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## A-Kinase Anchoring Proteins That Regulate Cardiac Remodeling

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### Abstract

In response to injury or stress, the adult heart undergoes maladaptive changes, collectively defined as pathological cardiac remodeling. Here, we focus on the role of A-kinase anchoring proteins (AKAPs) in 3 main areas associated with cardiac remodeling and the progression of heart failure: excitation–contraction coupling, sarcomeric regulation, and induction of pathological hypertrophy. AKAPs are a diverse family of scaffold proteins that form multi-protein complexes, integrating cAMP signaling with protein kinases, phosphatases, and other effector proteins. Many AKAPs have been characterized in the heart, where they play a critical role in modulating cardiac function.

### Keywords

A-kinase anchoring protein (AKAP); signal transduction; cardiac remodeling; heart failure; excitation-contraction coupling; sarcomeric regulation; pathological hypertrophy; cAMP; protein kinase; protein phosphatase; protein phosphorylation

## INTRODUCTION

The adult heart responds to injury or stress by activating a variety of intracellular signaling pathways that promote reexpression of an embryonic gene program, myocyte hypertrophy, and remodeling of the extracellular matrix.<sup>1–3</sup> Collectively, these changes, defined as pathological cardiac remodeling, are associated with the progression of heart failure, leading to a decline in ejection fraction and dilated cardiomyopathy. It is estimated that about 1 in 3 cases of congestive heart failure is due to dilated cardiomyopathy, which can be viewed as the final phenotype of a number of primary diseases, including coronary artery disease, hyper-tension, diabetes, and valvular disease.<sup>4,5</sup>

Typically, cardiac stress occurs through injury to the ventricles due to acute myocardial infarction, promoting myocardial necrosis and left ventricular remodeling, associated with the progression of heart failure. The initial remodeling phase after a myocardial infarction results in repair of the necrotic area and myocardial scarring. This may be considered beneficial to some extent, because there is an improvement in or maintenance of left ventricle function and cardiac output. However, over time, ventricular remodeling is a maladaptive process leading to a progressive decline in left ventricle performance.<sup>1–5</sup>

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The concept of cardiac remodeling was initially developed to describe cardiac changes after myocardial infarction. It has also been extended to cardiomyopathies of nonischemic origin, such as idiopathic dilated cardiomyopathy or chronic myocarditis, suggesting common mechanisms for the progression of cardiac dysfunction. Factors causing increased pressure or volume overload, including chronic hypertension, congenital heart disease, and valvular heart disease, will induce cardiac remodeling.

The cardiac myocyte is the major cell involved in remodeling and will be the main focus of this review. Fibroblasts, collagen, the interstitium, and the coronary vessels also play a role in cardiac remodeling.<sup>5</sup>

## A-KINASE ANCHORING PROTEINS

A-kinase anchoring proteins (AKAPs) are a diverse family of scaffold proteins that regulate the spatiotemporal signaling within a cell by providing a framework for the formation of multienzyme signaling complexes. Dysregulation of these signaling complexes may cause a breakdown in the organization of signal transduction underlying pathophysiological conditions leading to the development of disease.<sup>6,7</sup>

All members of the AKAP family possess a conserved protein kinase A (PKA) anchoring domain and binding sites for additional signaling components. AKAPs act to directly couple PKA to upstream activators (ie, adenylyl cyclases), feedback inhibitors (ie, phosphodiesterases and protein phosphatases), and other signal transduction pathways (ie, small molecular weight GTPases).<sup>8</sup> Importantly, these scaffold proteins target signaling complexes to distinct subcellular locations, thereby generating substrate specificity.<sup>9</sup> Many AKAPs have been characterized in the heart, where they play a critical role in modulating phosphorylation of numerous PKA-dependent substrates that regulate cardiac function.<sup>10–12</sup> AKAPs also modulate signal transduction through additional protein kinases, phosphatases, and effector proteins. Thus, the altered expression of AKAPs may result in drastic consequences, through dysregulation of localized signal transduction events.

## CARDIAC PROTEIN KINASE A SIGNALING AND HEART FAILURE

PKA is important in mediating the effects of adrenergic stimulation on the heart. In response to sympathetically released catecholamines, PKA regulates contractility in cardiac myocytes through the phosphorylation of numerous substrates, including the L-type  $\text{Ca}^{2+}$ -channel, the ryanodine receptor (RyR), phospholamban (PLB), and cardiac troponin I (cTnI).<sup>13</sup> Although acute stimulation of PKA has beneficial effects on heart function, chronic heart failure is associated with elevated catecholamines and is characterized by dysregulation in  $\beta$ -adrenergic receptor (AR) function and downstream PKA signaling.<sup>14,15</sup> Overexpression of  $\beta_1$ -ARs in transgenic mice initially increases contractile function and responsiveness to the  $\beta$ -AR agonist isoproterenol. However, chronic over-stimulation of  $\beta$ -ARs leads to progressive deterioration of cardiac performance, cardiac hypertrophy, and heart failure.<sup>16</sup> Transgenic overexpression of the catalytic subunit of PKA results in hypertrophy and fibrosis, suggesting that prolonged signaling through this protein kinase causes some of the detrimental consequences associated with chronically elevated  $\beta$ -adrenergic signaling.<sup>17</sup>

