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Exploring the complex interplay in the regulation of cardiac pathophysiological functions by protein kinases and phosphatases

Chrysanthus Chukwuma Sr
The Chrysanthus Centre for Future-Oriented Studies, CTR Future-Oriented Ltd, Abakaliki, Ebonyi State, Nigeria

Abstract
Cardiovascular disease manifests as an intricately complex entity presenting as a derangement of the cardiovascular system. Cardiac or heart failure connotes the pathophysiological state in which deficient cardiac output compromises the body burden and requirements. Protein kinases regulate several pathophysiological processes and are emerging targets for drug lead or discovery. The protein kinases are family members of the serine/threonine phosphatases. Protein kinases and phosphatases are pivotal in the regulatory mechanisms in the reversible phosphorylation of diverse effectors whereby discrete signaling molecules regulate cardiac excitation and contraction. Protein phosphorylation is critical for the sustenance of cardiac functionalities. The two major contributory ingredients to progressive myocardium derangement are dysregulation of Ca2+ processes and contemporaneous elevated concentrations of reactive oxygen species, ROS. Certain cardiac abnormalities include cardiac myopathy or hypertrophy due to response in untoward haemodynamic demand with concomitant progressive heart failure. The homeostasis or equilibrium between protein kinases and phosphatases influence cardiac morphology and excitability during pathological and physiological processes of the cardiovascular system.

Keywords: oxidative stress, heart failure, cardiac hypertrophy, cardiac myopathy, serine, threonine, Ca2+, spatiotemporal variations

Introduction

Cardiovascular disease [1, 2] or pathological heart disease conditions have devastating effects on the global population causing disruption to the normal physiologic milieu, as is characteristically evident in numerous instances, especially heart failure. Cardiac or heart failure constitutes the condition where there is deficiency in the cardiac output to meet body requirements. It is a clinical syndrome defined as dysfunctional efficient capability of the left ventricle to invariably fill and/or pump blood.

It is a disorder due to varied causative agents resulting in progressive cardiac debility, and as a leading etiology of global mortality influenced by diverse risk factors or determinants and comorbidities [3-5].

On that score, remodelling is crucial to understand the pathogenesis of cardiac failure as a stress response to an index event as observed in myocardial ischaemia or superimposed mechanical burden culminating in multiple morphological alterations in viable myocardium.

The human genome comprises a plethora of protein kinase genes which modify approximately one- third of the human genome; thereby, regulating most of the cellular transduction pathways with alterations in protein kinase signaling as a protagonist of cardiovascular disease development. Current experimentations elucidating morphologically interrelated control mechanisms of protein kinases incorporate the enzyme as potential target to develop novel therapeutic regimen, such as general interference with protein kinase activity or target disease-specific kinase activities via the regulation of spatiotemporal variations [6], and protein-protein interactions [7-9] with their cellular compartmentalizations.

Morphological features of protein kinases in cardiovascular disease

Protein kinase C, PKC isozymes comprise a family of serine/threonine kinases. In response to circulating hormones, PKC activation elicits numerous intracellular events controlling varied physiological processes in the heart as a pivotal enzyme in growth regulation, hypertrophy, signal transduction pathway regulator, cardiac rate, contraction and relaxation [10]. Other characteristics of protein kinases are their covalent transformation of proteins by the attachment of phosphate groups from ATP, invariably to serine, threonine or tyrosine residues. Thus, the functional attributes of substrates of the protein kinase become modified. Protein kinases drive signal transduction into the cell interior from the outer cell membrane. These signals do not merely emanate from ligand- receptor interactions but inclusively, environmental perturbations, such as membrane mechanized disruption with resultant reprogramming of gene expression via direct transcription factor or via regulation of protein translation or mRNA stabilization [11]. Although, protein kinases regulate diverse dimensions of physiologic cellular activity, the pathologic impairment of protein kinase signaling pathway is the molecular basis of several oncologic and cardiovascular disease presentations. Due to their versatility in pluralistic disease conditions, protein kinases are increasingly emerging as attractive targets for drug lead/discovery [12, 13] following heterotrimeric G protein-coupled receptors like angiotensin II [14].

