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Phosphorylation, compartmentalization, and cardiac function

Kerrie B. Collins,

John D. Scott*

Department of Pharmacology, University of Washington, School of Medicine, 1959 NE Pacific Ave, Seattle WA, 98195

Summary

Protein phosphorylation is a fundamental element of cell signaling. First discovered as a biochemical switch in glycogenolysis, we now know that this posttranslational modification permeates all aspects of cellular behavior. In humans, over 540 protein kinases attach phosphate to acceptor amino acids, whereas around 160 phosphoprotein phosphatases remove phosphate to terminate signaling. Aberrant phosphorylation underlies disease, and kinase inhibitor drugs are increasingly used clinically as targeted therapies. Specificity in protein phosphorylation is achieved in part because kinases and phosphatases are spatially organized inside cells. A prototypic example is compartmentalization of the cAMP dependent protein kinase A through association with A-kinase anchoring proteins. This configuration creates autonomous signaling islands where the anchored kinase is constrained in proximity to activators, effectors, and selected substates. This article primarily focuses on AKAP signaling in the heart with an emphasis on anchoring proteins that spatiotemporally coordinate excitation-contraction coupling and hypertrophic responses.

Historical Overview

Seminal Discoveries

Phosphorylation is a posttranslational modification that is a cornerstone of many intracellular signaling cascades. This simple chemical cue has evolved into a sophisticated signaling paradigm that controls a myriad of physiological processes. This reaction occurs when the γ-phosphate group of adenosine 5'-triphosphate (ATP) is covalently linked to serine, threonine, tyrosine or histidine side chains[1]. The forward reaction, carried out by protein kinases, introduces negative charge, or changes the shape of the modified sidechain to alter the biochemical properties of the substrate protein[2,3]. The reverse reaction is catalyzed by phosphoprotein phosphatases that remove phosphate groups from substrates[3]. Although protein phosphorylation was first reported in the 1930's, we're only now beginning to grasp the full extent to which this covalent modification governs the biology of cells and underlies disease. Hence, pharmacological control of protein phosphorylation is a major therapeutic objective with 76 kinase inhibitor drugs currently approved for use and many more in clinical trials[4].

*To whom correspondence should be addressed: scottjdw@uw.edu.

Carl and Gerty Cori laid the groundwork for the study of phosphorylation through their pioneering research into the process of glycogen metabolism undertaken at the University of Washington St. Louis[5]. They discovered an intermediate compound that assisted in the breakdown of glycogen called glucose-1-phosphate, and identified glycogen phosphorylase as the rate limiting enzyme in glycogen production. They received the Nobel prize for Physiology in 1947 for this discovery.

The next breakthrough was the discovery of cyclic nucleotides as intracellular second messengers of hormone action. Sutherland and Rall, working at Vanderbilt University in 1957, showed that phosphorylase kinase was activated in a cyclic adenosine 3',5'-monophosphate (cAMP) dependent manner[6,7]. They showed that the primary messengers epinephrine and glucagon signaled the formation of cAMP by adenylyl cyclase (AC), which led to the activation of phosphorylase kinase[6,8]. This work won the Nobel Prize in 1971.

Following up on earlier work into glycogen metabolism, biochemists Edmond H. Fischer and Edwin G. Krebs at the University of Washington would expand the study of glycogen phosphorylase. This enzyme exists in active and inactive forms termed phosphorylase a and b respectively. Fischer and Krebs demonstrated that the transfer of a phosphoryl group donated by Mg-ATP was necessary for the phosphorylase b to a transition[9,10]. We now know that phosphorylation of Ser14 converts dormant phosphorylase b into active phosphorylase a. This phosphoryl group is removed by an enzyme which came to be known as phosphoprotein phosphatase 1[10]. Hence Fischer and Krebs became the first to define the reversible nature of protein phosphorylation. This was followed by the discovery of cAMP dependent protein kinase (also called protein kinase A or PKA) by Krebs, Walsh, and Perkins in 1968[11]. Fischer and Krebs were awarded the Nobel Prize in 1992 for their discovery of protein regulation by reversible phosphorylation[12].

The utility of phosphorylation as a commonly used signaling mechanism gained further prominence in 1979 when Tony Hunter and colleagues at the Salk institute revealed phosphorylation on tyrosine while studying the Rous Sarcoma virus[13,14]. Tony Pawson in Toronto and Joseph Schlessinger, now at Yale, independently defined phosphotyrosine as a recognition motif for Src homology 2 (SH2) domains in the assembly of macromolecular signaling complexes[15,16]. From then onward, the study of protein phosphorylation has been inextricably linked to research advances related to cancer, diabetes, and the cardiovascular system. A timeline of key developments in our understanding of PKA phosphorylation is presented in figure 1.

cAMP Dependent Protein Kinase (PKA)

The utility of protein phosphorylation as an adaptable form of cellular regulation is underscored by evidence that 1–2% of most genomes encode protein kinases. This includes over 540 genes in humans[17–19]. Protein kinase A signaling is often hailed as an archetype to understand the action of eukaryotic protein kinases. Yet, this enzyme is atypical in many respects[20]. Of the eukaryotic protein kinases, only PKA and casein kinases exist as tetrameric holoenzymes whose catalytic activity is autoinhibited by a separate family of regulatory subunits[20]. When steroids, neurotransmitters, or hormones engage G-protein coupled receptors (GPCRs), they mobilize adenylyl cyclases to promote a rapid rise

in intracellular levels of cAMP[21]. Importantly, activation of PKA is dependent upon cAMP binding rather than autophosphorylation within the active site of the enzyme[22,23]. PKA acts a master regulator of diverse cellular processes including (but not limited to) glycogenolysis, transcription, proliferation, hormone synthesis and release, and excitation-contraction coupling[20]. Moreover, the specificity and spatiotemporal resolution of PKA action is determined by a family of A Kinase Anchoring Proteins (AKAPs) that sequester this key enzyme with preferred substrates[24–26]

