M, Otsu K, Nakayama H, Hikoso S, Takeda T, Gramolini AO, et al. Cardiac-specific overexpression of sarcolipin inhibits sarco(endo)plasmic reticulum Ca^{2+} ATPase (SERCA2a) activity and impairs cardiac function in mice. *Proc Natl Acad Sci USA.* 2004;101(25):9199–204.
81. Smeazzetto S, Armanious GP, Moncelli MR, Bak JJ, Lemieux MJ, Young HS, et al. Conformational memory in the association of the transmembrane protein phospholamban with the sarcoplasmic reticulum calcium pump SERCA. *J Biol Chem.* 2017;292(52):21330–9.
82. Drago GA, Colyer J. Discrimination between two sites of phosphorylation on adjacent amino acids by phosphorylation site-specific antibodies to phospholamban. *J Biol Chem.* 1994;269(40):25073–7.
83. Weber DK, Reddy UV, Wang S, Larsen EK, Gopinath T, Gustavsson MB, et al. Structural basis for allosteric control of the SERCA-Phospholamban membrane complex by Ca^{2+} and phosphorylation. *Elife.* 2021. <https://doi.org/10.7554/eLife.66226>.
84. Morales ED, Yue Y, Watkins TB, Han J, Pan X, Gibson AM, et al. Dwarf open reading frame (DWORF) gene therapy ameliorated Duchenne muscular dystrophy cardiomyopathy in aged mdx mice. *J Am Heart Assoc.* 2023;12(3):e027480.
85. Bonilaui B, Dallagiovanna B. Microproteins in skeletal muscle: hidden keys in muscle physiology. *J Cachexia Sarcopenia Muscle.* 2022;13(1):100–13.
86. Minamisawa S, Hoshijima M, Chu G, Ward CA, Frank K, Gu Y, et al. Chronic phospholamban-sarcoplasmic reticulum calcium ATPase interaction is the critical calcium cycling defect in dilated cardiomyopathy. *Cell.* 1999;99(3):313–22.
87. Bednarski TK, Rahim M, Hasenour CM, Banerjee DR, Trenary IA, Wasserman DH, et al. Pharmacological SERCA activation limits diet-induced steatohepatitis and restores liver metabolic function in mice. *J Lipid Res.* 2024;65(6):100558.
88. Zhou H, Liu R. ER stress and hepatic lipid metabolism. *Front Genet.* 2014;5:112.
89. Song MJ, Malhi H. The unfolded protein response and hepatic lipid metabolism in non alcoholic fatty liver disease. *Pharmacol Ther.* 2019;203:107401.
90. Parthasarathy G, Malhi H. Assessment of lipotoxic endoplasmic reticulum (ER) stress in nonalcoholic steatohepatitis (NASH). *Methods Mol Biol.* 2022;2455:243–54.
91. Qin J, Zhang J, Lin L, Haji-Ghassemi O, Lin Z, Woycechowsky KJ, et al. Structures of PKA-phospholamban complexes reveal a mechanism of familial dilated cardiomyopathy. *Elife.* 2022. <https://doi.org/10.7554/eLife.75346>.
92. Shu G, Sun H, Zhang T, Zhu A, Lei X, Wang C, et al. Theaflavine inhibits hepatic stellate cell activation by modulating the PKA/LKB1/AMPK/GSK3 β cascade and subsequently enhancing Nr2f2 signaling. *Eur J Pharmacol.* 2023;956:175964.
93. Grote Beverborg N, Später D, Knöll R, Hidalgo A, Yeh ST, Elbeck Z, et al. Phospholamban antisense oligonucleotides improve cardiac function in murine cardiomyopathy. *Nat Commun.* 2021;12(1):5180.
94. Karakikes I, Stillitano F, Nonnenmacher M, Tzimas C, Sanoudou D, Ter-mglinch V, et al. Correction of human phospholamban R14del mutation associated with cardiomyopathy using targeted nucleases and combination therapy. *Nat Commun.* 2015;6(1):6955.