Protein kinase A constitutes a central regulator of cardiac morphology. The activation of myocardial PKA is induced by an array of hormones, neurotransmitters and stress signals,

particularly catecholamines elicited by the sympathetic nervous system. The stimulation of cAMP-dependent PKA activation in cardiomyocytes is due to binding of catecholamines to *B*-adrenergic receptors. Increased PKA activity promotes Ca2+ cycling and enhances the contractility of cardiac muscle. Effective PKA control is pertinent for cardiac homeostasis as PKA signaling dysregulation is inextricably-linked with multiple cardiac disorders, such that aberrant PKA activation or inactivation is associated with the etiopathogenesis of cardiac failure, myocardial ischaemia, hypertrophy, and anthracycline diabetic state, or takotsubo cardiomyopathies. PKA may establish sex-dependent disparities in contractility and susceptibility to cardiac impairment. The presenting cardiac frailties and processes may dictate the applicability of PKA activators or inhibitors as treatment for cardiac perturbations [15].

Protein kinase C is a family member of signal-regulated enzymes that presents pleiotropic attributes in conducting numerous pathophysiological responses. PKC platforms are usually allosterically activated enzymes with adherence to membranes via growth factor receptor-induced lipid cofactors. This common model of the activation of PKCs is that their actions are restricted to membrane- delimited substrates, and that PKCs catalytic activities are intrinsic attributes of the enzymes which are not altered by the activation mechanism [16]. The conventional PKC activation model has been unable to adequately explicate the numerous established PKC enzyme activities in cardiac, mitochondria and nuclear sarcomeric or non-sarcolemmal subcellular cubicles. These have been expressed via the identification of stimulus-specific disparities in processes of the activation of PKC isoform during the activation of growth factor versus oxidative stress [16].

Although, certain redox-activated mechanisms function as structural determinants which are ubiquitous per PKCs, the redox-dependent process for the activation of PKC*d* relies on Src-dependent tyrosine phosphorylation motif on the enzyme with its isoform specificity [17]. Inasmuch as oxidative stress participates in the pathogenesis of multiple clinical perturbations, the stimulus-specific disparities in the regulation and repercussions of the activation of PKC must have implications for the design, implementation, monitoring and evaluation of PKC targeted therapeutic regimen. The activation of PKC is vital in numerous cellular responses, such as expression of diverse growth factors, activation of signaling pathway, and aggravation of oxidative stress. However, there are extant polemics regarding the role of PKC activation in pro-atherogenic and anti-atherogenic mechanisms [17].

Protein kinase C is almost coeval to protein kinase N, PKN; and as family members of serine/threonine protein kinases are involved in essential cellular activities [18].

The protein kinase D, PKD family belongs to the calcium/calmodulin-dependent protein kinase group of serine/threonine kinases, CAMK of the mammalian genome or branch of the human kinome within the protein kinase complement. The PKD-mediated signaling pathways of the cardiovascular system are involved in the regulation of myocardial contraction, hypertrophy and mortality [19]. The PKD family comprises 3 isoforms. The morphological attributes of PKD contrast it to PKC isoforms. PKD does not phosphorylate many recognized PKC substrates. PKC is disparate from the AGC limb comprising the PKC isoforms. PKD responds to physiologically vital stimuli, and it may lead to novel targets for therapeutics.