## CARDIAC FIBROBLASTS AND CARDIAC REMODELING

Cardiac fibroblasts are interspersed between cardiac myocytes and comprise the majority of nonmyocytic cells in all species.<sup>18</sup> Crosstalk between fibroblasts and myocytes is important for both cardiac development and in response to tissue injury during remodeling. Cardiac fibroblasts act mainly as a structural support during ventricular wall thickening from embryogenesis until adulthood, but they also serve as a source of mitogens, extracellular

matrix proteins, cytokines, and growth factors. Intracellular communication between cardiac fibroblasts and myocytes occurs through paracrine signals (cytokines and growth factors), direct interactions (via connexins and cadherins), and indirectly by collagen and fibronectin secretion from fibroblasts to influence extracellular matrix composition, or by activating matrix metalloproteinases to promote integrin signaling through the extracellular matrix, thereby mediating hypertrophy.<sup>18,19</sup>

Fibrosis is one of the largest groups of diseases for which there is no therapy. It is believed to occur because of a persistent tissue repair program. During connective tissue repair, “activated” fibroblasts migrate into the wound area, where they synthesize and remodel newly created extracellular matrix.<sup>20</sup> Currently, very little is known regarding the specific expression and roles of AKAPs in cardiac fibroblasts and whether they play a role in fibrosis. This is one area of research that might benefit from insight into AKAP-mediated signal transduction. Interestingly, a role for PKA in fibroblast cell migration has been demonstrated, including a defect in migration when anchored PKA is disrupted. Using mouse embryonic fibroblasts and T cells, Lim et al<sup>21</sup> report that  $\alpha 4$  integrins are type I PKA AKAPs. PKA-RI interacts with the integrin  $\alpha 4\beta 1$  and the isolated  $\alpha 4$  cytoplasmic domain and is required for the localized phosphorylation of  $\alpha 4$  and other substrates at the leading edge. Integrin signaling is a compelling therapeutic target for autoimmune disease and inflammation and may also be of use in the treatment of fibrosis.

## CARDIAC MYOCYTES AND CARDIAC REMODELING

Diverse disease pathways have been identified in cardiac myocytes, implicating perturbations in force generation, force transmission, intracellular calcium homeostasis, myocardial energetics, and cardiac metabolism.<sup>1-4</sup> AKAPs function in many of these processes, as indicated in Figure 1. This review will focus on the role of these anchoring proteins in 3 main areas: excitation-contraction coupling, sarcomeric regulation, and induction of pathological hypertrophy.

### MODULATION OF EXCITATION- CONTRACTION COUPLING

Abnormal calcium handling and dysregulation in calcium homeostasis is a prominent feature in the transition from compensatory hypertrophy to heart failure. Several AKAPs play a role in the regulation of calcium homeostasis, including isoforms of AKAP15/18 (which target PKA to the L-type  $\text{Ca}^{2+}$  channel<sup>22</sup> and the sarcoplasmic reticulum (SR)  $\text{Ca}^{2+}$ -ATPase (SERCA),<sup>23</sup> muscle-specific A-kinase anchoring protein (mA-KAP; which targets PKA in the proximity of the RyR and integrates calcineurin signaling).<sup>24</sup>

#### AKAP15/18 (AKAP7)

Cardiac AKAP15/18 isoforms modulate the cardiac L-type  $\text{Ca}^{2+}$  channel and SERCA2 activity<sup>22,23</sup>; however, it is not known exactly how these complexes are affected during cardiac remodeling and the progression of heart failure.

Alternative splicing of the *AKAP7* gene yields several isoforms that possess distinct subcellular localizations. Shorter isoforms  $\alpha$  and  $\beta$  are expressed in the heart and are located at the plasma membrane due to an N-terminal lipid-anchoring domain. Lipid modification of 3 residues in the N-terminus of the protein is required for association with the plasma membrane, whereas a leucine zipper-like motif in the C-terminus facilitates interaction of the cytoplasmic domain with the L-type  $\text{Ca}^{2+}$  channel.<sup>25,26</sup> Thus, AKAP15/18 provides an anchored pool of PKA that is readily available to phosphorylate and regulate the channel. AKAP15/18 expression potentiates cAMP-responsive  $\text{Ca}^{2+}$  currents, whereas expression of

a peptide to disrupt PKA–AKAP interaction results in the inhibition of L-type  $\text{Ca}^{2+}$  channel activity.<sup>27</sup>