PKA exists as a holoenzyme composed of a dimer of regulatory subunits (R) that bind and constrain catalytic subunits (C)[27]. In 1970, Gill and Garren were the first to resolve the regulatory and catalytic components of the holoenzyme using bovine adrenal cortical PKA[28]. At the same time, Tao, Salas and Lipmann used sucrose density gradients to fractionate rabbit reticulocyte PKA holoenzymes into catalytic and regulatory subunits[29]. Elegant follow-up studies by Susan Taylor, Jackie Corbin and Edwin G. Krebs showed that the R subunits existed in two forms (I and II), and that each protomer was capable of binding two molecules of cAMP[30,31–33]. We now know that binding of cAMP to regulatory subunits relieves autoinhibitory control over the catalytic subunits; thereby activating the intact holoenzyme[34–36]. Around the same time Walsh and Krebs uncovered a heat stable protein inhibitor of PKA catalytic activity isolated from rabbit skeletal muscle, termed PKI[37]. Kinetic studies of PKI and peptide analogues by Scott, Fischer and Krebs defined the mechanism of kinase inhibition[38–40]. Concurrent studies by Kemp, Walsh and colleagues came to the same conclusions[41]. PKI peptides proved to be a valuable tool utilized by Sodwaski and Taylor to lock the PKA catalytic subunit into a conformation that allowed it's successful crystallization[42] (Figure 1). The significance of this latter work cannot be understated, as it revealed the bilobal fold that is a recognizable hallmark of all protein kinases[43,44].

Several laboratories have amassed considerable evidence that cAMP signaling events are much more spatially controlled than originally considered. Recent work on the boundaries of cAMP nanodomains shows that discrete and autonomous pockets of cAMP are generated upon the mobilization of G-protein coupled receptors[45–47]. Discerning the structure of AKAP signaling islands provides a molecular basis for how PKA is constrained within second messenger signaling compartments[34,35]. These studies show that the anchored PKA holoenzyme is maintained within 200–400 angstroms of selected substrates[25]. An implication of this revised view of cAMP signaling is that local phosphorylation events often occur within the narrow confines of AKAP signaling islands. Consequently, mutations that alter AKAP function or impact the localization of PKA underlie disease[48,49].

A Kinase Anchoring Proteins (AKAPs)

As the utility of cAMP signaling became more apparent, investigators realized that molecular mechanisms must exist to simultaneously coordinate multiple phosphorylation events inside cells. This led to the notion that PKA was compartmentalized[50]. Three independent observations set the stage for the discovery of AKAPs: PKA was reported to be attached to microtubules via its regulatory subunits[51], a calmodulin binding protein was identified as a contaminant with purified R subunits[52], and RII-binding proteins were

identified by far western blots using phosphorylated RII as the bait[53]. This technique is commonly referred to as an RII overlay[54]. Still, a systematic interrogation of localized PKA action was not possible until resolution of the PKA-AKAP binding interface[27,55,56] (Figure 2A). Deletion screens of RII carried out by Scott in 1990 identified the first 79 amino acids of RII as necessary and sufficient for binding to microtubule associated protein 2 (MAP2)[56]. Moreover, removal of the first 14 amino acids of RII not only abolished dimerization, but also prevented interaction with MAP2[56]. By the late 1990's the structure of the AKAP binding interface with RII was solved. This is now known as the docking and dimerization domain[57,58]. A hydrophobic cleft is formed by dimerization of the R subunits which fold into an antiparallel x-type helical bundle[27]. This motif is a common structural feature of all PKA regulatory subunits, as well as a newly identified family of 16 AKAP-interacting factors called R1D2 and R2D2 proteins[59–62] (Figure 2A).

Reciprocal studies carried out by Scott and colleagues defined PKA binding motifs on AKAPs. Using human thyroid protein clone 31 (Ht31, now called AKAP-Lbc) as a model, mutational analysis revealed a 14–18 amino acid sequence that was both essential for RII binding and predicted to form an amphipathic α-helix[63]. Site-directed mutagenesis of Ht31 aimed at disrupting its secondary structure confirmed that AKAPs bound RII via an amphipathic α-helix[27,54,63]. Cell soluble, stapled, and chemically stabilized peptide disruptors of AKAP/RII binding have subsequently been developed based on this RII binding sequence[61,64–67]. These reagents and small molecule inhibitors have become valuable tools for investigating anchored PKA function[68–72]. Acquiring this fundamental understanding of the AKAP/PKA binding interface has provided a molecular toolkit to study all AKAPs and primed the field for significant advancement (Figure 2A).

One angstrom resolution crystal structures of the RIIα docking and dimerization (DD) domain in complex with AKAP peptides add molecular detail to this protein-protein interface[27,59,73]. Two isoforms exist of each regulatory subunit (RI_{α}, RI_{β}, RII_{α}, and RII_{β}). The topology of the DD domain varies depending on the isoform of the R subunit present (Figure 2A). The depth of the cleft affects the number of points of contact with the AKAP α-helix. Consequently, AKAPs exhibit different binding affinities for each subtype of PKA, with the majority preferentially binding type II (so named for the R subunit)[24,27,59,73]. Additionally, RI selective, and dual specificity AKAPs have been defined[74–80]. Through these high affinity protein-protein interactions, PKA holoenzymes are sequestered at defined locations within cells (Figure 2B). To date, sixty human genes encoding over 150 isoforms have been classified as AKAPs[25]. As depicted in figure 2B, multiple AKAPs can be targeted to the same subcellular compartment. This does not necessarily reflect a redundancy of function, but rather the exquisite degree of spatial organization provided by AKAPs.