Activated Rho-related kinases, ROCK1 and ROCK2 play central roles in processes resulting in cardiovascular perturbations, such as atherosclerosis, diabetes, vasospastic angina, stroke [20], pulmonary arterial hypertension, essential hypertension, and cardiac ischaemia/reperfusion, I/R derangement and cardiac failure. ROCK1 and ROCK2 are serine/threonine kinases and downstream targets of the small GTPases: RhoA, RhoB, and Rho C. ROCKS are connected with varied cellular functions, such as organization of actin cytoskeleton, cell motility and adhesion, apoptosis and proliferation, contraction of smooth muscle cells, and extracellular matrix remodelling [21]. Ostensibly, the roles of ROCK1 and ROCK2 are identical but the functions are similar. Depending on the subcellular compartmentalization and certain environmental considerations, ROCK1 and ROCK2 signaling present disparate impacts on cellular activity respectively; in cardiac hypertrophy and fibrosis. As a potential biomarker, enhanced ROCK activity may be central in mechanisms resulting in cardiovascular abnormalities as deteced. Pharmacological ROCK suppression diminishes the augmented ROCK functionality in patients, with commensurate appreciable prognosis in healthcare status. ROCK2-selective inhibitor, SLx-2 reduces human dermal fibroblast CTGF expression, with undergirding function per ROCK2 in fibrotic processes [22]. The Application of selective ROCK inhibitors for the treatment of cardiac disorders may ameliorate the side effects realised in certain inhibitors, for instance, fasudil.

Phosphatases in cardiac pathophysiology

Cardiovascular experimentations depict that protein phosphorylations are vital for the sustenance of cardiac functionality. The complexity between phosphorylated and dephosphorylated status of proteins is undergirded by an intricate association of phosphatases, especially the protein phosphatase, PP family members influence the dephosphorylation of a vast majority of the presenting cardiac proteins. PPs do not merely dephosphorylate erstwhile phosphorylated proteins as passive regulatory mechanisms but regulate PK functionality, invariably via disparate signaling pathways. The regulatory mechanisms may occur on epigenetic, posttranslational or posttranscriptional phases [23]. Also, PPs are exclusively targets for numerous proteinaceous interaction partners controlling their endogenous functionality. These supplement the intricate complexity and feedback regulation of the system. Novel strategies are being configured to pharmacologically regulate PPs and obviate abberant PK activity in cardiac disorder [23]. Strategies to augment PP targeting drugs in cardiovascular disorders include subcellular and isotype-specific regulation of PPs with differential control subunits and inhibitors coupled with compartment specific PP1 target drugs for enhanced potency. It is pertinent to explicate the importance of phosphatase and kinases when reversible protein phosphorylation of a defined substrate occurs [24].

Protein kinase-phosphatase interactions in cardiac pathophysiology

Amino acid side-chain reversible phosphorylation protein is commonly utilised in cellular signal transduction and modifications in cardiovascular perturbations. They are patterned to expose alterations in protein kinase and phosphatase activities

linking signaling pathways. In contrast to the phosphorylation of serine, threonine and tyrosine residues which have been extensively researched in vertebrates, an established regulatory signal in lower organisms, namely the reversible histidine phosphorylation has assumed inchoate investigation, as being irrelevant or insignificant to vertebrates. However, in mammals, it is perspicuous that the nucleoside diphosphate kinase isoform B, NDPK-B, an enzyme that is generally expressed in nucleotide metabolism and a high specificity phosphatidine phosphatase, PHP constitute a regulatory histidine protein kinase/phosphatase system [25]. It is realisable that there are three established substrates of NDPK-B, *viz*: the *beta* subunit of heterotrimeric G-proteins, G*B,* an intermediate conductance potassium channel, SK4 and the Ca2+regulating TRP channel family member, TRPV5. A defined histidine residue controls cellular signal transduction or channel functionality in the aforementioned proteins. The recognition of essential substrates, such as SK4, *GBy*, and TRPV5 has inculcated the significance or relevance of NDPK- mediated protein histidine phosphorylation in conducting mammalian cell functionality. The two substrates, *GBy* and SK4 are both targeted by NDPK-B as protein histidine kinase with essential activities in cardiovascular morphology and pathogenesis. The ostensible contribution by respectively, NDPK-B/SK4- NDPK-B/*GBy* -interaction with target proteins connote trajectories for future therapeutic modalities in cardiovascular disorders [26].