The active transport of  $\text{Ca}^{2+}$  back into the lumen of the SR initiates myocyte relaxation. The SERCA2 pump and PLB control this process. PLB inhibits SERCA2 activity; however,  $\beta$ -adrenergic stimulation enhances PKA phosphorylation of PLB, which promotes its oligomerization and the derepression of SERCA2 activity.<sup>28–31</sup>

The interaction of the long splice variant of AKAP15/18 with PLB is necessary for PKA-mediated phosphorylation of PLB at Ser16, leading to the effects of adrenergic stimulation on calcium reuptake. Disruption of AKAP15/188-anchored PKA, interferes with PLB phosphorylation, preventing the release of PLB from SERCA2, thereby attenuating  $\text{Ca}^{2+}$  reuptake and myocyte relaxation.<sup>23</sup> Reversible control of the cAMP response may be provided by an anchored pool of type 4 PDE, which is believed to associate with AKAP15/188.<sup>32,33</sup> Decreased SERCA expression/activity and PLB hypophosphorylation are intricately involved in heart failure; thus, AKAP15/188 plays a crucial role in maintaining cardiac function. Previous studies have demonstrated that expression of a pseudophosphorylated PLB<sup>34</sup> or enhanced expression/activity of SERCA<sup>35</sup> is sufficient not only to halt the progression of cardiomyopathy but can also restore cardiac function. Because AKAP15/188 mediates PLB phosphorylation and a subsequent increase in SERCA activity, the modulation of AKAP15/188 may represent a novel pharmacologic target for restoring heart function.

### **AKAP79/150 (AKAP5)**

AKAP79/150 also modulates the entry of extracellular  $\text{Ca}^{2+}$  through L-type calcium channels in arterial myocytes. In addition to PKA, AKAP79/150 targets the protein phosphatase calcineurin (PP2B) and protein kinase C (PKC) to the plasma membrane.<sup>36</sup> AKAP79/150-associated pools of PKC $\alpha$  participate in the induction of persistent  $\text{Ca}^{2+}$  sparklets.<sup>37</sup> These sparklets are local  $\text{Ca}^{2+}$  signals produced by recurrent openings of L-type  $\text{Ca}^{2+}$  channels in arterial myocytes that enhance arterial tone.

AKAP79/150 may also be involved in the regulation of gene expression in the vascular smooth muscle during the development of hypertension. In these cells, activated PKC $\alpha$  stimulates persistent  $\text{Ca}^{2+}$  sparklets and an increase in local  $\text{Ca}^{2+}$  influx that activates AKAP150-targeted PP2B. Upon activation, PP2B dephosphorylates NFATc3 to allow for translocation into the nucleus of arterial myocytes where the transcription factor can modulate gene expression. In cases of hypertension, there is an upregulation of PKC $\alpha$  activity that increases persistent  $\text{Ca}^{2+}$  sparklet activity, leading to elevated PP2B activity and NFATc3-mediated transcription.<sup>38</sup> *AKAP5*<sup>-/-</sup> mice were found to lack persistent  $\text{Ca}^{2+}$  sparklets and have lower arterial wall intracellular calcium and decreased myogenic tone. These mice were hypotensive and did not develop angiotensin II-induced hypertension.<sup>37</sup> Cardiomyocytes from these mice exhibit disrupted  $\beta$ -adrenergic regulation of  $\text{Ca}^{2+}$  transients and phosphorylation of proteins involved in calcium handling.<sup>39</sup> Thus, AKAP79/150 is likely to play a role in cardiac remodeling.

### **MUSCLE-SPECIFIC A-KINASE ANCHORING PROTEIN (AKAP6)**

The mAKAP is highly expressed in cardiac myocytes where it is localized to the perinuclear membrane and junctional SR.<sup>40,41</sup> By serving as a scaffold for a wide range of molecules including PKA, PDE4D3, ERK5, and Epac1, this anchoring protein assembles a highly regulated signaling network that can act upon nearby substrates.<sup>42</sup> For example, mAKAP interacts with the RyR, which is regulated in response to phosphorylation by PKA.<sup>13,40</sup> The FK506-binding protein FKBP12.6, PP2A, and PP1 form a complex with RyR2, and PKA

phosphorylation of the RyR2 promotes the dissociation of FKBP12.6 from the channel, resulting in an increased probability of channel opening.<sup>43,44</sup> Increasing the open probability of the channel enhances EC coupling gain, resulting in increased cardiac muscle contraction. Thus, localization of PKA to the RyR2 by mAKAP is critical in modulating RyR2 activity and cardiac Ca<sup>2+</sup> transients.