AKAP Signaling Islands

Arguably the most important feature of AKAPs is their ability to organize combinations of enzymes into macromolecular signaling complexes[81,82] (Figures 3&4). In this way, these anchoring proteins spatially integrate distinct cell signaling pathways and temporally control activation and termination of cAMP signaling cascades. First evidence for the multivalence of AKAPs came from the observation that the calcium/calmodulin dependent phosphatase

Calcineurin/PP2B was an interacting partner for the neuronal anchoring protein AKAP79[83]. Functional evidence in hippocampal neurons demonstrated that localization of PKA with PP2B by AKAP79 regulated aspects of synaptic transmission[84,85]. Subsequent studies on the same signaling complex identified protein kinase C (PKC) as an additional binding partner[86]. Biochemical, genetic, and functional studies have gone on to show how different combinations of AKAP79-anchored enzymes modulate transmembrane receptors and ion channels in neuronal, endocrine and muscle tissues[84,87–91].

Additional interactions with AKAP79 preferentially place PKA in proximity to adenylyl cyclase 5, the enzyme that generates intracellular cAMP[21 92–94]. This configuration creates an internally constrained negative feedback loop as anchored PKA phosphorylation of adenylyl cyclase 5 inhibits cAMP synthesis. Elegant work by Carmen Dessauer and colleagues has defined AKAP-AC interactions in various cellular systems[94–96]. AKAPs also associate with GPCRs, as indicated by initial work focused on anchored regulation of β-adrenergic signaling[97–99]. More recently it has been shown that PKA can anchor to other GPCR's. For example, Stefan and colleagues report that PKA is directly anchored to orphan receptor Gpr161 in primary cilia[100].

Spatiotemporal control of cAMP signal termination is achieved by AKAP association with phosphodiesterases (PDEs). The was first reported in 2001 when it was demonstrated that muscle-selective mAKAP, maintains a cAMP signaling module, including PKA and the cAMP-specific phosphodiesterase (PDE4D3) in the heart[101–104]. Around the same time, it was noted that AKAP450 constrains PKA and PDE4 at the centrosomes in Sertoli cells[105,106]. Importantly the long isoforms of PDE4's are substrates for anchored PKA, and phosphorylation enhances cAMP degradation[103,107]. These reports suggest that proximity of PKA and PDE's in AKAP signaling islands sustain a negative feedback loop to restore basal cAMP levels[24]. Further support for tight spatial control of cAMP signaling was provided when it was shown that mAKAP anchoring of PDE4D3 not only reduces local cAMP concentrations, but also provides spatial control over the cAMP responsive guanine nucleotide exchange factor EPAC-1[102,108]. Thus, AKAP signaling complexes participate in all aspects of cAMP signaling from the initiation of second messenger responses, to the termination cAMP signals, and bi-directional control of phosphorylation events.

Tissue Specific AKAP Regulation of Physiological Function

AKAPs in the Reproductive and Central Nervous Systems

Upwards of 150 tissue specific AKAP isoforms are transcribed from the human genome[24]. AKAPs are particularly prevalent in male and female germ cells, where they contribute to sperm development and motility as well as maturation of the female genital tract[109]. The distinctive morphology of sperm and their specialized intracellular environment favor the local activation of anchored cAMP signaling elements. AKAP110, AKAP220 and sAKAP84 are linked to sperm motility via the clustering of phosphodiesterases alongside PKA[110,111]. Local cAMP production in sperm is mediated by a soluble adenylyl cyclase called sAC or AC10 to create local nanodomains of second messenger[112]. Consideration of the aforementioned observations may help to explain the abundance of AKAPs expressed in male germ cells. In the female reproductive system, D-AKAP1 has been linked to oocyte

maturation as evidenced by infertility in female knockout mice. In addition to the regulation of germ cell development, the anchoring protein Gravin is required for proper gastrulation in zebra fish[113]. This AKAP is thought to mediate axis elongation via inhibition of the Rho/ROCK pathway[113].

One of the first neuronal AKAPs characterized, AKAP79 (or its murine ortholog AKAP150), facilitates synaptic signaling events[71]. AKAP79 scaffolds calcineurin (PP2B) with PKA and PKC by associating with both the plasma membrane and postsynaptic density proteins. This affects synaptic plasticity on multiple levels, principally by regulating the activity of various ion channels[86,84,114] Other AKAPs also contribute to neuronal functionality. For example, WAVE-1 anchors PKA and the tyrosine kinase Abl to the actin cytoskeleton to mediate synaptic remodeling. Analysis of WAVE-1 knockout mice revealed that loss of this signaling complex underlies defects in axonal guidance, sensory motor function and hippocampal learning and memory formation[115–117]. As these topics have been extensively reviewed, we have chosen to focus on AKAP signaling in the heart.

AKAPs in the Heart

According to the American Heart Association and National Institutes of Health, cardiovascular diseases in 2020 accounted for nineteen million deaths worldwide. This represents an increase of 18.7% over the previous decade. Hence, the development of molecular therapies for the prevention and treatment of cardiomyopathies is a critical healthcare initiative. The abundance of cardiac AKAPs makes them attractive therapeutic targets. Consequently, a significant body of work has focused on characterizing AKAP signaling in the heart. Cardiac AKAPs identified to date include: AKAP79/150, AKAP18, mAKAP, AKAP-Lbc, dAKAP1, dAKAP2, p110γ, myomegalin, troponin T, AKAP95, AKAP220, gravin, ezrin, synemin, SKIP, BIG2, cypher/zasp, and yotiao. These anchoring proteins coordinate physiological processes including excitation contraction coupling, calcium homeostasis, myogenic tone, contractility, gene transcription, pathological cardiac remodeling and hypertrophy as well as oxidative stress responses[24,118]

AKAP Regulation of EC Coupling

The recurrent contraction and relaxation of cardiomyocytes requires the synchronized coordination of cAMP and Ca2+ signaling events (Figure 3A). This process, known as excitation-contraction (EC) coupling, occurs when an action potential from the sinoatrial node is transduced into a chemical cue via voltage-gated ion channels localized to introversions of the sarcolemma called the transverse tubules[119] (Figure 3B–D). Following membrane depolarization, Ca^{2+} enters the cell through L-type Ca^{2+} channels. This stimulates further Ca^{2+} release from intracellular stores via ryanodine receptors (RyRs) within the membrane of the Sarcoplasmic Reticulum (SR). This transient rise in intracellular Ca^{2+} triggers contraction of the myofibrils[120]. The final phase of relaxation is largely dependent upon reuptake of calcium through the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA2)[119,121,122] (Figure 3A). EC coupling is a high fidelity process, with one action potential corresponding to one contraction[123]. Consequently, disruption of signaling

events at any level of this tightly controlled cascade (EC uncoupling) can result in cardiac arrhythmias and eventually heart failure.

