Published in final edited form as:

J Mol Cell Cardiol. 2016 December ; 101: 127–133. doi:10.1016/j.yjmcc.2016.11.003.

Roles and regulation of protein phosphatase 2A (PP2A) in the heart

Ellen R. Lubbers^{a,b} and Peter J. Mohler^{a,b,c,*}

^aDorothy M. Davis Heart and Lung Research Institute, The Ohio State University Wexner Medical Center, Columbus, OH, United States

^bDepartment of Physiology & Cell Biology, The Ohio State University Wexner Medical Center, Columbus, OH, United States

^cDepartment of Internal Medicine, Division of Cardiovascular Medicine, The Ohio State University Wexner Medical Center, Columbus, OH, United States

Abstract

Reversible protein phosphorylation is central to a variety of cardiac processes including excitation-contraction coupling, Ca^{2+} handling, cell metabolism, myofilament regulation, and cell-cell communication. While kinase pathways linked with elevated adrenergic signaling have been a major focus for the cardiovascular field over the past half century, new findings support the critical role of protein phosphatases in both health and disease. Protein phosphatase 2A (PP2A) is a central cardiac phosphatase that regulates diverse myocyte functions through a host of target molecules. Notably, multiple mechanisms have evolved to dynamically tune PP2A function, including modulation of the composition, phosphorylation, methylation, and localization of PP2A holoenzyme populations. Further, aberrations in this regulation of PP2A function may contribute to cardiac pathophysiology. In summary, PP2A is a critical regulatory molecule in both health and disease, with a myriad of targets in heart. Based on their unique structure, localization, and regulatory properties, PP2A subunits represent exciting therapeutic targets to modulate altered adrenergic signaling in cardiovascular disease.

Keywords

PP2A; Cardiac disease; Protein phosphatases; Arrhythmia; Ion channel

1. Introduction

More Americans die of cardiovascular disease than of any other cause, a number greater than all cancers combined [1,2]. On average, one person dies of cardiovascular disease every 40 s, accounting for about 31% of all deaths in the United States [1]. Economic costs of cardiovascular disease are vast. Direct and indirect costs of cardiovascular diseases total more than \$207.3 billion dollars in the United States, with ~one of every six healthcare

*Corresponding author at: 473 W. 12th Avenue, DHLRI 110G, Columbus, OH 43210. peter.mohler@osumc.edu (P.J. Mohler).

dollars spent on cardiovascular disease [3]. Due to its prevalence, research on the mechanisms of cardiovascular disease pathogenesis is essential to public health.

Increased adrenergic activity is a hallmark of multiple forms of cardiovascular disease. While beta-blockers have been a mainstay for treatment of cardiac diseases for half a century due to their ability to balance excessive sympathetic activity, they lack specificity, resulting in side-effects and necessitating the development of more targeted therapies [4–6]. While kinase pathways linked with elevated adrenergic signaling have remained a major emphasis for cardiovascular medicine, new findings support the critical role of phosphatases in both health and disease. This review will focus primarily on the role of the protein phosphatase 2A (PP2A) family of phosphatases, their unique structure, function, and regulation as well as their diverse roles in cardiovascular disease. Finally, this review will focus on the potential of PP2A-based regulation to treat cardiovascular disease.

2. Kinase/phosphatase-dependent regulation of cardiac signaling

Normal metazoan cellular activity is dependent on the highly orchestrated regulation of protein function. This function may be regulated by a variety of mechanisms, including modulation of protein transcription, translation, and/or degradation. However, perhaps the most versatile mode of regulation, due to its speed and reversibility, is phosphorylation. Proteins are phosphorylated by kinases that have a range of specificities regulated by diverse mechanisms including complementary structure of the kinase and target, chemical interactions between kinase and target, local environment (e.g. local Ca^{2+} concentration) and participation of scaffolding or adaptor proteins [7]. These disparate mechanisms allow kinases to act on specific sets of target proteins, as supported by the expression of >400 kinases in mammalian cells [8,9]. Notably, over half the proteins in human cells have the capacity to undergo reversible phosphorylation, highlighting the potential importance of phosphorylation pathways [10]. The critical roles of phosphorylation for physiologic regulation of various cell and tissue types have been reviewed many times over [11–15].

As noted above, phosphorylation is reversible. Removal of phosphate groups is catalyzed by protein phosphatases. Unlike kinases, vertebrates express relatively few phosphatases, whose specificity is not primarily regulated through direct target-phosphatase interactions [16–19]. Rather, the bulk of phosphatase regulation is modulated through interactions with phosphatase-interacting proteins [17]. Partially due to differences in specificity, kinases have been studied in much more depth than phosphatases, particularly in the context of human disease and drug development. Because phosphorylation of proteins must be carefully regulated by the balance of kinase and phosphatase activities, further study of protein phosphatases as potential drug targets is of critical importance in cardiovascular research [19].

In the heart, reversible protein phosphorylation is central to a myriad of processes. In fact, many cardiac phosphoproteins display multiple phosphorylation sites [16]. The central role of kinase/phosphatase balance for normal cardiac function is clearly illustrated by defects in protein phosphorylation in both congenital and acquired forms of human disease including arrhythmia and heart failure [19–21]. As noted above, due to their broad suppression of

kinase activity, beta-blockers have been a mainstay for treatment of cardiac diseases since their discovery in the 1960's [4–6].

3. Protein phosphatase families

Protein phosphatases (PP) are generally divided into three major families based on their endogenous phosphorylation sites: tyrosine, serine-threonine, and dual-specificity phosphatases. Of these families, the serine/threonine phosphatases are responsible for the majority of dephosphorylation events in the human heart. In fact, in the heart, ~90% of dephosphorylation events are catalyzed by just three phosphatases: PP1, PP2A and PP2B (calcineurin) [18,22]. These phosphatases are not single proteins, but rather holoenzymes, composed of a catalytic unit with one or more regulatory and structural units.

The catalytic subunit of PP1 is encoded by one of three genes: *PPP1CA*, *PPP1CB*, or *PPP1CC*. Further diversity is achieved through alternative splicing of *PPP1CA* and *PPP1CC*. Each resultant isoform is suggested to have cell- and tissue-specific expression [16,23]. The activity of PP1 is further regulated through ~200 regulatory subunits/proteins that combine with the catalytic PP1C subunit to modulate holoenzyme activity [24]. While the roles and regulation of PP1 have been widely reviewed [16,25–29], it is relevant for this review to note that PP1 and PP2A may serve overlapping roles for dephosphorylation of cardiac proteins (e.g. RyR2).