95. Dash R, Kadambi VJ, Schmidt AG, Tepe NM, Biniakiewicz D, Gerst MJ, et al. Interactions between phospholamban and β -adrenergic drive may lead to cardiomyopathy and early mortality. *Circulation.* 2001;103(6):889–96.
96. Nagy N, Kormos A, Kohajda Z, Szebeni Á, Szepesi J, Pollesello P, et al. Selective $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger inhibition prevents Ca^{2+} overload-induced triggered arrhythmias. *Br J Pharmacol.* 2014;171(24):5665–81.
97. Eijgenraam TR, Stege NM, Oliveira Nunes Teixeira V, de Brouwer R, Schouten EM, Grote Beverborg N, et al. Antisense therapy attenuates phospholamban p.(Arg14del) cardiomyopathy in mice and reverses protein aggregation. *Int J Mol Sci.* 2022. <https://doi.org/10.3390/ijms23052427>.
98. Deiman FE, Bomer N, van der Meer P, Grote Beverborg N. Review: Precision medicine approaches for genetic cardiomyopathy: targeting phospholamban R14del. *Curr Heart Fail Rep.* 2022;19(4):170–9.

99. Bovo E, Jamrozik T, Kahn D, Karkut P, Robia SL, Zima AV. Phosphorylation of phospholamban promotes SERCA2a activation by dwarf open reading frame (DWORF). *Cell Calcium*. 2024;121:102910.
100. Cleary SR, Fang X, Cho EE, Pribadi MP, Seflova J, Beach JR, et al. Inhibitory and stimulatory micropeptides preferentially bind to different conformations of the cardiac calcium pump. *J Biol Chem*. 2022;298(7):102060.
101. Benitah JP, Perrier R, Mercadier JJ, Pereira L, Gómez AM, RyR2 and calcium release in heart failure. *Front Physiol*. 2021;12:734210.
102. Haghighi K, Kolokathis F, Pater L, Lynch RA, Asahi M, Gramolini AO, et al. Human phospholamban null results in lethal dilated cardiomyopathy revealing a critical difference between mouse and human. *J Clin Invest*. 2003;111(6):869–76.
103. Ali ES, Petrovsky N. Calcium signaling as a therapeutic target for liver steatosis. *Trends Endocrinol Metab*. 2019;30(4):270–81.
104. McTiernan CF, Frye CS, Lemster BH, Kinder EA, Ogletree-Hughes ML, Moravec CS, et al. The human phospholamban gene: structure and expression. *J Mol Cell Cardiol*. 1999;31(3):679–92.
105. Yin C, Evason KJ, Asahina K, Stainier DY. Hepatic stellate cells in liver development, regeneration, and cancer. *J Clin Invest*. 2013;123(5):1902–10.
106. Zádor E. The meeting of micropeptides with major Ca^{2+} pumps in inner membranes—consideration of a new player, SERCA1b. *Membranes*. 2023. <https://doi.org/10.3390/membranes13030274>.
107. Chen X, Zhang L, Zheng L, Tuo B. Role of Ca^{2+} channels in non-alcoholic fatty liver disease and their implications for therapeutic strategies (Review). *Int J Mol Med*. 2022. <https://doi.org/10.3892/ijmm.2022.5169>.
108. Xu X, Poulsen KL, Wu L, Liu S, Miyata T, Song Q, et al. Targeted therapeutics and novel signaling pathways in non-alcohol-associated fatty liver/steatohepatitis (NAFL/NASH). *Sig Transduct Target Ther*. 2022;7(1):287.
109. Lee JW, Gu HO, Jung Y, Jung Y, Seo SY, Hong JH, et al. Candesartan, an angiotensin-II receptor blocker, ameliorates insulin resistance and hepatosteatosis by reducing intracellular calcium overload and lipid accumulation. *Exp Mol Med*. 2023;55(5):910–25.