EC coupling is regulated at many levels by PKA signaling downstream of adrenergic stimulation[124]. Catecholamines engage β-adrenergic receptors coupled to the stimulatory $G_{\alpha s}$ pathway. This stimulates adenylyl cyclase to produce cAMP, followed by PKA phosphorylation of substrates[125] including L-type calcium channels (primarily $Ca_v1.2$)[126], phospholamban (PLN)[127,128], and ryanodine receptors[129]. Anchoring of PKA is crucial for maintenance of proper calcium homeostasis and EC coupling. Anchoring proteins, including AKAP79/150, AKAP18, mAKAP, Gravin and Yotiao have been implicated in this process. Each AKAP coordinates distinct elements of this highly choreographed, vital, and repetitive physiological process.

AKAP79/150—Early biochemical and electrophysiological studies demonstrated that AKAP79 localized PKA to L-type calcium channels at the plasma membrane to mediate phosphorylation dependent modulation of ion conductance[130,131] (Figure 3A). It has also been shown that PKA inhibition in native cardiomyocytes negatively impacts calcium currents downstream of β-adrenergic stimulation[130]. Yet, mouse models lacking *AKAP5* (the gene encoding AKAP79/150) demonstrate that cardiomyocytes do not respond to β-adrenergic stimulation in the absence of this anchoring protein[132]. Calcium influx is mediated, in part, by the association of AKAP79 with $Ca_v1.2$[133]. This heteromeric channel is comprised of a transmembrane subunit and variable accessory subunits. AKAP79/150 associates with $Ca_v1.2$ via the C-terminus to target kinases and phosphatases capable of modifying the channel[134]. AKAP5$^{-/-}$mice display improper trafficking of β-adrenergic receptors, suggesting a role for this AKAP signaling island in receptor resensitization[135]. Other regulatory events may also participate in modulating $Ca_v1.2$ conductance.

AKAP18—AKAP18 is concentrated at the Z bands of cardiomyocytes (Figure 3B–D). Initial studies characterized the association of AKAP18 (also called AKAP15) with cardiac L-type calcium channels[136,137]. *AKAP7*, the gene encoding AKAP18, is subject to alternative splicing. The resultant AKAP18 isoforms vary in length, localization, tissue specific distribution, and function[138,139]. Splice variation results in the formation of at least five major AKAP18 isoforms, two short and three long (AKAP18α, AKAP18β, AKAP18γ, AKAP18δ and AKAP18ε)[138,140,141]. These isoforms are all expressed in the heart. AKAP18α is targeted to plasma membranes by lipid modification of its N-terminus in the form of myristoylation and palmitoylation[136]. Once at the membrane, AKAP18α associates with L-type calcium channels via a conserved leucine zipper motif on the C-terminus of the channels[142,143] (Figure 3A). Numerous studies have shown that $Ca_v1.2$ is phosphorylated by PKA on multiple sites (Ser1700, Thr1704, Ser1928, and Ser1518) and that this modification increases calcium channel conductance and contractile force[126,142,144–149]. Although anchoring of PKA with Cav1.2 is required for the maintenance of calcium homeostasis, it remains unclear exactly how channel activity is regulated from a molecular standpoint[150]. For example, PKA phosphorylation of the monomeric G protein Rad has recently been shown to contribute to channel activation[151].

As previously mentioned, the long isoforms of AKAP18 lack membrane targeting sequences. AKAP18γ and AKAP18δ contain unique localization sequences which direct them to organelles such as the sarcoplasmic reticulum (Figure 3A). It's well established that SERCA2 activity is mediated by its association with a small transmembrane protein called phospholamban. Depending on its phosphorylation state, PLN modifies the activity of SERCA2. Unphosphorylated PLN binds SERCA2 and inhibits calcium transport activity. Phosphorylated PLN releases its inhibitory hold on SERCA2, thus allowing for calcium reuptake into the SR and cardiomyocyte relaxation. Previous studies have shown that AKAP18δ scaffolds PKA with SERCA2 and PLN[152]. PKA is thus positioned to phosphorylate PLN, facilitating SERCA2 function, cardiomyocyte relaxation and maintenance of excitation-contraction coupling[152] (Figures 3B–D).

The localized activity of other kinases and phosphatases also participate in maintaining EC coupling. For example, calcium/calmodulin-dependent protein kinase II (CAMKII) has been linked to the regulation of calcium homeostasis. As described above, adrenergic stimulation elicits cellular calcium entry through L-type calcium channels. This influx triggers further release of calcium from intracellular stores within the sarcoplasmic reticulum into the cytosol via ryanodine receptors. Recent work has demonstrated an additional role for AKAP18δ in scaffolding CAMKII to ryanodine receptors[153]. Researchers have employed the use of peptide arrays, surface plasmon resonance, structural modeling, and advanced microscopy to show that different regions of AKAP18δ differentially regulate CAMKII activity. The N-terminal region of AKAP18δ binds and inhibits activation of CAMKII. Paradoxically, binding at the C-terminal region of AKAP18δ enhances CAMKII activation and promotes PLN phosphorylation. The net effect being faster Ca^{2+} release by RyRs and reuptake into the SR[153,154]. This represents a more nuanced AKAP-mediated mechanism of regulating calcium homeostasis.