PP2B is a Ca^{2+} -dependent phosphatase with critical roles in gene transcription. Like PP1, PP2B is a holoenzyme, composed of a catalytic subunit ($\text{CNA}\alpha$, β , or γ), a Ca^{2+} -binding subunit ($\text{CNB}\alpha$ or β) and additional regulatory subunits [30]. While reviewed in depth elsewhere [16, 29,31,32], the broad role of PP2B is to link Ca^{2+} and phosphorylation-dependent signaling pathways.

4. Organization of Protein Phosphatase 2A holoenzyme

PP2A functions as a dimer or trimer holoenzyme with a diverse array of interchangeable subunits (Fig. 1). The core enzyme is comprised of a catalytic subunit ($\text{PP2A}\alpha$ or $\text{C}\beta$) and a structural subunit ($\text{PP2A}\alpha\alpha$ or $\text{PP2A}\alpha\beta$). Binding of the core enzyme to a third regulatory subunit transitions the complex into the mature holoenzyme. There are four families of PP2A regulatory subunits (PP2AB , $\text{PP2AB}'$, $\text{PP2B}''$, $\text{PP2AB}'''$). These families are encoded by separate genes that produce multiple splice variants. This complexity is further confounded in the literature by the use of multiple names for single PP2A subunits. Table 1 provides classification, variants, and alternative names for PP2A subunits.

5. Cardiac PP2A regulatory targets

Through dephosphorylation of a disparate collection of target proteins, PP2A activity regulates a host of critical myocyte functions. However, it is important to note that unlike single subunit or homogeneous enzymes, 'global' PP2A activity is comprised of the collective activities of numerous subpopulations of PP2A holoenzymes. Each subpopulation is uniquely regulated by subunit composition, post-translational modifications, and local interacting proteins. While a comprehensive review of all PP2A targets is too extensive for a

single review, Fig. 2 illustrates the great diversity of PP2A protein targets in the literature. Here, we review a select group of these targets that not only represent the critical nature of PP2A-dependent regulation of myocyte adrenergic signaling, but also the mechanisms by which PP2A impacts effector protein regulation (e.g. modulation of target function versus target trafficking), as well as key PP2A interacting molecules essential for in vivo target selectivity.

5.1. PP2A regulation of ion channels and transporters

PP2A plays a key role in regulation of cardiac excitability through dephosphorylation of cardiac ion channels, transporters, and their respective regulatory proteins. Notable PP2A membrane targets include the L-type calcium-channel (Cav1.2), ryanodine receptor 2 (RyR2), Na⁺/Ca²⁺ exchanger (NCX), and Na⁺/K⁺ ATPase, four membrane proteins essential for cardiac excitation-contraction coupling. For example, PP2A reduces cAMP-dependent protein kinase A (PKA)-dependent phosphorylation of Cav1.2, resulting in decreased I_{Ca,L} and ultimately reduced inward (depolarizing) current [37]. Activities of PP2A and PP1 are further critical for the dephosphorylation of multiple residues of RyR2, the primary calcium-release channel of the myocyte sarcoplasmic reticulum (SR). Whereas PKA (via RyR2 Serine 2808) and Ca²⁺/calmodulin-dependent kinase (CaMKII) (via RyR2 Serine 2814) dependent phosphorylation favor increased RyR2 channel open probability and Ca²⁺ release [38,39], PP2A and PP1 reverse this process resulting in reduced RyR2 activity [21]. Notably, altered regulation of this axis resulting in RyR2 hyperphosphorylation and increased RyR2 open probability is directly linked to potentially fatal human catecholaminergic polymorphic ventricular tachycardia (CPVT) [40,41]. Essential for maintaining the cardiac electrochemical gradient, Na⁺/K⁺ ATPase and NCX are also modulated by PP2A [42–44]. However, unlike RyR2, PP2A-dependent regulation of Na⁺/K⁺ ATPase governs membrane trafficking (versus channel biophysical properties) by modulating the interaction with the arrestin complex [42]. Finally, new PP2A myocyte membrane targets are still emerging. For example, the primary cardiac voltage-gated Na_v channel (Nav1.5) is highly regulated by CaMKII signaling in health and disease [45–47]. While regulation is likely modulated by both PP2A and PP1, the specific phosphatase, and mode of regulation responsible for Nav1.5 dephosphorylation is still unknown and represents an important area for future research. It is worth noting that in most cases above, PP2A target regulation is dependent on association of the core enzyme with a unique PP2A regulatory (B) subunit or phosphatase interacting protein. For example, PP2A regulatory subunits B56α and PR59 are suggested to modulate Cav1.2 regulation by PP2A [37,48], PP1 and PP2A are localized to the RyR2 complex via spinophilin and regulatory subunit PR130, respectively [49,50], and PP2A modulation of NCX requires regulatory subunit B56α [29,43].

Finally, membrane gap junctions, comprised of connexins, are essential for myocyte-myocyte communication and synchronous cardiac contraction. Connexin 43 is suggested to be regulated by both PP1 and PP2A based on the phosphorylation sites on connexin 43, the localization of the protein phosphatases to the myocyte intercalated disc, and evidence supporting reduced gap junction communication linked with increased phosphatase activity [51,52]. As further support of this regulation, PP2A is required for the dephosphorylation of connexin 43 at serine 368 in a pituitary cell line [53]. Similar to Nav1.5 discussed above,

given the critical role of connexin 43 regulation by phosphorylation in health and disease, it will be important to investigate the PP selectivity and mode of regulation for this essential cardiac protein.

5.2. PP2A regulation of cardiac contractility/relaxation

Beyond regulation of membrane targets, PP2A and PP1 are important regulatory molecules for cardiac contractility and relaxation (Fig. 2). Most notably, cardiac myosin binding protein-C (cMyBP-C) [54] and the inhibitory subunit of troponin (TnI) [55] are dephosphorylated by both PP1 and PP2A. The phosphorylation status of TnI alters contractile machinery function by modulating Ca^{2+} sensitivity, while cMyBP-C phosphorylation at multiple residues modulates contractility by altering cross-bridge cycling kinetics [54,56]. While both PP1 and PP2A dephosphorylate TnI, the target residues are different; PP1 dephosphorylates Serine 23 and 24 specifically, while PP2A contributes to more general hypophosphorylation of TnI [57]. This residue-specificity may exist for many targets, analogous to the phosphorylation of particular residues by individual protein kinases. As discussed for membrane protein regulation, local phosphatase activity is dependent on core enzyme interacting proteins and/or PP2A regulatory subunit diversity. For example, targeting of PP2A to the contractile apparatus is dependent upon the PP2A regulatory subunit, B56 α [58]. Interestingly, this targeting of PP2A by B56 α is lost following β -adrenergic stimulation, likely contributing to the physiologic effects of β -adrenergic signaling [58]. Multiple excellent reviews further detail the comprehensive roles of cardiac PP in regulation of contractile machinery [16,29].