Class 1 phosphoinositide 3-kinases, P13Ks constitute a family of lipid kinases which are activated by cell membrane receptors, such as G-protein-coupled receptors, GPCRs or receptor tyrosine kinases in the catalytic formation of the lipid second messenger phosphatidylinositol (3;4;5)- triphosphate (PIP3). These enzymes interact numerous downstream intracellular signaling pathways regulating the migration, proliferation and survival of the cell [27]. Within the cardiovascular system, the four Class 1 PI3K isoforms: Pi3K*a,* PI3K*B,* Pi3k*d* and PI3K*y* undergo differential expressions in specific cell subsets, such as fibroblasts, cardiomyocytes, leucocytes, endothelial and vascular smooth muscle cells. Thus, they posit specific roles for PI3K isoenzymes. Genetic disruption experimentation of disparate PI3K genes has enunciated the influence of specific isoenzymes to the regulatory mechanism of cardiovascular functionality in both maladaptive and adaptive contributory stances. Also, distinct PI3K isoforms may be associated via crosstalk which act as both kinases and scaffold proteins manipulating vital signalosomes in the complex interaction of health and disease of the cardiovascular ambient [27]. On that trajectory, both the adaptive and maladaptive stances of PI3K signaling during cardiovascular homeostasis have been explored [28]. The Class 1 PIK3*a* depict adequate impacts, augmented physiological contractility and hypertrophy as well as PI3K*y* mediating aberrant signals resulting in the inhibition of *B*-AR cascade. These interactive debilitating and advantageous impacts are ostensibly dependent on specific upstream/downstream effectors and subcellular PI3K compartmentalization [28].

Protein kinases and phosphatases are central to the regulatory mechanisms concerned in the reversible phosphorylation of disparate effectors, wherein diverse signaling molecules regulate cardiac excitation and contraction [29] as evident in the established *B*-adrenergic stimulation mediated by cAMP-dependent protein kinase, PKA. However, phosphatase regulation that diminishes the impact of *B*-adrenergic stimulation is relevant. p21 activated kinase-1, Pak 1 exhibits a potential function as an upstream signal for cardiac protein phosphatase PP2A. Pak1 is a serine/threonine protein kinase that is dirctly activated by Cdc42 9 1r which are small GTPases. Pak1 has elevated expression in disparate cardiac regions and modulates the functionalities of ion channels, sarcomeric proteins, and pertinent phosphoproteins via up-regulation in the activity of PP2A. Coordinating Pak1 and PP2A activities is not merely potentially associated with regulation of conventional cardiac functionality but ostensibly in pathophysiologic states [29]. In that case, reversible protein phosphorylation is pivotal to varied cardiac processes, *viz*: excitation-contraction, Ca2* handling, cell-cell interaction, myofilament regulation and cell metabolism. PP2A is a central cardiac phosphatase regulator of different myocyte activities via multiple target molecules which have evolved mechanisms to enhance PP2A functionality as well as to modulate the component formulation, phosphorylation, methylation and locale of PP2A holoenzyme populations. Eccentric regulation of PP2A activity is liable to enhance cardiac pathophysiological conditions; and thus, constitute potential therapeutic targets for the modulation of aberrant adrenergic signaling in cardiovascular disorders [30].

Voltage-gated Na+ channel, INa activity is crucial for conventional cardiac excitation; although, the Na+ channel late moiety (INa,L) is indubitably involved in perspicuous lethality of congenital and acquired human arrythmia, CaMKII (Ca2+/calmodulin-dependent kinase II) augments INa,L) as a result of elevated adrenergic tone [31]. PP1 is a predominant cardiac phosphatase, of which the intricate complexity of INa regulatation is dependent on several phosphorylations and secondary post-translational variations [32].

Abundance of type 1 phosphatases PP1 activity has been realised in endstage human cardiac failure but its role in cardiac functionality remains obscure. Investigations revealed that overexpression, that is, threefold of PP1 was associated with suppressed cardiac activity, cardiomyopathy, and premature death, commensurate with heart failure [33]. The elevated PP1 activity is ostensibly partly due to dephosphorylation or inhibited activation. Expression of constitutively active inhibitor was related to *B* -adrenergic response in frail human myocytes. It is indicative that PP1 constitutes a viable regulator of cardiac functionality and a novel therapeutic target of cardiac function.