Gravin and Yotiao—Gravin scaffolds protein kinase A and protein kinase C with β_2-adrenergic receptors (β_2-ARs)[155,156] (Figure 3A). This product of the *AKAP12* gene positively regulates cardiac contractility. Gravin influences positive ionotropic effects by mediating β_2-AR desensitization[157]. Interestingly, contractility is increased with and without β-adrenergic stimulation in mouse models lacking gravin[157,158]. In fact, the phosphorylation state of PLN and SERCA2 remains unchanged in these animals as compared with wild type controls[158]. While details of this molecular mechanism need to be clarified, gravin signaling islands are thought to maintain receptor sensitivity.

PKA-mediated phosphorylation of slow acting potassium channels is also important for the maintenance of EC coupling. These outward potassium currents (I_{Ks}) help to repolarize the membrane and contribute to myocardial relaxation or lusitropy. Elegant studies have shown that Yotiao scaffolds PKA and protein phosphatase 1 (PP1) with the KCNQ1 subunit of the channel[131] (Figure 3A). Interestingly, yotiao itself is phosphorylated on Serine43 by PKA following adrenergic stimulation[131]. Mutational analysis revealed that substitution of Ser43 with alanine diminished channel conductance but did not alter channel phosphorylation, or the association of Yotiao with KCNQ1. Additionally, allosteric interactions that proceed through AC9 may prime KCNQ1 for phosphorylation by PKA[95].

Therefore, the yotiao macromolecular complex is allosterically modulating the activity of the potassium channel[159].

AKAP coordination of Cardiac Hypertrophy

Cardiac hypertrophy is the heart's primary adaptive response to pressure or volume stressors, and/or damage to the overall contractile machinery (Figure 4A). Damage to the heart can result from a variety of factors including injury and disease. Hypertrophy describes either the concentric enlargement or elongation of cardiomyocytes as a compensatory mechanism in place of mitotic proliferation. Acute hypertrophic signaling can be beneficial for the heart. For example, the muscle cells in the heart can enlarge in response to exercise in order to compensate for the increased demand for cardiac output[160]. In contrast, chronic hypertrophic signaling underlies cardiomyopathies such as ischemia and hypertension that eventually lead to heart failure[118]. This pathological hypertrophy comprises a thickening of the myocardioum, reduction in chamber volume, interstitial fibrosis and reduced cardiac output. These systemic changes are accompanied by alterations in gene expression and cellular metabolism[118] (Figure 4A). Adult cardiomyocytes are largely terminally differentiated and are therefore particularly susceptible to pathological hypertophy. Cardiac AKAPs can elicit pro or anti-hypertrophic effects depending upon the composition of binding partners within each signaling island (Figure 4A).

AKAP-Lbc—Multiple signaling elements converge to regulate the heart's complex hypertrophic response. These include cytokines, MAP kinases, protein phosphatases, adenylyl cyclases, phosphodiesterases and transcription factors. The ability of AKAPs to coordinate these disparate enzymes make them key molecular platforms for the integration and propagation of intracellular signals. Activation of hypertrophic gene regulatory programs results in changes in cellular metabolism and cytoskeletal remodeling associated with disease. AKAP-Lbc signaling islands interface with the myocyte enhancer factor (MEF) pathway that is turned on in response to elevated catecholamines to promote pathological remodeling[113,161]. In particular, the transcription factor MEF2 is dephosphorylated by calcineurin in complex with AKAP-Lbc, allowing for its translocation to the nucleus and upregulation of hypertrophic gene expression (Figure 4A). AKAP-Lbc is also associated with class II histone deacetylases (HDACs 4 and 5)[161]. These enzymes repress the transcription of certain genes. AKAP-Lbc positions PKC to phosphorylate PKD, allowing for the latter to be translocated into the nucleus[161]. Once there, PKD phosphorylates HDACs, eliciting their nuclear export. This anchored signaling event facilitates MEF-mediated activation of gene regulatory pathways associated with pathological hypertrophy[113,131,161].

AKAP-Lbc signaling islands mediate other aspects of hypertrophic signaling. This anchoring protein also encodes a guanine nucleotide exchange factor for Rho (Rho GEF), which then induces p38 MAPK signaling downstream of α-adrenergic receptor stimulation in cardiomyocytes to induce hypertrophy[162–164] (Figure 4A). AKAP-Lbc therefore acts as an intermediate, linking α-adrenergic signaling to the mobilization of MAP kinase activity. Oxidative stress, a scenario in which the generation of reactive oxygen species (ROS) exceeds the cell's natural clearing capacity by antioxidant enzymes, has

also been linked with the onset of hypertrophy[165,166]. This imbalance can derive from physical and chemical stressors; and may lead to impaired contractility and apoptosis in addition to hypertrophy[118,167]. AKAP-Lbc protects against ROS induced damage by several mechanisms. In response to α1-adrenergic stimulation, AKAP-Lbc associated protein kinase D (PKD) phosphorylates and inactivates the phosphatase slingshot 1L (SSH1L). This circumvents the activation of a cofilin2/Bax subcomplex at the mitochondria[168]. This protects the cell from the increased ROS production that is emblematic of hypertrophy. In this way, AKAP-Lbc elicits a cardioprotective effect. AKAP-Lbc mediated activation of PKD also results in the phosphorylation of CREB which in turn upregulates expression of the anti-apoptotic gene Bcl2[118,168]. Hence, the pleiotropic effects elicited by AKAP-Lbc signaling make it a complex therapeutic target for the treatment of heart disease.