5.3. PP1 versus PP2A target selectivity

While the sections above highlight only a fraction of PP2A targets in myocytes, the findings clearly illustrate both the spectrum of roles and impact of PP2A function in myocytes. However, as discussed briefly above, it is important to note the significant overlap between PP1 and PP2A target proteins. While these findings may initially suggest functional redundancy between the two PP's, the specific residues dephosphorylated in by PP1 and PP2A are often specific to each PP and may differentially modulate target function. Nonetheless, these issues reinforce the potential difficulty of directing global PP2A agonists/antagonists for modulation of specific myocyte targets/activities in vivo.

6. PP2A regulation in healthy hearts

6.1. PP2A regulation through holoenzyme subunit composition

Precise regulation of PP activity is essential to the function of cardiomyocytes. Multiple molecular mechanisms have evolved to dynamically tune PP2A function. Perhaps the most significant of these mechanisms is the ability to create unique PP2A holoenzymes through PP2A subunit diversity. The two catalytic subunits, PP2A-C α and PP2A-C β are nearly identical, and are not thought to exhibit major differences in function or regulation [59]. However, the vast array of 13 regulatory subunits plays a major role in modulating the function of PP2A (Table 1). Additionally, five additional regulatory subunit splice variants add to regulatory subunit diversity (Table 1). Regulatory subunits are differentially expressed at a tissue and subcellular level [34] and, when integrated into the PP2A holoenzyme affect

the function of PP2A by either modulating the activity level or by targeting the enzyme to certain subcellular compartments [19,34]. As noted above, PP2A is targeted to the cardiac dyad by the regulatory subunits PR130 and B56 α , where it modulates RyR2 phosphorylation [60–62]. Interestingly, B56 α that is trafficked to the cardiac dyad by ankyrin-B [43,63] appears to act as an auto-inhibitor of PP2A activity at the dyad causing increased phosphorylation at RyR2 Ser2808 and Ser2814 [21]. Other PP2A populations are targeted to the nucleus via B56 γ [64]. While the mechanisms underlying holoenzyme assembly are not fully elucidated, it appears that PP2A subunits are combined into a mature PP2A holoenzyme through a complex equilibrium, with subunits competing for position in the holoenzyme [65]. Thus, the subunit-makeup of PP2A is generally dynamic, depending on local cellular conditions resulting in diverse populations of PP2A with unique activities [19,29].

6.2. PP2A regulation by post-translational modification

PP2A subunits are regulated by post-translational modifications including phosphorylation and methylation. Often the phosphorylation of a PP2A subunit facilitates a feedback loop regulating phosphorylation. For example, phosphorylation of the PP2A regulatory subunit B56 δ by PKA increases PP2A activity [66]. PP2A, in turn, dephosphorylates targets shared with PKA, thus mitigating the PKA activity. The catalytic subunit of PP2A may also undergo posttranslational modifications. Phosphorylation of PP2A-C at Tyr307 reduces phosphatase activity, while methylation of PP2A-C at nearby Leu309 increased PP2A phosphatase activity [34,52]. The susceptibility of subunits to modification may also be tuned by PP2A interactions with non-subunit proteins. For example, the binding of p21-activated kinase 1 (PAK-1) to the holoenzyme results in a conformational change in PP2A-C which results in a reduction in phosphorylation at Tyr307 [52]. It is important to note, that the identification of the roles of the various PP2A subunits is complicated by additional variation by species, tissue type, cardiac chamber, cell type, and even subcellular compartment [34]. Thus, caution must be used when extrapolating data from between model systems.

6.3. PP2A regulation by microRNAs

In addition to protein modulators of PP2A function, recent studies have elucidated a role for microRNAs for regulating phosphatase activity. Specifically, miR-1 and miR-133 have been suggested to contribute to arrhythmogenesis through changes in the dephosphorylation of RyR2 by PP2A, leading to aberrant sarcoplasmic reticulum calcium handling [60]. Reactive oxygen species (ROS) may also indirectly impact PP2A activity, with implications for metabolic aberrations in the heart and for reperfusion injuries [34]. Future studies will be important to understand how these multiple regulatory mechanisms converge to modulate local PP2A activity in vivo at baseline and in disease.

7. Models of modulated PP2A activity display cardiac phenotypes

In vivo animal models of overexpression, knockdown, or knockout of the PP2A-C α subunit support evidence suggesting significant roles of PP2A subunits in cardiac physiology and pathophysiology. Findings from these studies have elucidated the essential role of PP2A in

cellular and cardiac hypertrophy, fibrosis, cardiac contractility, and signaling through the Akt/GSK3 β / β -catenin pathway [67–70]. For example, a mouse model with ~2-fold overexpression of PP2A-C α , developed by Gergs et al. displayed dilated cardiomyopathy, cellular hypertrophy, and fibrosis at baseline [67]. Additionally, L-type calcium current (I_{Ca,L}) was reduced and the Akt/GSK3 β / β -catenin pathway was disrupted, highlighting the roles for PP2A in cardiac electrical and structural function, respectively. However, these results have also raised new questions, as models of *reduced* cardiomyocyte-specific PP2A-C α expression generated by Dong et al. and Li et al. also display cellular hypertrophy, cardiac dilation, fibrosis, and disrupted Akt/GSK3 β / β -catenin pathway signaling [67–70]. Cardiac phenotypes observed in models of altered cardiac PP2A-C α expression are summarized in Table 2. Finally, it is important to note that both in vivo and in vitro studies have illustrated that select subunit activity is critical for mature PP2A holoenzyme function [21,60,62,67]. However, more critical are the relative local levels of PP2A subunits. For example, while one might predict that loss of the PP2A regulatory subunit would decrease PP2A activity [60, 62], other structural and functional studies suggest that it instead may increase enzymatic activity [21,67,71]. Further, chronic overexpression or deletion of a single subunit, while acutely altering PP2A activity, may result in transcriptional remodeling to compensate for altered signaling. This is an important future area in the cardiac phosphatase field and obviously a fundamental concept critical for the ability to design therapies that target PP2A.