110. Kang JK, Kim O-H, Hur J, Yu SH, Lamichhane S, Lee JW, et al. Increased intracellular Ca^{2+} concentrations prevent membrane localization of PH domains through the formation of Ca^{2+} -phosphoinositides. *Proc Natl Acad Sci USA*. 2017;114(45):11926–31.
111. He X, Du T, Long T, Liao X, Dong Y, Huang Z-P. Signaling cascades in the failing heart and emerging therapeutic strategies. *Sig Transduct Target Ther*. 2022;7(1):134.
112. Catalucci D, Latronico MVG, Ceci M, Rusconi F, Young HS, Gallo P, et al. Akt increases sarcoplasmic reticulum Ca^{2+} cycling by direct phosphorylation of phospholamban at Thr17. *J Biol Chem*. 2009;284(41):28180–7.
113. Gu H-O, Noh SW, Kim O-H, Oh B-C. Crucial roles of calcium ATPases and phosphoinositides: insights into pathophysiology and therapeutic strategies. *Mol Cells*. 2025;48(9):100254.
114. Wang J, He W, Tsai P-J, Chen P-H, Ye M, Guo J, et al. Mutual interaction between endoplasmic reticulum and mitochondria in nonalcoholic fatty liver disease. *Lipids Health Dis*. 2020;19(1):72.
115. Bahar E, Kim H, Yoon H. ER stress-mediated signaling: action potential and Ca^{2+} as key players. *Int J Mol Sci*. 2016. <https://doi.org/10.3390/ijms17091558>.
116. Missiroli S, Patergnani S, Caroccia N, Pedriali G, Perrone M, Prevati M, et al. Mitochondria-associated membranes (MAMs) and inflammation. *Cell Death Dis*. 2018;9(3):329.
117. Civelek M, Manduchi E, Riley RJ, Stoeckert CJ, Davies PF. Chronic endoplasmic reticulum stress activates unfolded protein response in arterial endothelium in regions of susceptibility to atherosclerosis. *Circ Res*. 2009;105(5):453–61.
118. Xie S, Xu S-C, Deng W, Tang Q. Metabolic landscape in cardiac aging: insights into molecular biology and therapeutic implications. *Sig Transduct Target Ther*. 2023;8(1):114.
119. Park SW, Ozcan U. Potential for therapeutic manipulation of the UPR in disease. *Semin Immunopathol*. 2013;35(3):351–73.
120. Hiramatsu N, Chiang W-C, Kurt TD, Sigurdson CJ, Lin JH. Multiple mechanisms of unfolded protein response-induced cell death. *Am J Pathol*. 2015;185(7):1800–8.
121. He J, Zhou Y, Sun L. Emerging mechanisms of the unfolded protein response in therapeutic resistance: from chemotherapy to immunotherapy. *Cell Commun Signal*. 2024;22(1):89.
122. Shim Y-R, Jeong W-I. Recent advances of sterile inflammation and inter-organ cross-talk in alcoholic liver disease. *Exp Mol Med*. 2020;52(5):772–80.
123. Mihm S. Danger-associated molecular patterns (DAMPs): molecular triggers for sterile inflammation in the liver. *Int J Mol Sci*. 2018. <https://doi.org/10.3390/ijms19103104>.
124. Soliman EM, Rodrigues MA, Gomes DA, Sheung N, Yu J, Amaya MJ, et al. Intracellular calcium signals regulate growth of hepatic stellate cells via specific effects on cell cycle progression. *Cell Calcium*. 2009;45(3):284–92.
125. Chen CC, Hsu LW, Chen KD, Chiu KW, Kung CP, Li SR, et al. Calreticulin regulates hepatic stellate cell activation through modulating TGF-beta-induced Smad signaling. *Cell Calcium*. 2024;121:102895.
126. Park KS, Sin PJ, Lee DH, Cha SK, Kim MJ, Kim NH, et al. Switching-on of serotonergic calcium signaling in activated hepatic stellate cells. *World J Gastroenterol*. 2011;17(2):164–73.
127. Zhang W, Zhu L, Fang F, Zhang F, Wang R, Yang K, et al. Activin A plays an essential role in migration and proliferation of hepatic stellate cells via Smad3 and calcium signaling. *Sci Rep*. 2024;14(1):20419.