Oxidative stress, protein kinase and phosphatases in cardiac pathophysiological states

Oxidative stress is increased oxidant concentrations in biosystems. Although, it depicts reactive oxygen species, ROS in cells or tissues; the term stress denotes a debilitative role or contemporaneously that oxidants are enabling factors in the sustenance of homeostasis or adaptive signaling that can restrict injurious impact. This is realised by regulatorily inducing oxidative post- translational variations of proteins by changing their interactions or activities; and permitting alterations in cell oxidant contents by coupling to controlled changes in enzymatic activity as actuated in signal transduction, providing the latitude for redox signaling [34].

Homeostatic cardiac functionality is sustained via an intricately complex network involving interdependent signaling pathways which may be impaired simultaneously with disease progression.

In essence, excitation-contraction-coupling designated as the electrical signal translation to contractile response depends on the strictly controlled sequence of occurrences, with resultant increase in intracellular Ca2+ accompanied by myocardium contraction. The two major supportive aetiologic factors to progressive myocardium derangement are dysregulation of Ca2+ systematic operation coupled with elevated concentrations of ROS. ROS production via cellular oxidases and by-products of cellular metabolism are substantially reactive oxygen derivatives with contribution to physiologic homeostatic functionality [35]. In a disease state, excess generation of ROS perspicuously interacts with kinases for the regulation of Ca2+. Thus, this post-transational oxidative change links alterations in the redox state of the myocardium to phospho-regulated pathways critical for its functionality. The intracellular ROS ambient is sustained via variations in oxidant generating systems, peroxidases and reducing proteins. Variations in the redox condition of biosystems invariably modify protein morphology.

The kinases, PKA and CaMKII are vital mediators in cardiophysiology during oxidative morphology. The oxidation of both kinases results in their activation, concomitantly translating intercellular variations into phosphorylation-mediated signaling [36]. Excess oxidant generation leads to eccentric signaling pathways with progressive cardiac failure. Paucity of information and understanding of the discrete biochemical pathways undergirding these modifications contribute to the poor prognosis of anti-oxidant clinical interventions, and obviate explicating the mechanisms associated with protein oxidation, and specific therapeutic development which may mask or treat progressive cardiac perturbations.

It is indicative that PKGI*a* disulphide dimerization constitutes a vital regulatory process associated with health sustenance regarding kidney filtration, diastolic relaxation and regulation of blood pressure but untoward regulation of diverse aberrant processes, such as cardiac failure, sepsis and hypoxia may aetiologically influence cardiovascular pathogenesis [37].

Cardiac failure is a major aetiology of mortality in industrialised nations. Cardiac remodelling antecdent to cardiac function disability is observed by expansive molecular alterations impacting on the cardiomyocyte. Superimposed on these, changes in protein kinase pathways frequently engage as key mediators because they are inextricably-linked with upstream pathologic stress signaling and downstream regulatory processes with resultant impact on the morphological integrity of cardiac muscle [38]. In cardiac disorder, the elucidation of pre-cuurent mechanisms regulating protein kinase functionality, such as protein-protein interactions, post-translational alterations [7-9, 12, 13], or the usage of anchoring proteins in targeting are pertinent to develop defined and effective therapeutic regimen for the debilitating myocardium. The mammalian cardiac apparatus reacts to induced stress via remodelling mechanism characterized by myocyte hypertrophy, changes in ion currents and abberant contractility with resultant cardiac failure. The numerous resultant alterations associated with pathologic cardiac remodelling include changes in the expression, enzymatic morphology, and invariable localization of subcellular protein kinases, frequently inculcated in maladaptive signaling. As a family member of the protein-kinase, CaMKII constitutes a vital nodular molecule translating disparate stresses into the pathophysiologic downstream pathways; thus, emerging as a therapeutic target in cardiac failure [39]. It is important to elucidate the regulatory mechanism of CaMKII-based therapeutic regimen that enjoins enhanced treatment efficiency with decreased potential for off-target impacts.