8. PP2A regulation in disease

Many of the PP2A regulatory mechanisms discussed above are altered in heart failure and arrhythmia. Heart failure is a complex diagnosis, encompassing many etiologies and disease progressions. Thus, any data on heart failure as a whole should be considered carefully, as heterogeneity almost certainly exists. This is illustrated by the increase in PP2A-A expression in non-ischemic, but not ischemic human heart failure [34]. Alternately, PP2A-A is increased in both ischemic and non-ischemic canine heart failure, highlighting species differences that must be considered when generalizing experimental results [34].

p21-activated kinase 1 (PAK-1) is increased in heart failure, leading to local increases in PP2A activity and reduced phosphorylation of connexin 43, causing destabilization and lateralization of the gap junctions, contributing to arrhythmia susceptibility [52,72–74]. Conversely, RyR2 is hyperphosphorylated in heart failure and atrial fibrillation samples, despite overall increases in PP2A activity [29]. This highlights the differential regulation of the activity of PP2A composed of different subunits and/or residing in different sub-cellular domains. That is, regulation of specific subunits of PP2A in disease states may contribute to changes in localization and seemingly disparate regulation of target phosphorylation. For example, the miR-1 and miR-133-mediated reduction in B56 α could contribute to the reduced localization of PP2A to the sarcoplasmic reticulum membrane, thus allowing hyperphosphorylation of RyR2 while many other PP2A targets are hypophosphorylated [60].

Modulation of PP2A function itself may contribute to the pathophysiology of cardiac disease. For example, PP2A likely contributes to cardiac fibrosis through its

dephosphorylation of class IIa histone deacetylases [75]. This dephosphorylation prevents the nuclear localization of the histone deacetylases, leading to a loss of inhibition of transcription of hypertrophic and fibrotic genes [52]. The large contribution of PP2A to this process is supported by the hypertrophy and fibrosis seen in PP2A transgenic animals, as described above [67,68].

Recent work illustrates the impact of PP2A regulatory subunits in disease. In vivo, the PP2A regulatory subunit B56 α acts as a critical node modulating cardiac excitability. In mice with viral B56 α overexpression, excess B56 α decreases PP2A activity [21] resulting in increased phosphorylation of RyR2 at serine 2808 and serine 2814, increased heart rate, and decreased parasympathetic activity. Conversely, mice with reduced B56 α expression display increased PP2A activity, reduced phosphorylation of RyR2, and reduced Ca²⁺ sparks [21].

Physiologically, these phenotypes resulted in reduced heart rate, heart rate variability, conduction abnormalities and resistance to catecholamine-induced arrhythmias, highlighting the potential of targeting specific PP2A subunits therapeutically [21]. Interestingly, a second study has shown that acute overexpression of B56 α may lead to increased PP2A activity in the cytoplasm and myofilament fractions of heart lysates [76]. This may indicate differential functions of B56 α depending on cellular compartment that may be facilitated by the phosphorylation of B56 α at Ser41 (modifies PP2A-C-B56 α affinity) [43,76]. B56 α has also been implicated in the pathophysiology of “Ankyrin-B Syndrome”, as the loss of ankyrin-B function, essential to B56 α localization, may lead to altered RyR2 phosphorylation and arrhythmia [43,77].

9. Therapeutic potential of PP2A regulation

As PP2A activity is often increased in heart failure and atrial fibrillation, inhibition of PP2A is a potential strategy for treatment of cardiovascular disease [21]. PP2A is inhibited by naturally occurring compounds, including okadaic acid, canthadrin, and calyculin-A [19]. Unfortunately, these inhibitors are promiscuous, generally also inhibiting PP1 and/or PP2B, and likely have negative effects in other tissues, making them unfit for therapeutic use. However, subtle differences in the affinities of the inhibitors for the various phosphatases suggest they may be used as leads for future modifications to increase specificity and potency.

Select PP2A-modulating compounds are currently being investigated. A norcanthadrin analog, LB-100, is currently in phase 1 clinical trials for the treatment of patients with advanced solid tumors. LB-100 is a potent inhibitor of PP2A, with little cross inhibition of PP1 [78]. While the clinical trial is ongoing, the compound was utilized in mice for two weeks without significant toxicity phenotypes. [79,80]. LB-100 has also been used in mice to successfully prevent vascular disease, including arterial dysfunction and increased blood pressure in the context of diet-induced obesity [78]. Interestingly, FTY720 (fingolimod), an activator of PP2A has also been associated with bradycardia and blood pressure reduction in patients treated for multiple sclerosis [81–83]. Further, treatment with FTY720 protected mice from ischemia-reperfusion injuries and mitigated hypertrophy following transverse aortic constriction [84–86]. While these findings appear initially contradictory to the general association of increased PP2A activity with cardiac disease, observations in PP2A-C α

transgenic mice following MI support an important and essential role for acute PP2A activation following cardiac injury [68]. Due to the diverse and complex functions of PP2A, we hypothesize that either blanket PP2A inhibition or activation will be ineffective for treating cardiac disease. Rather, drugs altering PP2A activity will need to be carefully targeted to specific functions of PP2A. Specifically, it may be possible to target specific subunits of PP2A to inhibit specific cardiac PP2A actions. The targeting of a specific subunit, such as B56 α (an auto-inhibitor of PP2A [21]), may also mitigate the risk of side effects caused by cellular or systemic off-target effects by utilizing the differential expression of various PP2A subunits.

10. Conclusion

The dynamic, yet tightly regulated, balance of kinase and phosphatase activity in the heart is essential to the coordination of essential cardiac processes, including excitation-contraction coupling, Ca²⁺ handling, cell metabolism, myofilament regulation, and cell-cell communication. Further, alterations in adrenergic balance are tightly linked with heart failure and arrhythmia. Our understanding of basic cardiac function and the development of targeted therapies modulating cardiac phosphorylation (to improve upon the current standard-of-care, beta-blockers [4–6]) is contingent upon an understanding of the mechanisms underlying this balance. The broad and versatile role of PP2A in cardiomyocytes while daunting, presents a valuable opportunity to improve our understanding of cardiac function and to elucidate future therapeutic targets for the management of cardiovascular disease.

Acknowledgments

Funding for this work was provided by National Institutes of Health [grant numbers HL084583, HL083422, and HL114383]; American Heart Association (Established Investigator); and the William D. and Jacquelyn L. Wells Fund for Cardiovascular Research at The Ohio State University.