128. Schwabe RF, Brenner DA. Hepatic stellate cells: balancing homeostasis, hepatoprotection and fibrogenesis in health and disease. *Nat Rev Gastroenterol Hepatol*. 2025;22(7):481–99.
129. Hanquier Z, Misra J, Baxter R, Maier JL. Stress and liver fibrogenesis: understanding the role and regulation of stress response pathways in hepatic stellate cells. *Am J Pathol*. 2023;193(10):1363–76.
130. Huang Y, Li X, Wang Y, Wang H, Huang C, Li J. Endoplasmic reticulum stress-induced hepatic stellate cell apoptosis through calcium-mediated JNK/P38 MAPK and calpain/caspase-12 pathways. *Mol Cell Biochem*. 2014;394(1–2):1–12.
131. Shen Z-Q, Chen Y-F, Chen J-R, Jou Y-S, Wu P-C, Kao C-H, et al. C1SD2 haploinsufficiency disrupts calcium homeostasis, causes nonalcoholic fatty liver disease, and promotes hepatocellular carcinoma. *Cell Rep*. 2017;21(8):2198–211.
132. Gregolin CS, do Nascimento M, de Borges Souza SL, Ferreira Mota GA, Bomfim GF, de Azevedo Melo Luvizotto R, et al. Myocardial dysfunction in cirrhotic cardiomyopathy is associated with alterations of phospholamban phosphorylation and IL-6 levels. *Arch Med Res*. 2021;52(3):284–93.
133. Andrade RJ, Chalasani N, Björnsson ES, Suzuki A, Kullak-Ublick GA, Watkins PB, et al. Drug-induced liver injury. *Nat Rev Dis Primers*. 2019;5(1):58.
134. Gao X, Guo S, Zhang S, Liu A, Shi L, Zhang Y. Matrine attenuates endoplasmic reticulum stress and mitochondrion dysfunction in nonalcoholic fatty liver disease by regulating SERCA pathway. *J Transl Med*. 2018;16(1):319.
135. Pant M, Bal NC, Periasamy M. Cold adaptation overrides developmental regulation of sarcolipin expression in mice skeletal muscle: SOS for muscle-based thermogenesis? *J Exp Biol*. 2015;218(Pt 15):2321–5.
136. Torre E, Arici M, Lodrini AM, Ferrandi M, Barassi P, Hsu S-C, et al. SERCA2a stimulation by istaroxime improves intracellular Ca^{2+} handling and diastolic dysfunction in a model of diabetic cardiomyopathy. *Cardiovasc Res*. 2021;118(4):1020–32.
137. Ai X, Curran JW, Shannon TR, Bers DM, Pogwizd SM. Ca^{2+} /Calmodulin-dependent protein kinase modulates cardiac ryanodine receptor phosphorylation and sarcoplasmic reticulum Ca^{2+} leak in heart failure. *Circ Res*. 2005;97(12):1314–22.
138. Eijgenraam TR, Boogerd CJ, Stege NM, Oliveira Nunes Teixeira V, Dokter MM, Schmidt LE, et al. Protein aggregation is an early manifestation of phospholamban p(Arg14del)-related cardiomyopathy: development of PLN-R14del-related cardiomyopathy. *Circ Heart Fail*. 2021;14(11):e008532.
139. Ferrandi M, Barassi P, Tadini-Buoninsegni F, Bartolommei G, Molinari I, Tripodi MG, et al. Istaroxime stimulates SERCA2a and accelerates calcium cycling in heart failure by relieving phospholamban inhibition. *Br J Pharmacol*. 2013;169(8):1849–61.
140. Greenberg B, Yaroshinsky A, Zsebo KM, Butler J, Felker GM, Voors AA, et al. Design of a phase 2b trial of intracoronary administration of AAV1/SERCA2a in patients with advanced heart failure: the CUPID 2 trial (calcium up-regulation by percutaneous administration of gene therapy in cardiac disease phase 2b). *JACC Heart Fail*. 2014;2(1):84–92.