dAKAP1—Mitochondrial AKAPs affect cellular respiration, ROS production, and survival[169,170]. For example, the dual specificity anchoring protein dAKAP1 (a product of the *AKAP1* gene, also called S-AKAP84, AKAP121 or AKAP149) has been linked to cardiac hypertrophy via its regulation of mitochondrial ROS generation[74,171–173]. One isoform, AKAP121 acts in a cardioprotective manner by controlling mitochondrial morphology via the phosphorylation of Drp1 (Figure 4A–D). Further support for the cardioprotective role of AKAP121 is provided by evidence that these signaling islands repress nuclear translocation of the nuclear factor of activated T-cells NFATc3 that would otherwise enable hypertrophic gene expression[174]. *In vivo* studies consolidate this notion by showing that under conditions mimicking pressure overload, AKAP121 expression is depleted. This results in mitochondrial dysfunction, oxidative stress, and cell death[172]. Thus, cardiac function at the level of the mitochondria may proceed through dAKAP1/AKAP121 (Figures 4B–D). However, other anchoring proteins may also participate in this process. For example, SKIP, an entirely RI-selective AKAP, is located at the inner mitochondrial membrane where it regulates metabolic processes[80]. Consequently, local control of the hypertrophic response undoubtedly involves the concerted influence of multiple AKAP signaling islands (Figure 4A).

mAKAP—mAKAP is also associated with hypertrophic gene expression. This anchoring protein, originally called AKAP100, was identified in the original RII overlay screen for AKAPs conducted in the Scott laboratory[175]. Due to splice variation, there are two main isoforms of mAKAP (mAKAPα and mAKAPβ). Full length mAKAPα is a 255 kDa protein mainly localized to neurons, with mAKAPβ (230 kDa) being the predominant isoform in the heart. mAKAPβ associates with the nuclear envelope in cardiomyocytes through direct binding to an integral membrane protein called nesprin1-α[176]. Biochemical analyses have identified numerous mAKAP binding partners including PKA[177], PDE4D3[101], adenylyl cyclases[94], PP2A and calcineurin[178,179], RyRs[129,178,180,181], Rap1 and EPAC1[108], and the MAP kinases MEK and ERK[108,182] (Figure 4A).

Extensive *in vitro* and *in vivo* studies indicate that the primary directive of the mAKAP signaling complex is to alter gene expression coincident with myocyte remodeling. The transcripton factors NFATc and MEF2 are dephosphorylated by mAKAP associated calcineurin. This triggers their translocation to the nucleus and the upregulation of gene

expression associated with hypertrophic cardiac remodeling[183–185]. PKD is also activated in complex with mAKAP, leading to phosphorylation of HDAC4 and the subsequent derepression of hypertophic genes[183,186]. Interestingly, knockout of mAKAPβ expression has been shown to elicit a cardioprotective effect in mouse models of pressure overload and hypertrophy[183]. Conversely, it has been shown that mAKAP scaffolding of E3 ubiquitin ligases with hypoxia-inducible factor 1 (HIF-1α) mediates the stability of HIF-1α. In response to hypoxia, HIF-1α is stabilized so that it can translocate to the nucleus and promote the transcription of cell survival genes[187]. These studies demonstrate that mAKAP provides a multipurpose molecular platform to coordinate enzyme activities necessary for the processing of multiple hypertrophic signals.

Conclusions and Perspectives

From its humble beginnings as a regulatory element of glycogen metabolism, we now recognize that protein phosphorylation is a universal biochemical regulatory mechanism on par with protein ubiquitination, acetylation and proteolysis[4]. Many pivotal studies on phosphorylation were conducted in the heart, illustrating how this mode of covalent modification controls force generation and contractility. Spatiotemporal control of protein phosphorylation by AKAPs may be particularly important in this context because of the speed and repetition required for EC coupling. Likewise, modulation of adaptive responses such as physiological and pathological cardiac hypertrophy require the relay of signals from the plasma membrane to the transcriptional machinery embedded in the nucleus. Thus, mechanisms that confer local control of protein phosphorylation events have evolved to accommodate the specialized function of cardiomyocytes (Figures 3A & 4A).

Elegant fluorescent spectroscopy studies show that physiological accumulation of cAMP occurs within nanometer-sized domains[45–47]. This new model is consistent with our own molecular evidence that anchored, intact, and active PKA holoenzymes operate within a 200 to 400-A° radius[34,35]. This creates discrete and autonomous pockets of activity where anchored PKA phosphorylates preferred substrates; and could explain why multiple AKAPs are located at the SR, plasma membranes, mitochondria, and nuclear envelope in cardiomyocytes. For example, AKAP79, AKAP18α and Cypher/Zasp control phosphorylation of L-type Ca^{2+} channels to initiate EC coupling. Close by, mAKAP modulates ryanodine receptors to promote further calcium release, while AKAP18γ facilitates calcium reuptake by SERCA2. This highlights the remarkable degree of spatial organization provided by AKAPs that is necessary to ensure processive implementation of distinct phosphorylation events (Figure 3A).

Perhaps not surprisingly, aberrant AKAP signaling can have pathological ramifications. As previously mentioned, depletion of mitochondrial AKAP121 occurs under conditions of pressure overload. Polymorphisms in AKAP18α that abolish PKA anchoring alter regulation of cardiac L-type Ca^{2+} channels and are linked with increased susceptibility to febrile seizures[138]. Likewise, polymorphisms in d-AKAP2/AKAP10 are linked to arrythmias and may be related to increased cardiac dysfunction within the aging population[188]. In another pathological context, Cushing’s syndrome, mutations in PKAc that prevent its incorporation into AKAP signaling islands underlie hypertension, arrythmia and other

cardiovascular complications[49]. Taken together, these examples underscore the exquisite degree of subcellular organization provided by AKAPs. Thus, targeting drugs to AKAPs offers an appealing therapeutic strategy to exploit this sophisticated signaling terrain. Such precision pharmacological regimens would endeavor to minimize off-target effects. While local kinase inhibition is currently effective at tethering modified drug adducts to their sites of action[189,190], there is hope that this strategy can be refined to deliver small molecules that allosterically inhibit anchored kinases. In closing, Eddy Fischer and Ed Krebs would be astonished at the advances made in understanding reversible protein phosphorylation. They would be equally enthusiastic and intrigued to find out what the next generation of researchers will discover.