Abbreviations

PP2A	protein phosphatase 2A
NCX1	Na/Ca exchanger
MI	myocardial infarction
cMyBP-C	cardiac myosin binding protein-C
TnI	inhibitory subunit of troponin
RyR2	ryanodine receptor 2
PKA	protein kinase A
CaMKII	Ca ²⁺ /calmodulin-dependent protein kinase II
PAK-1	p21-activated kinase 1

References

- Centers for Disease Control and Prevention. Statistics NCfH, Health, United States, 2014. Centers for Disease Control and Prevention; Hayattsville, MD: 2015. p. 473
- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. *Circulation*. 2015; 131:e29–322. [PubMed: 25520374]
- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. M. Writing Group. Heart disease and stroke statistics–2016 update: a report from the American Heart Association. *Circulation*. 2016; 133:e38–360. [PubMed: 26673558]
- Marx SO, Reiken S, Hisamatsu Y, Jayaraman T, Burkhoff D, Rosemblyt N, et al. PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. *Cell*. 2000; 101:365–376. [PubMed: 10830164]
- Reiken S, Wehrens XH, Vest JA, Barbone A, Klotz S, Mancini D, et al. Beta-blockers restore calcium release channel function and improve cardiac muscle performance in human heart failure. *Circulation*. 2003; 107:2459–2466. [PubMed: 12743001]
- Black JW, Crowther AF, Shanks RG, Smith LH, Dornhorst AC. A new adrenergic betareceptor antagonist. *Lancet*. 1964; 1:1080–1081. [PubMed: 14132613]
- Ubersax JA, Ferrell JE Jr. Mechanisms of specificity in protein phosphorylation. *Nat. Rev. Mol. Cell Biol.* 2007; 8:530–541. [PubMed: 17585314]
- Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. *Science*. 2002; 298:1912–1934. [PubMed: 12471243]
- Cohen P. Protein kinases—the major drug targets of the twenty-first century? *Nat. Rev. Drug Discov.* 2002; 1:309–315. [PubMed: 12120282]
- Hornbeck PV, Kornhauser JM, Tkachev S, Zhang B, Skrzypek E, Murray B, et al. PhosphoSitePlus: a comprehensive resource for investigating the structure and function of experimentally determined post-translational modifications in man and mouse. *Nucleic Acids Res.* 2012; 40:D261–D270. [PubMed: 22135298]
- Ruvolo PP. The broken “off” switch in cancer signaling: PP2A as a regulator of tumorigenesis, drug resistance, and immune surveillance. *BBA Clin.* 2016; 6:87–99. [PubMed: 27556014]
- Cohen P. The origins of protein phosphorylation. *Nat. Cell Biol.* 2002; 4:E127–E130. [PubMed: 11988757]
- Sato PY, Chuprun JK, Schwartz M, Koch WJ. The evolving impact of g protein-coupled receptor kinases in cardiac health and disease. *Physiol. Rev.* 2015; 95:377–404. [PubMed: 25834229]
- Harvey RD. Regulation of cardiac Na-Ca exchange activity by selective tyrosine kinase inhibition. *Br. J. Pharmacol.* 2004; 143:929–930. [PubMed: 15545292]
- Johnson LN. The regulation of protein phosphorylation. *Biochem. Soc. Trans.* 2009; 37:627–641. [PubMed: 19614568]
- Weber S, Meyer-Roxlau S, Wagner M, Dobrev D, El-Armouche A. Counteracting protein kinase activity in the heart: the multiple roles of protein phosphatases. *Front. Pharmacol.* 2015; 6:270. [PubMed: 26617522]
- Chatterjee J, Kohn M. Targeting the untargetable: recent advances in the selective chemical modulation of protein phosphatase-1 activity. *Curr. Opin. Chem. Biol.* 2013; 17:361–368. [PubMed: 23647984]
- Cohen P. The structure and regulation of protein phosphatases. *Annu. Rev. Biochem.* 1989; 58:453–508. [PubMed: 2549856]
- Virshup DM, Shenolikar S. From promiscuity to precision: protein phosphatases get a makeover. *Mol. Cell.* 2009; 33:537–545. [PubMed: 19285938]
- Lei M, Wang X, Ke Y, Solaro RJ. Regulation of Ca(2+) transient by PP2A in normal and failing heart. *Front. Physiol.* 2015; 6:13. [PubMed: 25688213]
- Little SC, Curran J, Makara MA, Kline CF, Ho HT, Xu Z, et al. Protein phosphatase 2A regulatory subunit B56alpha limits phosphatase activity in the heart. *Sci. Signal.* 2015; 8:ra72. [PubMed: 26198358]