Another important regulatory mechanism of cardiac contractility is mediated through phosphodiesterases that are able to rapidly hydrolyze cAMP and restore PKA to an inactive state. By scaffolding phosphodiesterases, mAKAP functions to regulate localized PKA signaling thereby maintaining efficient heart function. Recently, it has been shown that type 4 phosphodiesterases (PDE4) are important for the spatiotemporal control of cAMP after  $\beta$ -AR receptor stimulation.<sup>45</sup> The alternatively spliced PDE4 isoform D3 (PDE4D3) binds to mAKAP and regulates the levels of cAMP in the vicinity of the mAKAP complex. Together, cAMP, PKA, and PDE4D3 constitute a negative feedback loop that modulates both local cAMP levels and PKA activity. Under resting conditions, the PDE maintains low cAMP levels and keeps PKA inactive. However, in response to elevated cAMP levels, mAKAP-bound PKA phosphorylates PDE4D3 on serine residues 13 and 54, resulting in increased catalytic activity of the PDE and accelerated degradation of local cAMP levels.<sup>46</sup> In addition to its phosphodiesterase activity, mAKAP-bound PDE4D3 also acts as an adapter protein by recruiting the mitogen-activated protein kinase ERK5 and its upstream activator MEK5, and the cAMP-dependent Rap1-guanine nucleotide exchange factor Epac1 to mAKAP complexes. Activation of ERK5 leads to phosphorylation of PDE4D3 on serine residue 579, resulting in phosphodiesterase inhibition, promotion of cAMP accumulation and PKA activation. Elevated cAMP levels will also activate mAKAP-associated Epac1. Through Rap1, Epac1 suppresses ERK5 activity and prevents PDE4D3 inhibition. Thus, Epac1, ERK5, and PDE4D3 compose a second negative feedback loop through which the mAKAP signaling complex controls local cAMP levels.<sup>42</sup> Importantly, both of these negative feedback loops depend upon regulation of PDE4D3 activity by mAKAP-bound PP2A, which catalyzes dephosphorylation of PDE4D3 Ser-54 and inhibits phosphodiesterase activity.<sup>47</sup> In addition to regulating calcium handling, mAKAP also functions in the induction of pathological hypertrophy (Fig. 2).

## **PATHOLOGICAL HYPERTROPHY**

Adult myocytes respond to an increase in workload through an increase in cell size (hypertrophy), rather than proliferation. Concentric hypertrophy occurs in response to pressure overload, increasing myocyte thickness, whereas eccentric hypertrophy is due to volume overload, causing the myocytes to elongate.<sup>2</sup>

Hypertrophy is initially a beneficial compensatory process as it decreases wall stress and increases cardiac output and stroke volume. However, prolonged cardiac hypertrophy is maladaptive, transitioning to decompensation and cardiac failure, where there is downregulation of  $\beta$ -ARs and dysregulation of PKA signaling events.<sup>14</sup> A decreased phosphorylation of the type II regulatory subunit of PKA is observed, and as a result, there may be a change in the localization of PKA due to a difference in the affinity of AKAPs for phosphorylated and unphosphorylated RII.<sup>48</sup>

Many major pathways for pathological hypertrophy converge on a set of transcriptional regulators. mAKAP and AKAP121 have been implicated in the induction of hypertrophy through the activation of nuclear factor of activated T cells (NFAT)-mediated transcription.<sup>49,50</sup> AKAP-Lbc promotes the induction of hypertrophy through the modulation of myocyte enhancer factor 2 (MEF2)-mediated gene remodeling.<sup>51</sup>

### **mAKAP (AKAP6)**

Activation of the cytokine gp130 receptor by leukemia inhibitory factor through the ERK5 signaling pathway induces cardiac hypertrophy.<sup>52</sup> The hypertrophic effects of leukemia inhibitory factor are ablated by the activation of Epac1, suggesting the importance of the cAMP-mediated inhibition of mAKAP-bound ERK5.<sup>53</sup> It is not entirely clear as to how the mAKAP complex is involved in the hypertrophic ERK5 signal transmission. A proposed mechanism is that ERK5-induced inhibition of PDE4D3 results in PKA potentiation of RyR-mediated release and activation of the calcineurin/NFAT pathway.<sup>54</sup> Thus, mAKAP functions in the hypertrophic response through the coordination of multiple feedback mechanisms as depicted in Figure 3.

### **AKAP121 (AKAP1)**

In contrast to mAKAP and AKAP-Lbc, AKAP121, has recently been identified as a negative regulator of cardiomyocyte hypertrophy. Knockdown of AKAP121 induces hypertrophy, whereas overexpression reduces cell size and inhibits the effect of the hypertrophic adrenergic agonist, isoproterenol. The effect of AKAP121 knockdown is mediated by the calcineurin/NFAT pathway, illustrated by an increase in NFATc3 nuclear localization, which can be blocked through the inhibition of calcineurin by cyclosporine A.<sup>50</sup> The NFAT pathway is a potent inducer of cardiac hypertrophy, and its activity is tightly regulated. It is possible that calcineurin may be maintained in an inactive state due to spatial sequestration and inhibition of phosphatase activity in the AKAP121 complex. Thus, the loss of AKAP121 results in the release of an active pool of calcineurin in the cytosol. A critical target of calcineurin is the NFAT transcription factor family, which includes NFATc3. Phosphorylated NFAT is largely restricted to the cytosol. Upon dephosphorylation, NFAT translocates to the nucleus where it promotes hypertrophic gene expression.<sup>2</sup>