The pivotal downstream signaling pathway activated within cardiac myocyte in mechanized and agonist-mediated hypertrophy is a mitogen-actuated protein kinase, (MAPK)-extracellular regulated kinase 1/2(ERK 1/2) pathway [40]. Investigations in genetic mouse models deficient in ERK-related MAPK moieties pathway have increasingly undergirded a perspicuous function for the pathway in stress-induced hypertrophic cardiomyopathy. These signaling pathways may superimpose their regulatory activities in an increasingly localized pattern in cardiac muscle. Findings revealed specific MAPK/ERK signaling in cardiac muscle sarcomere and plasma membrane. These explicate the lacunae in the scaffolding proteins distortion of ERK functionality and phosphorylation. These become critical in varying the cardiomyocyte response to stress- induced hypertrophy and pathogenesis. There is resultant simplification of the response regarding distinct hypertrophic stimuli, for instance, G*a*q pressure overload and phenyl-ephrine. Dissipation or loss of function research in mouse models lacking MAPK scaffold proteins, such as FCL1 and ANKRD1, respectively bound to the sacomere, ostensibly portray a debilitative role in G*a*q and phenylephrine hypertrophic cardiomyopathy. Conversely, investigations pertaining to MAPK scaffold proteins, *viz*: IQGAP1 and Sur-8 scaffold may provide the latitude to harness MAPK signaling with clinical intervention in the debilitative impact inextricably-related to cardiac failure and hypertrophic cardiomyopathy [41].

Protein kinases and phosphatases effects on hypertrophic cardiomyopathy

Generally, there are three varieties of cardiac hypertrophy as conventional growth due to physical conditioning, resultant physiologic hypertrophy, and growth due to pathologic stimulus. Morphologic explication of several ingredients from the PI3K pathway revealed a function for the signaling cascade in conventional, exercise-elicited, and reactive stress-mediated hypertrophic cardium. This pathway comprises two limbs, the MTOR and GSK-3 pathways. The pathway is a key determinant of mammalian cardiomyocyte and cardiac dimension [42]. Ostensibly, adaptive or maladaptive cardiac hypertrophy is determined by neurohormonal-stimulated/calcium activated pathways, calcineurin or PKCs. Multiple isoforms are differentially regulated and activated, and specifically targeted to subcellular locale, granting latitude for discrete and overlapping functional profiles of PKCs [42]. Cardiac hypertrophy emanates from elevated mechanized burden on the heart and by the activities of localalized and systemic neuro-humoral and growth factors as well as cytokines. These neuro-endocrine and mechanized factors function via stretch, G-protein-coupled receptors and tyrosine kinases to actuate various intracellular signal-regulated kinases 1/2(ERK1/2) [43]. As a vast majority of stimuli which influence myocardiac hypertrophy, trigger acute phosphorylation of the threonine-glutamate-tyrosine, TE1 motif embedded in the activation loops of ERK1 and ERK2 kinases, and with concomitant activation, ERKs are realised as actuators of cardiac hypertrophy. Models produced to understand the etiologic function of ERK1/2 activation in the heart include

perspicuous ERK1/2 manipulation, such as over-expression, mutagenesis or knockout. Other models include upstream kinase manipulations, such as MEK1, and phosphatase manipulations which dephosphorylate ERK1/2, *viz*, DUSP6. Indubitably, ERK1/2 activation or its deficiency modulates the hypertrophic trajectory or the hypertrophy variety that emerges, and ostensibly indicates extant disparities in the activation. Therefore, MEK-ERK1/2 signaling is essential for cardiac hypertrophy. Sustained baseline activation, activation of post-stimulus climax, activation magnitude, activation frequency or duration of cytoplasmic localization in contrast to disparate nuclear activated ERK function [44]. Stimuli which trigger coaxial hypertrophy, for instance, pressure overload and the activation of Gq-coupled receptor lead to ostensibly acute cascade activation; and advantages of function models have demonstrated elevated cardiac hypertrophy. Conversely, loss of function model portrayed cardiac dilatation and eccentric hypertrophy.