22. MacDougall LK, Jones LR, Cohen P. Identification of the major protein phosphatases in mammalian cardiac muscle which dephosphorylate phospholamban. *Eur. J. Biochem.* 1991; 196:725–734. [PubMed: 1849481]
23. Liu R, Correll RN, Davis J, Vagnozzi RJ, York AJ, Sargent MA, et al. Cardiac-specific deletion of protein phosphatase 1 β promotes increased myofilament protein phosphorylation and contractile alterations. *J. Mol. Cell. Cardiol.* 2015; 87:204–213. [PubMed: 26334248]
24. Heroes E, Lesage B, Gornemann J, Beullens M, Van Meervelt L, Bollen M. The PP1 binding code: a molecular-lego strategy that governs specificity. *FEBS J.* 2013; 280:584–595. [PubMed: 22360570]
25. Bollen M, Peti W, Ragusa MJ, Beullens M. The extended PP1 toolkit: designed to create specificity. *Trends Biochem. Sci.* 2010; 35:450–458. [PubMed: 20399103]
26. Brady MJ, Saltiel AR. The role of protein phosphatase-1 in insulin action. *Recent Prog. Horm. Res.* 2001; 56:157–173. [PubMed: 11237211]
27. Ceulemans H, Bollen M. Functional diversity of protein phosphatase-1, a cellular economizer and reset button. *Physiol. Rev.* 2004; 84:1–39. [PubMed: 14715909]
28. Han Y, Haines CJ, Feng HL. Role(s) of the serine/threonine protein phosphatase 1 on mammalian sperm motility. *Arch. Androl.* 2007; 53:169–177. [PubMed: 17852041]
29. Heijman J, Dewenter M, El-Armouche A, Dobrev D. Function and regulation of serine/threonine phosphatases in the healthy and diseased heart. *J. Mol. Cell. Cardiol.* 2013; 64:90–98. [PubMed: 24051368]
30. Merat DL, Cheung WY. Calmodulin-dependent protein phosphatase: isolation of subunits and reconstitution to holoenzyme. *Methods Enzymol.* 1987; 139:79–87. [PubMed: 3035332]
31. Molkenstein JD. Calcineurin-NFAT signaling regulates the cardiac hypertrophic response in coordination with the MAPKs. *Cardiovasc. Res.* 2004; 63:467–475. [PubMed: 15276472]
32. Shibasaki F, Hallin U, Uchino H. Calcineurin as a multifunctional regulator. *J. Biochem.* 2002; 131:1–15. [PubMed: 11754729]
33. Wijnker PJ, Boknik P, Gergs U, Muller FU, Neumann J, dos Remedios C, et al. Protein phosphatase 2A affects myofilament contractility in non-failing but not in failing human myocardium. *J. Muscle Res. Cell Motil.* 2011; 32:221–233. [PubMed: 21959857]
34. DeGrande ST, Little SC, Nixon DJ, Wright P, Snyder J, Dun W, et al. Molecular mechanisms underlying cardiac protein phosphatase 2A regulation in heart. *J. Biol. Chem.* 2013; 288:1032–1046. [PubMed: 23204520]
35. Herzig S, Neumann J. Effects of serine/threonine protein phosphatases on ion channels in excitable membranes. *Physiol. Rev.* 2000; 80:173–210. [PubMed: 10617768]
36. El-Armouche A, Boknik P, Eschenhagen T, Carrier L, Knaut M, Ravens U, et al. Molecular determinants of altered Ca²⁺ handling in human chronic atrial fibrillation. *Circulation.* 2006; 114:670–680. [PubMed: 16894034]
37. Hall DD, Feekes JA, Arachchige Don AS, Shi M, Hamid J, Chen L, et al. Binding of protein phosphatase 2A to the L-type calcium channel Cav1.2 next to Ser1928, its main PKA site, is critical for Ser1928 dephosphorylation. *Biochemistry.* 2006; 45:3448–3459. [PubMed: 16519540]
38. Kocksamper J, Pieske B. Phosphorylation of the cardiac ryanodine receptor by Ca²⁺/calmodulin-dependent protein kinase II: the dominating twin of protein kinase A? *Circ. Res.* 2006; 99:333–335. [PubMed: 16917097]
39. O'Brien F, Venturi E, Sitsapasan R. The ryanodine receptor provides high throughput Ca²⁺-release but is precisely regulated by networks of associated proteins: a focus on proteins relevant to phosphorylation. *Biochem. Soc. Trans.* 2015; 43:426–433. [PubMed: 26009186]
40. Yano M, Yamamoto T, Ikemoto N, Matsuzaki M. Abnormal ryanodine receptor function in heart failure. *Pharmacol. Ther.* 2005; 107:377–391. [PubMed: 15951021]
41. Wehrens XH, Lehnart SE, Huang F, Vest JA, Reiken SR, Mohler PJ, et al. FKBP12.6 deficiency and defective calcium release channel (ryanodine receptor) function linked to exercise-induced sudden cardiac death. *Cell.* 2003; 113:829–840. [PubMed: 12837242]
42. Kimura T, Han W, Pagel P, Nairn AC, Caplan MJ. Protein phosphatase 2A interacts with the Na,K-ATPase and modulates its trafficking by inhibition of its association with arrestin. *PLoS One.* 2011; 6:e29269. [PubMed: 22242112]

43. Bhasin N, Cunha SR, Mudannayake M, Gigena MS, Rogers TB, Mohler PJ. Molecular basis for PP2A regulatory subunit B56alpha targeting in cardiomyocytes. *Am. J. Physiol. Heart Circ. Physiol.* 2007; 293:H109–H119. [PubMed: 17416611]
44. Lecuona E, Dada LA, Sun H, Butti ML, Zhou G, Chew TL, et al. Na,K-ATPase alpha1-subunit dephosphorylation by protein phosphatase 2A is necessary for its recruitment to the plasma membrane. *FASEB J.* 2006; 20:2618–2620. [PubMed: 17065225]
45. Glynn P, Musa H, Wu X, Unudurthi SD, Little S, Qian L, et al. Voltage-gated sodium channel phosphorylation at Ser571 regulates late current, arrhythmia, and cardiac function in vivo. *Circulation.* 2015; 132:567–577. [PubMed: 26187182]
46. Marionneau C, Abriel H. Regulation of the cardiac Na⁺ channel NaV1.5 by posttranslational modifications. *J. Mol. Cell. Cardiol.* 2015; 82:36–47. [PubMed: 25748040]
47. Herren AW, Weber DM, Rigor RR, Margulies KB, Phinney BS, Bers DM. CaMKII phosphorylation of Na(V)1.5: novel in vitro sites identified by mass spectrometry and reduced S516 phosphorylation in human heart failure. *J. Proteome Res.* 2015; 14:2298–2311. [PubMed: 25815641]
48. Xu H, Ginsburg KS, Hall DD, Zimmermann M, Stein IS, Zhang M, et al. Targeting of protein phosphatases PP2A and PP2B to the C-terminus of the L-type calcium channel Ca v1.2. *Biochemistry.* 2010; 49:10298–10307. [PubMed: 21053940]
49. Bers DM. Excitation-Contraction Coupling and Cardiac Contractile Force (2). 2001
50. Lanner JT, Georgiou DK, Joshi AD, Hamilton SL. Ryanodine receptors: structure, expression, molecular details, and function in calcium release. *Cold Spring Harb. Perspect. Biol.* 2010; 2:a003996. [PubMed: 20961976]
51. Marquez-Rosado L, Solan JL, Dunn CA, Norris RP, Lampe PD. Connexin43 phosphorylation in brain, cardiac, endothelial and epithelial tissues. *Biochim. Biophys. Acta.* 1818; 2012:1985–1992.
52. Ai X, Jiang A, Ke Y, Solaro RJ, Pogwizd SM. Enhanced activation of p21-activated kinase 1 in heart failure contributes to dephosphorylation of connexin 43. *Cardiovasc. Res.* 2011; 92:106–114. [PubMed: 21727092]
53. Meilleur MA, Akpovi CD, Pelletier RM, Vitale ML. Tumor necrosis factor-alpha-induced anterior pituitary folliculostellate TtT/GF cell uncoupling is mediated by connexin 43 dephosphorylation. *Endocrinology.* 2007; 148:5913–5924. [PubMed: 17872368]
54. Kuster DW, Bawazeer AC, Zaremba R, Goebel M, Boontje NM, van der Velden J. Cardiac myosin binding protein C phosphorylation in cardiac disease. *J. Muscle Res. Cell Motil.* 2012; 33:43–52. [PubMed: 22127559]
55. Solaro RJ, Kobayashi T. Protein phosphorylation and signal transduction in cardiac thin filaments. *J. Biol. Chem.* 2011; 286:9935–9940. [PubMed: 21257760]
56. Kooij V, Holewinski RJ, Murphy AM, Van Eyk JE. Characterization of the cardiac myosin binding protein-C phosphoproteome in healthy and failing human hearts. *J. Mol. Cell. Cardiol.* 2013; 60:116–120. [PubMed: 23619294]
57. Jideama NM, Crawford BH, Hussain AK, Raynor RL. Dephosphorylation specificities of protein phosphatase for cardiac troponin I, troponin T, and sites within troponin T. *Int. J. Biol. Sci.* 2006; 2:1–9. [PubMed: 16585947]
58. Yin X, Cuello F, Mayr U, Hao Z, Hornshaw M, Ehler E, et al. Proteomics analysis of the cardiac myofilament subproteome reveals dynamic alterations in phosphatase subunit distribution. *Mol. Cell. Proteomics.* 2010; 9:497–509. [PubMed: 20037178]
59. Janssens V, Goris J. Protein phosphatase 2A: a highly regulated family of serine/threonine phosphatases implicated in cell growth and signalling. *Biochem. J.* 2001; 353:417–439. [PubMed: 11171037]
60. Belevych AE, Sansom SE, Terentyeva R, Ho HT, Nishijima Y, Martin MM, et al. MicroRNA-1 and -133 increase arrhythmogenesis in heart failure by dissociating phosphatase activity from RyR2 complex. *PLoS One.* 2011; 6:e28324. [PubMed: 22163007]
61. Marks AR, Marx SO, Reiken S. Regulation of ryanodine receptors via macromolecular complexes: a novel role for leucine/isoleucine zippers. *Trends Cardiovasc. Med.* 2002; 12:166–170. [PubMed: 12069756]