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Abbreviations

PKA	protein kinase A
AKAPs	A-Kinase Anchoring proteins
ATP	adenosine 5’-triphosphate
cAMP	cyclic adenosine 3’,5’-monophosphate
AC	adenylyl cyclase
SH2	Src homology 2 domain
GPCR	G protein coupled receptor
R subunit	PKA regulatory subunit
C subunit	PKA catalytic subunit
Ht31	human thyroid protein clone 31
PKI	heat stable peptide inhibitor of PKA
DD	docking and dimerization domain of PKA holoenzyme
PKC	protein kinase C
PDE	phopsphodiesterase
SAC	soluble adenylyl cyclase
PP2B	protein phosphatase 2B, calcineurin

CaN	calcineurin
EC coupling	excitation-contraction coupling
Ca^{2+}	calcium
RYR	ryanodine receptors
SR	sarcoplasmic reticulum
SERCA2	sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase
PLN	phospholamban
CAMKII	calcium/calmodulin-dependent protein kinase II
β_2–AR	β_2-adrenergic receptors
I_{Ks}	outward potassium currents
PPI	protein phosphatase 1
MEF	myocyte enhancer factor
HDACs 4 and 5	histone deacetylases 4 and 5
Rho GEF	guanine nucleotide exchange factor for Rho
ROS	reactive oxygen species
SSH1L	slingshot 1L
PKD	protein kinase D
NFAT	nuclear factor of activated T-cells
HIF-1a	hypoxia-inducible factor 1a
MAP2	microtubule associated protein 2

References

1. Ubersax JA & Ferrell JE Jr Mechanisms of specificity in protein phosphorylation. Nature Reviews Molecular Cell Biology 8, 530–541, doi:10.1038/nrm2203 (2007). [PubMed: 17585314]
2. Ardito F, Giuliani M, Perrone D, Troiano G & Muzio LL The crucial role of protein phosphorylation in cell signaling and its use as targeted therapy (Review). International Journal of Molecular Medicine 40, 271–280, doi:10.3892/ijmm.2017.3036 (2017). [PubMed: 28656226]
3. Nishi H, Shaytan A & Panchenko AR Physicochemical mechanisms of protein regulation by phosphorylation. Front Genet 5, 270, doi:10.3389/fgene.2014.00270 (2014). [PubMed: 25147561]
4. Cohen P, Cross D & Jänne PA Kinase drug discovery 20 years after imatinib: progress and future directions. Nature Reviews Drug Discovery 20, 551–569, doi:10.1038/s41573-021-00195-4 (2021). [PubMed: 34002056]
5. Cori GT The Enzymatic Conversion of Phosphorylase b to a Journal of Biological Chemistry, 321–3321943).
6. Rall TW, Sutherland EW & Berthet J The relationships of epinephrine and glucagon to liver phosphorylase. J. Biol. Chem 224, 463–475 (1957). [PubMed: 13398422]

7. Rall TW & Sutherland EW Formation of cyclic adenine ribonucleotide by tissue particles. J. Biol. Chem 232, 1065–1076 (1958). [PubMed: 13549487]
8. Sutherland EW Studies on the mechanism of hormone action. Science 171, 401–408 (1972).
9. Fischer EH & Krebs EG Conversion of phosphorylase b to phosphorylase a in muscle extracts. J. Biol. Chem 216, 121–132 (1955). [PubMed: 13252012]
10. Krebs EG & Fischer EH The phosphorylase b to a converting enzyme of rabbit skeletal muscle. Biochimica et Biophysica Acta 20, 150–157, doi:10.1016/0006-3002(56)90273-6 (1956). [PubMed: 13315361]
11. Walsh DA, Perkins JP & Krebs EG An adenosine 3',5'-monophosphate-dependent protein kinase from rabbit skeletal muscle. J. Biol. Chem 243, 3763–3765 (1968). [PubMed: 4298072]
12. Cohen P Protein kinases--the major drug targets of the twenty-first century? Nat Rev Drug Discov 1, 309–315 (2002). [PubMed: 12120282]
13. Sefton BM, Hunter T & Beemon K Product of in vitro translation of the Rous sarcoma virus src gene has protein kinase activity. J Virol 30, 311–318, doi:10.1128/jvi.30.1.311-318.1979 (1979). [PubMed: 225522]
14. Eckhart W, Hutchinson MA & Hunter T An activity phosphorylating tyrosine in polyoma T antigen immunoprecipitates. Cell 18, 925–933 (1979). [PubMed: 229973]
15. Sadowski I, Stone JC & Pawson T A non-catalytic domain conserved among cytoplasmic protein-tyrosine kinases modifies the kinase function and transforming activity of Fujinami sarcoma virus P130gag-fps. Mol. Cell. Biol 6, 4396–4408 (1986). [PubMed: 3025655]
16. Lemmon MA & Schlessinger J Cell signaling by receptor tyrosine kinases. Cell 141, 1117–1134, doi:10.1016/j.cell.2010.06.011 (2010). [PubMed: 20602996]
17. Lehti-Shiu MD & Shiu S-H Diversity, classification and function of the plant protein kinase superfamily. Philosophical Transactions of the Royal Society B: Biological Sciences 367, 2619–2639, doi:10.1098/rstb.2012.0003 (2012).
18. Manning G, Whyte DB, Martinez R, Hunter T & Sudarsanam S The protein kinase complement of the human genome. Science 298, 1912–1934 (2002). [PubMed: 12471243]
19. Manning G, Plowman GD, Hunter T & Sudarsanam S Evolution of protein kinase signaling from yeast to man. Trends Biochem. Sci 27, 514–520 (2002). [PubMed: 12368087]
20. Turnham RE & Scott JD Protein kinase A catalytic subunit isoform PRKACA; History, function and physiology. Gene 577, 101–108, doi:10.1016/j.gene.2015.11.052 (2016). [PubMed: 26687711]
21. Dessauer CW Adenylyl cyclase--A-kinase anchoring protein complexes: the next dimension in cAMP signaling. Mol. Pharmacol 76, 935–941, doi:mol.109.059345 [pii] 10.1124/mol.109.059345 (2009). [PubMed: 19684092]
22. Corbin JD & Keely SL Characterization and regulation of heart adenosine 3': 5'- monophosphate-dependent protein kinase isozymes. J. Biol. Chem 252, 910–918 (1977). [PubMed: 190220]
23. Potter RL & Taylor SS Correlation of the cAMP binding domain with a site of autophosphorylation on the regulatory subunit of cAMP-dependent protein kinase II from porcine skeletal muscle. J Biol Chem 254, 9000–9005 (1979). [PubMed: 225318]
24. Langeberg LK & Scott JD Signalling scaffolds and local organization of cellular behaviour. Nat Rev Mol Cell Biol 16, 232–244, doi:10.1038/nrm3966 (2015). [PubMed: 25785716]
25. Omar MH & Scott JD AKAP Signaling Islands: Venues for Precision Pharmacology. Trends in Pharmacological Sciences 41, 933–946, doi:10.1016/j.tips.2020.09.007 (2020). [PubMed: 33082006]
26. Tasken K & Aandahl EM Localized effects of cAMP mediated by distinct routes of protein kinase A. Physiol Rev 84, 137–167, doi:10.1152/physrev.00021.2003 (2004). [PubMed: 14715913]
27. Gold MG et al. Molecular basis of AKAP specificity for PKA regulatory subunits. Mol Cell 24, 383–395 (2006). [PubMed: 17081989]
28. Gill GN & Garren LD A cyclic-3′,5′-adenosine monophosphate dependent protein kinase from the adrenal cortex: Comparison with a cyclic AMP binding protein. Biochemical and Biophysical Research Communications 39, 335–343, doi:10.1016/0006-291x(70)90581-4 (1970). [PubMed: 4316205]