AKAP121 may also facilitate PKA phosphorylation of a downstream target in the NFAT/calcineurin pathway resulting in the formation of a transcriptional complex with NFAT to activate hypertrophic gene expression. Inhibition of either calcineurin or PKA activity would therefore prevent the formation of the transcriptional complex and efficient gene expression.<sup>1</sup> Abrenica et al speculate that the identity of this putative PKA target is the transcription factor GATA4, which stimulates hypertrophic gene expression and directly interacts with NFAT.<sup>1,6-8,50</sup>

Interestingly, AKAP121 is generally thought to be located at the mitochondria; however, the relevance of this in the process of cardiac hypertrophy and remodeling was not addressed in this study. Additionally, an important question remains as to whether the loss of AKAP121 is critical for the induction of cardiac hypertrophy in vivo. Currently, it is unclear whether downregulation of AKAP121 expression is a significant mechanism in physiological or pathological hypertrophy.

### **AKAP-LBC (AKAP13)**

AKAP-Lbc plays central role in coordinating multiple pathways involved in the induction of pathological cardiac hypertrophy (Fig. 2). AKAP-Lbc expression is upregulated in hypertrophic cardiac myocytes, and siRNA-mediated silencing of AKAP-Lbc expression in primary rat neonatal ventricular myocytes leads to a reduction in phenylephrine-stimulated hypertrophy.<sup>51,55</sup> AKAP-Lbc serves as a scaffold for PKA, PKC, protein kinase D (PKD),<sup>54</sup> and also contains a DH (Dbl-homology)-PH (pleckstrin-homology) domain that acts as a guanine nucleotide exchange factor (GEF) for the low molecular weight GTPase Rho,<sup>56</sup> which is a known mediator of cardiac hypertrophy. Rho promotes the activation of mitogen-

activated protein kinase (MAPK) pathways downstream of  $\alpha$ 1-adrenergic receptors ( $\alpha$ 1-ARs).<sup>57,58</sup> Interestingly, AKAP-Lbc Rho-GEF activity is critical for  $\alpha$ 1-AR activation of Rho, through a G $\alpha$ 12-coupled receptor signaling pathway.<sup>55,56</sup> Recently, it has been reported that in HEK-293 cells, AKAP-Lbc organizes a p38 MAPK complex composed of the RhoA effector PKN $\alpha$  and the MAPKs: MLTK, MKK3, and p38 $\alpha$ . Thus, AKAP-Lbc assembles a signaling complex, which specifically promotes Rho-dependent activation of p38 in response to  $\alpha$ 1-AR stimulation.<sup>59</sup> The p38 MAPK family has been implicated in several signaling pathways including promotion of proliferation, growth, inflammation, and contraction, through cytokine and G protein-coupled receptors. Specifically,  $\alpha$ 1-AR activation of p38 $\alpha$  can regulate smooth muscle cell contractility and promote cardiomyocyte sarcomere remodeling during cardiac hypertrophy.<sup>59,60</sup> Inactivation of AKAP-Lbc Rho-GEF activity occurs via AKAP-Lbc-bound PKA phosphorylation, which induces oligomerization and recruitment of 14-3-3 proteins.<sup>61,62</sup> This promotes dissociation of the p38 $\alpha$  activation module and prevents AKAP-Lbc from activating Rho.<sup>56</sup> Together, these data indicate that AKAP-Lbc integrates signaling pathways that can regulate either activation or inhibition of p38 $\alpha$ . It would be interesting to determine if these molecular mechanisms controlling signaling specificity occur in the heart in vivo.

In addition to Rho-mediated myocardial hypertrophy, AKAP-Lbc also promotes the initiation of a developmental gene reprogramming paradigm (often termed the fetal gene response). These “fetal” cardiac genes encode proteins involved in contraction, calcium handling, and metabolism, and their activation accompanies cardiac hypertrophy.<sup>1-5</sup> AKAP-Lbc facilitates the activation of PKD in response to hypertrophic stimuli (phenylephrine and endothelin), through recruitment of its upstream activator, PKC.<sup>63</sup> Activated PKD can then phosphorylate class II histone deacetylases to promote their nuclear export, leading to the derepression of the transcription factor MEF2, resulting in cardiac hypertrophy and tissue remodeling through MEF2-dependent transcription of hypertrophic genes.<sup>51,64</sup> Although most of the study was conducted in rat neonatal ventricular myocytes, analysis of human heart tissue samples provides some further support for this mechanism. Samples obtained from individuals who exhibited cardiac hypertrophy showed that AKAP-Lbc mRNA increased  $2 \pm 0.5$ -fold over normal age-matched patient control samples.<sup>51</sup> Thus, further research is required to determine if AKAP-Lbc may possibly be a valid biomarker for cardiac hypertrophy.