62. Terentyev D, Belevych AE, Terentyeva R, Martin MM, Malana GE, Kuhn DE, et al. miR-1 overexpression enhances Ca(2+) release and promotes cardiac arrhythmogenesis by targeting PP2A regulatory subunit B56alpha and causing CaMKII-dependent hyperphosphorylation of RyR2. *Circ. Res.* 2009; 104:514–521. [PubMed: 19131648]
63. Cunha SR, Mohler PJ. Obscurin targets ankyrin-B and protein phosphatase 2A to the cardiac M-line. *J. Biol. Chem.* 2008; 283:31968–31980. [PubMed: 18782775]
64. Gigena MS, Ito A, Nojima H, Rogers TB. A B56 regulatory subunit of protein phosphatase 2A localizes to nuclear speckles in cardiomyocytes. *Am. J. Physiol. Heart Circ. Physiol.* 2005; 289:H285–H294. [PubMed: 15778281]
65. Brewis N, Ohst K, Fields K, Rapacciuolo A, Chou D, Bloor C, et al. Dilated cardiomyopathy in transgenic mice expressing a mutant A subunit of protein phosphatase 2A. *Am. J. Physiol. Heart Circ. Physiol.* 2000; 279:H1307–H1318. [PubMed: 10993798]
66. Dodge-Kafka KL, Bauman A, Mayer N, Henson E, Heredia L, Ahn J, et al. cAMP-stimulated protein phosphatase 2A activity associated with muscle A kinase-anchoring protein (mAKAP) signaling complexes inhibits the phosphorylation and activity of the cAMP-specific phosphodiesterase PDE4D3. *J. Biol. Chem.* 2010; 285:11078–11086. [PubMed: 20106966]
67. Gergs U, Boknik P, Buchwalow I, Fabritz L, Matus M, Justus I, et al. Overexpression of the catalytic subunit of protein phosphatase 2A impairs cardiac function. *J. Biol. Chem.* 2004; 279:40827–40834. [PubMed: 15247211]
68. Hoehn M, Zhang Y, Xu J, Gergs U, Boknik P, Werdan K, et al. Overexpression of protein phosphatase 2A in a murine model of chronic myocardial infarction leads to increased adverse remodeling but restores the regulation of beta-catenin by glycogen synthase kinase 3beta. *Int. J. Cardiol.* 2015; 183:39–46. [PubMed: 25662052]
69. Dong D, Li L, Gu P, Jin T, Wen M, Yuan C, et al. Profiling metabolic remodeling in PP2Aalpha deficiency and chronic pressure overload mouse hearts. *FEBS Lett.* 2015; 589:3631–3639. [PubMed: 26497085]
70. Li L, Fang C, Xu D, Xu Y, Fu H, Li J. Cardiomyocyte specific deletion of PP2A causes cardiac hypertrophy. *Am. J. Transl. Res.* 2016; 8:1769–1779. [PubMed: 27186301]
71. Cho US, Xu W. Crystal structure of a protein phosphatase 2A heterotrimeric holoenzyme. *Nature.* 2007; 445:53–57. [PubMed: 17086192]
72. Delmar M, Makita N. Cardiac connexins, mutations and arrhythmias. *Curr. Opin. Cardiol.* 2012; 27:236–241. [PubMed: 22382502]
73. Ai X, Pogwizd SM. Connexin 43 downregulation and dephosphorylation in nonischemic heart failure is associated with enhanced colocalized protein phosphatase type 2A. *Circ. Res.* 2005; 96:54–63. [PubMed: 15576650]
74. Remo BF, Qu J, Volpicelli FM, Giovannone S, Shin D, Lader J, et al. Phosphatase-resistant gap junctions inhibit pathological remodeling and prevent arrhythmias. *Circ. Res.* 2011; 108:1459–1466. [PubMed: 21527737]
75. Ling S, Sun Q, Li Y, Zhang L, Zhang P, Wang X, et al. CKIP-1 inhibits cardiac hypertrophy by regulating class II histone deacetylase phosphorylation through recruiting PP2A. *Circulation.* 2012; 126:3028–3040. [PubMed: 23151343]
76. Kirchhefer U, Brekle C, Eskandar J, Isensee G, Kucerova D, Muller FU, et al. Cardiac function is regulated by B56alpha-mediated targeting of protein phosphatase 2A (PP2A) to contractile relevant substrates. *J. Biol. Chem.* 2014; 289:33862–33873. [PubMed: 25320082]
77. DeGrande S, Nixon D, Koval O, Curran JW, Wright P, Wang Q, et al. CaMKII inhibition rescues proarrhythmic phenotypes in the model of human ankyrin-B syndrome. *Heart Rhythm.* 2012; 9:2034–2041. [PubMed: 23059182]
78. Bharath LP, Ruan T, Li Y, Ravindran A, Wan X, Nhan JK, et al. Ceramide-initiated protein phosphatase 2A activation contributes to arterial dysfunction in vivo. *Diabetes.* 2015; 64:3914–3926. [PubMed: 26253611]
79. Lu J, Kovach JS, Johnson F, Chiang J, Hodes R, Lonser R, et al. Inhibition of serine/threonine phosphatase PP2A enhances cancer chemotherapy by blocking DNA damage induced defense mechanisms. *Proc. Natl. Acad. Sci. U. S. A.* 2009; 106:11697–11702. [PubMed: 19564615]