Discussion

Protein kinases are enzymes associated with the phosphorylation of disparate proteins leading to functional variations in the proteins. They are serine-threonine kinase family members, and classified as the AGC, respectively Protein kinase A, G, and C protein families, and Rho-related kinse protein, ROCK. The AGC kinase family are connected with G-protein stimuli, platelet biology, lipid signaling, and muscle contraction. On the contrary, ROCK regulates actin cytoskeleton concerned with stress fibre development, and inflammation as the hallmark signal in ROCK-mediated disorders. ROCK generates the reaction cascade connecting diverse proinflammatory cytokine molecules. The ROCK inhibitors, such as Y27632 and fasudil have potent efficiency to diminish vascular smooth muscle cell hypercontraction, conscription of vascular inflammatory cell, cardiac remodelling and endothelial impairment in cardiovascular perturbations [45].

Perturbation of Ca2+ homeostasis is an adverse pathologic mechanism in cardiac failure. CaMKII- dependent hyperphosphorylation of ryanodine receptors in the sarcoplasmic reticulum enhances the arrythmogenic sarcoplasmic reticulum Ca*2+* leakage, and diminishing of sarcoplasm reticulum Ca2+ stores. It is not pellucid what is the contribution of the converse serine/threonine phosphatases [protein phosphatase 1(PP1) and 2A (PP2A)]. An investigation in the functionality of PP1/PP2A for Ca2+ homeostasis in perturbed human myocardium revealed that modulation of phosphatase activity is intensively effective on Ca2i cycling attributes. PP1 activation suppresses elevated kinase activity in cardiac failure and shuts the arrythmogenic sarcoplasmic reticulum Ca2+ leakage [46]. These portend an auspicious future for an anti-arrythmic therapeutic strategy. Therefore, the transition via human compensated cardiac Hy is depicted by discrete variations of Ca2+ cycling attributes, an elevated diastolic sarcoplasmic reticulum Ca2+ leak, decreased systolic Ca2+ and sarcoplasmic Ca2+ stores. Opposing protein phosphatases restrict elevated kinase functionality in impaired human myocardium. Obversely, human Hy protein phosphatase inhibition Ca2+ homeostasis to coeval cardiac failure-Ca2+ phenotype, PP1 activation in cardiac failure obliterates the sarcoplasmic reticulum Ca2+ leakage with normal inotropy. RyR2-directed PP1 activation portends anti-arrythmic approach for future investigation in cardiac failure [46].

PP2A regulates cardiac morphology; and the regulation occurs via integrative transcriptional, translational and post-translational control of three classes of subunits from >17 genes in conducting synthesis of holoenzyme, localization and sustenance; with altered mechanized pathways in cardiac perturbation. Multiple mechanisms are evident as related to acute and chronic control of distinct PP2A populations [47]. Potential phosphorylation functions as a central mechanism in the regulation of contractile cardiac state via the modulation of discrete levels of autonomic control on cardiac force/length interrelatedness [48].

Cardiac hypertrophy results in response to elevated haemodynamic demand, with concomitant progressive cardiac failure. PP2A regulates HDAC2 activity, and pathologic cardiac hypertrophy; and pretends as a target in therapeutic interventions for the future [49].

Conclusion

Cardiovascular disease denotes a symptom depicted by a perturbation of the cardiovascular system. This manifests as an intricately complex and organized systematic assemblage of pathophysiologic issues and challenges.

The balance of protein kinases and phosphatase influences cardiac morphology and excitability in pathophysiological processes. Thus, numerous trending modalities are being researched or investigated for targets, drug lead and discovery regarding therapeutic regimen in cardiovascular disease and its sequelae for the present and future.

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