AKAP-Lbc also acts to promote stress fiber formation downstream of Rho. This was demonstrated in NIH3T3 fibroblasts,<sup>56</sup> and the significance of this in cardiac cytoskeletal remodeling in response to stress is currently unknown. Other AKAPs have been identified that target PKA to the sarcomere for regulation of muscle fiber proteins.

## SARCOMERIC REGULATION

Regulation of myofilament proteins by PKA is necessary for optimal contractile function. Phosphorylation of both cTnI or myosin-binding protein C (MyBP-C) by PKA is essential in shortening the heart beat cycle time in response to an increased demand in cardiac output.<sup>13</sup> PKA-mediated phosphorylation is also associated with cardioprotection<sup>65</sup> and confers resistance to calpain-mediated proteolysis of cTnI and MyBP-C.<sup>65-67</sup> Furthermore, studies of human and experimental heart failure models show a significant decrease in the phosphorylation levels of myofilament proteins, which may account for a large part of the contractile dysfunction of the failing myocardium.<sup>68,69</sup> Collectively, these data suggest that sarcomeric PKA anchoring is critical for contraction and that altered PKA anchoring at the myofilaments may play a role in the progression of heart failure. Studies demonstrate that both PKA types I and II are located at the cardiac sarcomere; however, the identity, composition, and function of PKA complexes at the sarcomere remains poorly understood.

## SYNEMIN

Synemin colocalizes in the heart at the Z line with RII and desmin. By localizing PKA near intermediate filaments, synemin may enhance PKA phosphorylation of the substrates at the Z line such as desmin, vimentin, tubulin, and  $\alpha$ B-crystallin. This anchoring protein may also serve to localize PKA near myofibril filaments for potential phosphorylation of substrates such as cTnI or MyBP-C. Localization of synemin at the Z line and the plasma membrane would make it ideally suited to be involved in cardiac remodeling or cardiomyopathies, where altered phosphorylation of PKA substrates is observed.<sup>70</sup> In addition, Synemin is implicated in myofibrillar myopathy and other muscle diseases, suggesting an important pathological role.<sup>71</sup>

## MYOSPRYN

Myospryn is another striated muscle-specific AKAP. It interacts with  $\alpha$ -actinin and is located at the Z-discs. This AKAP has been studied in the context of muscle disease and in the dystrophin-deficient *mdx* mouse, a model of Duchenne muscular dystrophy (DMD), myospryn and its anchored PKA is mislocalized. It is thought that this is because myospryn is unable to interact with dystrophin.<sup>72</sup> Mislocalization and dysregulation of PKA activity in muscle tissue of DMD patients may play a role in cardiac pathology, leading to cardiac remodeling. Disrupted  $\text{Ca}^{2+}$  homeostasis, metabolism, vulnerability to mechanical stress, and cardiac hypertrophy are observed in the *mdx* mice, with a concomitant decrease in expression of mAKAP, RyR, and SERCA2A.<sup>73</sup> Interestingly, >95% of patients with DMD exhibit dilated cardiomyopathy, due to a cardiac dystrophin integrity defect, which is generally genetic, but can also be acquired.<sup>74</sup> In addition, the expression of myospryn is upregulated by MEF2A, under hypertrophic conditions, suggesting that it is likely to play a role in cardiac remodeling.<sup>75</sup>

## CARDIAC TROPONIN T

Cardiac troponin T (cTnT) has recently been reported as a novel dual-specificity sarcomeric AKAP, associating with thin filaments in isolated rat myofibrils. Sumandea et al identified cTnT as a PKA–RII interacting protein through a yeast 2-hybrid screen. Immunoprecipitation and mapping studies demonstrate that cTnT can bind both type I and II PKA through a characteristic amphipathic helix domain in cTnT. The displacement of sarcomeric PKA–cTnT complexes leads to reduced myofibrillar PKA activity.<sup>76</sup> Currently, there are no data relating to the role of this signaling complex in the progression of heart failure.

## SUMMARY/FUTURE DIRECTIONS

The regulation and localization of PKA activity is very important for proper cardiac function, and perturbation of this can lead to heart failure. We are now just beginning to understand the spatiotemporal aspects of AKAP-mediated signaling in the heart. Therapeutically, although the global inhibition of PKA activity may not be efficacious, there may be great utility in specifically inhibiting localized PKA activity that contributes to cardiac dysfunction, for example, in the modulation of calcium-handling proteins, such as the L-type  $\text{Ca}^{2+}$  channel, SERCA pump, and RyR. Additionally, targeting PKA for regulation of sarcomeric proteins may be important for the modulation of contractile function in heart failure and muscle diseases.