80. Martiniova L, Lu J, Chiang J, Bernardo M, Lonser R, Zhuang Z, et al. Pharmacologic modulation of serine/threonine phosphorylation highly sensitizes PHEO in a MPC cell and mouse model to conventional chemotherapy. *PLoS One*. 2011; 6:e14678. [PubMed: 21339823]
81. Linker RA, Wendt G. Cardiac safety profile of first dose of fingolimod for relapsing-remitting multiple sclerosis in real-world settings: data from a German prospective multi-center observational study. *Neurol. Ther.* 2016
82. Tocci G, Giuliani M, Canichella F, Timpano J, Presta V, Francia P, et al. Tp-Te interval predicts heart rate reduction after fingolimod administration in patients with multiple sclerosis. *Int. J. Cardiol.* 2016; 221:881–885. [PubMed: 27434365]
83. Rosini JM, Rajasimhan S, Fellows SE, Nomura JT. Delayed cardiac dysrhythmias after fingolimod administration. *Am. J. Emerg. Med.* 2015; 33:987, e1–3.
84. Liu W, Zi M, Naumann R, Ulm S, Jin J, Taglieri DM, et al. Pak1 as a novel therapeutic target for antihypertrophic treatment in the heart. *Circulation*. 2011; 124:2702–2715. [PubMed: 22082674]
85. Egom EE, Ke Y, Musa H, Mohamed TM, Wang T, Cartwright E, et al. FTY720 prevents ischemia/reperfusion injury-associated arrhythmias in an ex vivo rat heart model via activation of Pak1/Akt signaling. *J. Mol. Cell. Cardiol.* 2010; 48:406–414. [PubMed: 19852968]
86. Liu W, Zi M, Tsui H, Chowdhury SK, Zeef L, Meng QJ, et al. A novel immunomodulator, FTY-720 reverses existing cardiac hypertrophy and fibrosis from pressure overload by targeting NFAT (nuclear factor of activated T-cells) signaling and periostin. *Circ. Heart Fail.* 2013; 6:833–844. [PubMed: 23753531]

Fig. 1. PP2A holoenzyme organization. PP2A holoenzyme, including PP2A-A scaffolding subunit, PP2A-C catalytic subunit, and one or more PP2A-B regulatory subunits. Posttranslational modifications known to modify PP2A-C function are shown. The combinatorial assembly of PP2A subunits confers holoenzyme localization and activity.

Fig. 2. Diversity of cardiac PP2A targets. Summary of key PP2A targets, separated by cellular function. Targets listed in *italics* indicate dephosphorylation by both PP1 and PP2A.

Table 1

Human PP2A subunits.

Role	Class	Isoform	Gene name (human)	Alternate names	Splice variants	Presence in cardiac tissue	Refs.
Scaffolding	A	PP2A-A α	<i>PPP2R1A</i>	PR65A, MRD36	n.d.	+	[33,34]
		PP2A-A β	<i>PPP2R1B</i>	PR65B	n.d.	+	
Regulatory	B	PP2A-B α	<i>PPP2R2A</i>	B55 α , PR55 α	n.d.	+	[34,35]
		PP2A-B β	<i>PPP2R2B</i>	B55 β	n.d.	+	
		PP2A-B γ	<i>PPP2R2C</i>	B55 γ	n.d.	–	
		PP2A-B δ	<i>PPP2R2D</i>	B55 δ	n.d.	–	
		PP2A-B' α	<i>PPP2R5A</i>	B56 α	B56 α 1 B56 α 2	+	[33,34]
	B'					+	
		PP2A-B' β	<i>PPP2R5B</i>	B56 β	n.d.	+	
		PP2A-B' γ	<i>PPP2R2C</i>	B56 γ	B56 γ 1 B56 γ 2 B56 γ 3 B56 γ 4	+	
						+	
		PP2A-B' δ	<i>PPP2R5D</i>	B56 δ	n.d.	+	
	B''	PP2A-B'' ϵ	<i>PPP2R5E</i>	B56 ϵ	n.d.	+	
		PP2A-B'' α	<i>PPP2R3A</i>	PR72/PR130	PR72 PR130	+	[34–36]
						+	
		PP2A-B'' β	<i>PPP2R3B</i>	PR48	n.d.	–	
		PP2A-B'' γ	<i>PPP2R3C</i>	PR59, G5pr	n.d.	–	
	B'''	PP2A-B'''	<i>PTPA</i>	PR53, PPP2R4	n.d.	+	[34]
		PP2A-C α	<i>PPP2CA</i>	RP-C	n.d.	+	[33,34]
Catalytic	C	PP2A-C β	<i>PPP2CB</i>		n.d.	+	

In the 'presence in cardiac tissue' column, + indicates presence of the subunit, while – indicates lack of the given subunit.

The abbreviation "n.d." indicates that splice variants have not been described. The list of alternative names is not inclusive.

Table 2

Mouse models of PP2A-Ca modulation. Results listed are not inclusive.

Model	Method	Results	Refs.
PP2A-Ca overexpression	Approximately 2-fold overexpression of PP2A-Ca catalytic subunit	At baseline <ul style="list-style-type: none"> Dilated cardiomyopathy Cellular hypertrophy Fibrosis Reduced $I_{Ca,L}$ Disrupted Akt/GSK3β/β-catenin pathway 	[67,68]
PP2A-Ca cKO	Approximately 80% reduction in PP2A, α -MHC Cre, flox of exons 3–5	Following myocardial infarction (MI) <ul style="list-style-type: none"> Restoration of normal Akt/GSK3β/β-catenin pathway Increased survival in 3 days post-MI Cellular hypertrophy Cardiac enlargement Reduced LV ejection fraction Reduced LV fractional shortening Increased LV diameter 	[69]
Tamoxifen-inducible PP2A-Ca cKO	Approximately 45% reduction in PP2A, tamoxifen-inducible- α -MHC Cre, flox of exon 2	<ul style="list-style-type: none"> Cellular hypertrophy Cardiac enlargement Reduced ejection fraction Reduced fractional shortening Increased LV volume Fibrosis Disrupted Akt/GSK3β/β-catenin pathway 	[70]