141. Wang K, Zhang Y, Wang G, Hao H, Wang H. FXR agonists for MASH therapy: lessons and perspectives from obeticholic acid. *Med Res Rev*. 2024;44(2):568–86.
142. Hu X, Ge J, Wen Y. Computational study of novel natural agonists targeting farnesoid X receptor. *Sci Rep*. 2024;14(1):17597.
143. Mengeste AM, Lund J, Katore P, Ghobadi R, Bakke HG, Lunde PK, et al. The small molecule SERCA activator CDN1163 increases energy metabolism in human skeletal muscle cells. *Curr Res Pharmacol Drug Discov*. 2021;2:100060.
144. Zhang J, Li Y, Jiang S, Yu H, An W. Enhanced endoplasmic reticulum SERCA activity by overexpression of hepatic stimulator substance gene prevents hepatic cells from ER stress-induced apoptosis. *Am J Physiol Cell Physiol*. 2014;306(3):C279–90.
145. Benders AA, Veerkamp JH, Oosterhof A, Jongen PJ, Bindels RJ, Smit LM, et al. Ca^{2+} homeostasis in Brody's disease. A study in skeletal muscle and

- cultured muscle cells and the effects of dantrolene and verapamil. *J Clin Invest.* 1994;94(2):741–8.
146. Odermatt A, Barton K, Khanna VK, Mathieu J, Escolar D, Kuntzer T, et al. The mutation of Pro789 to Leu reduces the activity of the fast-twitch skeletal muscle sarco(endo)plasmic reticulum Ca²⁺ ATPase (SERCA1) and is associated with Brody disease. *Hum Genet.* 2000;106(5):482–91.
147. Odermatt A, Taschner PEM, Khanna VK, Busch HFM, Karpati G, Jablecki CK, et al. Mutations in the gene encoding SERCA1, the fast-twitch skeletal muscle sarcoplasmic reticulum Ca²⁺ ATPase, are associated with Brody disease. *Nat Genet.* 1996;14(2):191–4.
148. Bergman R, Sezin T, Indelman M, Helou WA, Avitan-Hersh E. Acrokeratosis verruciformis of Hopf showing P602L mutation in ATP2A2 and overlapping histopathological features with Darier disease. *Am J Dermatopathol.* 2012;34(6):597–601.
149. Burge SM, Wilkinson JD. Darier-white disease: a review of the clinical features in 163 patients. *J Am Acad Dermatol.* 1992;27(1):40–50.
150. Dhitavat J, Cobbold C, Leslie N, Burge S, Hovnanian A. Impaired trafficking of the desmoplakins in cultured Darier's disease keratinocytes. *J Invest Dermatol.* 2003;121(6):1349–55.
151. Lehnart SE, Schillinger W, Pieske B, Prestle J, Just H, Hasenfuss G. Sarcoplasmic reticulum proteins in heart failure. *Ann NY Acad Sci.* 1998;853(1):220–30.
152. Zarain-Herzberg A, García-Rivas G, Estrada-Avilés R. Regulation of SERCA pumps expression in diabetes. *Cell Calcium.* 2014;56(5):302–10.
153. Belke DD, Dillmann WH. Altered cardiac calcium handling in diabetes. *Curr Hypertens Rep.* 2004;6(6):424–9.
154. Váradi A, Molnár E, Ostenson CG, Ashcroft SJ. Isoforms of endoplasmic reticulum Ca(2+)-ATPase are differentially expressed in normal and diabetic islets of Langerhans. *Biochem J.* 1996;319(Pt 2):521–7.
155. Varadi A, Lebel L, Hashim Y, Mehta Z, Ashcroft SJ, Turner R. Sequence variants of the sarco(endo)plasmic reticulum Ca(2+)-transport ATPase 3 gene (SERCA3) in Caucasian type II diabetic patients (UK prospective diabetes study 48). *Diabetologia.* 1999;42(10):1240–3.

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