It is likely that more cardiac AKAPs will be identified in the regulation of cardiac (patho)physiology. One area that has not been explored is cardiac metabolism, where a continuous production of ATP by oxidative phosphorylation is required to sustain the



contractile cycle. PKA plays a key role in regulating glycolysis and oxidative phosphorylation and is also located at the mitochondria. Changes in metabolism are observed in cardiac remodeling, which may be modulated through AKAP signaling complexes at the mitochondria, possibly in response to oxidative stress.

The progression of heart failure is a multifactorial process; therefore, we need to understand how multiple signals are integrated leading to a disease outcome. Currently, we do not know if and how AKAP signaling complexes are altered during heart disease progression and how this could affect cardiac remodeling. For example, is AKAP complex stoichiometry modified, and are enzymes regulated or targeted differently under pathological conditions? Clearly, more work is required to determine precisely how AKAP signaling complexes function in the progression of heart failure.

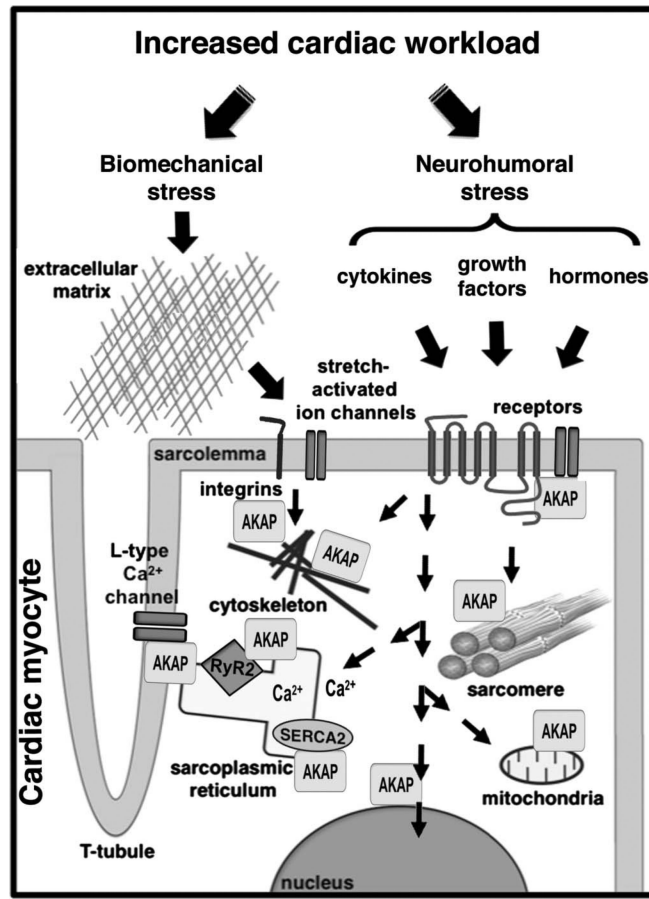
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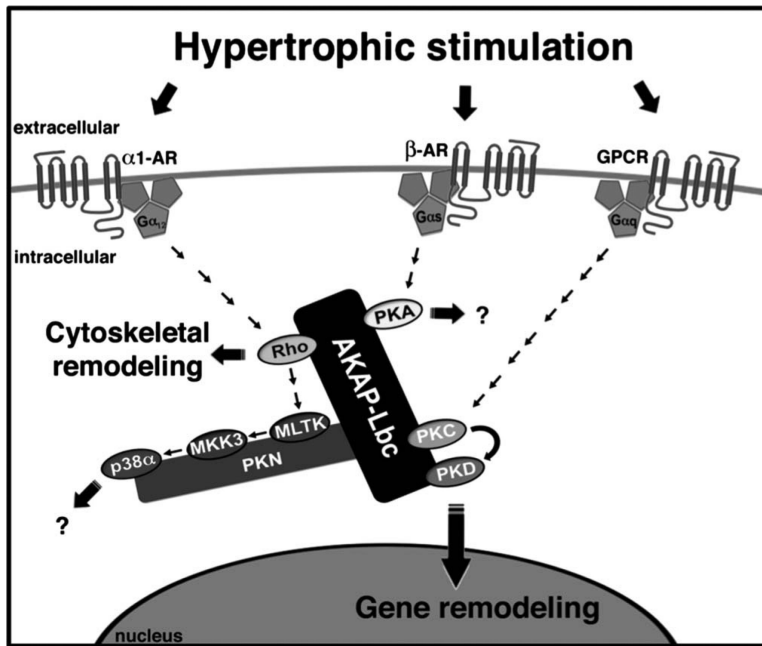
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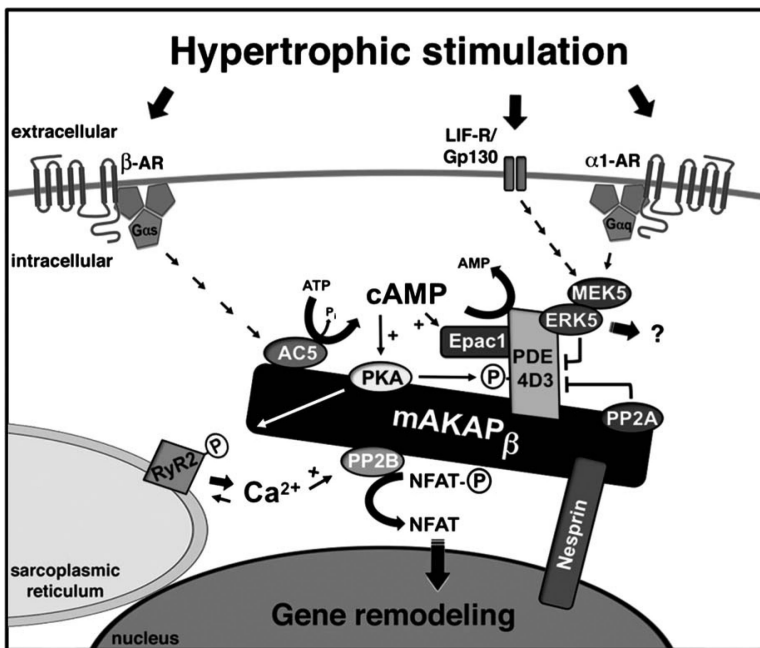
**FIGURE 1.**

AKAPs coordinate signaling complexes in cardiac myocytes that function in cardiac remodeling. The adult heart responds to injury or stress by activating a variety of intracellular signaling pathways that may affect calcium handling, the cytoskeleton, and sarcomeric and mitochondrial function. Different AKAPs in cardiac myocytes play a critical role in coordinating these signaling events to promote reexpression of an embryonic gene program, myocyte hypertrophy, and extracellular matrix remodeling. Refer to the text for specific details.



**FIGURE 2.**

AKAP-Lbc coordinates hypertrophic signaling to promote cytoskeletal and gene remodeling. AKAP-Lbc is present in the cytoplasm, displaying a cytoskeletal and perinuclear localization. This anchoring protein serves as a scaffold for PKA, PKD, and its upstream activating kinase PKC. By bringing PKC and PKD into close proximity, AKAP-Lbc facilitates the phosphorylation and subsequent activation of PKD by PKC. Upon activation, PKD translocates to the nucleus promoting hypertrophic gene expression through phosphorylation of a histone deacetylase (HDAC5), leading to HDAC5 nuclear export and derepression of Mef2 transcription. AKAP-Lbc is a GEF for Rho. The Rho-GEF activity of AKAP-Lbc is stimulated via the  $G\alpha_{12}$  family of heterotrimeric G-proteins in response to  $\alpha 1$ -adrenergic receptor (AR) activation. GEF activity can be inactivated by an AKAP-Lbc anchored PKA-dependent mechanism. AKAP-Lbc also coordinates a p38 $\alpha$  MAPK complex, downstream of Rho, composed of PKN $\alpha$ , MLTK, MKK3, and p38 $\alpha$ . Presently, the downstream targets and functional consequences of this AKAP-Lbc-associated signaling cascade are unknown.



**FIGURE 3.**

mAKAP $\beta$  coordinates hypertrophic signaling leading to cardiac gene remodeling. mAKAP $\beta$  is predominantly localized at the cardiomyocyte outer nuclear membrane through interaction with nesprin-1 $\alpha$ .  $\beta$ -AR stimulation will result in the production of cAMP through G $\alpha$ -coupled activation of mAKAP $\beta$ -bound adenylyl cyclase (AC5), likely present on transverse tubules adjacent to the nucleus. cAMP synthesis promotes mAKAP-bound PKA activation, leading to the phosphorylation of multiple substrates, including the RyR2, acting to potentiate  $Ca^{2+}$ -induced RyR2  $Ca^{2+}$  release. Local  $Ca^{2+}$  may activate mAKAP-associated PP2B (calcineurin  $\beta$ ), which will dephosphorylate the transcription factor NFATc, resulting in NFATc nuclear translocation and hypertrophic gene expression. cAMP metabolism is tightly regulated by the mAKAP signaling complex. PKA phosphorylates both AC5 and PDE4D3, inhibiting local cAMP production and increasing cAMP degradation, respectively. PKA also phosphorylates and stimulates PP2A, opposing PKA phosphorylation of PDE4D3, leading to greater, longer lasting cAMP signals. ERK5 will also phosphorylate and inhibit PDE4D3, thereby promoting PKA activity.  $\alpha$ 1-Adrenergic and gp130/leukemia inhibitory factor receptor (LIF-R) stimulation will result in MEK5 and ERK5 activation through a JAK/STAT/Ras/Raf pathway. Other substrates for mAKAP $\beta$ -associated ERK5 have not yet been identified. For simplicity, only a single mAKAP molecule is depicted.