29. Tao M, Salas ML & Lipmann F Mechanism of activation by adenosine 3':5'-cyclic monophosphate of a protein phosphokinase from rabbit reticulocytes. Proc Natl Acad Sci U S A 67, 408–414, doi:10.1073/pnas.67.1.408 (1970). [PubMed: 4318788]
30. Canaves JM & Taylor SS Classification and Phylogenetic Analysis of the cAMP-Dependent Protein Kinase Regulatory Subunit Family. Journal of Molecular Evolution 54, 17–29, doi:10.1007/s00239-001-0013-1 (2002). [PubMed: 11734894]
31. Corbin JD et al. Studies on the properties and mode of action of the purified regulatory subunit of bovine heart adenosine 3':5'-monophosphate-dependent protein kinase. J. Biol. Chem 253, 3997–4003 (1978). [PubMed: 206557]
32. Krebs EG, Blumenthal DK, Edelman AM & Hales CN in Mechanisms of Receptor Regulation (eds Crooke ST & Poste G) 324–367 (Plenum, 1985).
33. Hofmann F, Beavo JA, Bechtel PJ & Krebs EG Comparison of adenosine 3':5'-monophosphate-dependent protein kinases from rabbit skeletal and bovine heart muscle. J. Biol. Chem 250, 7795–7801 (1975). [PubMed: 170270]
34. Smith FD et al. Intrinsic disorder within an AKAP-protein kinase A complex guides local substrate phosphorylation. Elife 2, e01319, doi:10.7554/eLife.01319 (2013). [PubMed: 24192038]
35. Smith FD et al. Local protein kinase A action proceeds through intact holoenzymes. Science 356, 1288–1293, doi:10.1126/science.aaj1669 (2017). [PubMed: 28642438]
36. Wang Y, Scott JD, McKnight GS & Krebs EG A constitutively active holoenzyme from the cAMP-dependent protein kinase. Proc. Natl. Acad. Sci. USA 88, 2446–2450 (1991). [PubMed: 1848703]
37. Walsh DA et al. Purification and characterization of a protein inhibitory of adenosine 3',5'-monophosphate-dependent protein kinases. J. Biol. Chem 246, 1977–1985 (1971). [PubMed: 4324557]
38. Scott JD, Fischer EH, DeMaille JG & Krebs EG Identification of an inhibitory region of the heat-stable protein inhibitor of the cAMP-dependent protein kinase. Proc. Natl. Acad. Sci. U.S.A 82, 4379–4383 (1985). [PubMed: 2989819]
39. Scott JD, Fischer EH & Krebs EG The inhibitory region of the heat-stable protein inhibitor of the cAMP-dependent protein kinase. Proc. Natl.Acad. Sci. USA 84, 703–708 (1985).
40. Scott JD, Glaccum MB, Fischer EH & Krebs EG Primary-structure requirements for inhibition by the heat-stable inhibitor of the cAMP-dependent protein kinase. Proc. Natl. Acad. Sci. U.S.A 83, 1613–1616 (1986). [PubMed: 3456605]
41. Glass DB, Cheng H-C, Kemp BE & Walsh DA Differential and common recognition sites of the catalytic sites of the cGMP-dependent and cAMP-dependent protein kinases by the inhibitory peptides derived from the heat-stable inhibitor protein. J. Biol. Chem 261, 121611–112171 (1986).
42. Knighton DR et al. Structure of a peptide inhibitor bound to the catalytic subunit of cyclic adenosine monophosphate-dependent protein kinase. Science 253, 414–420 (1991). [PubMed: 1862343]
43. Taylor SS, Ilouz R, Zhang P & Kornev AP Assembly of allosteric macromolecular switches: lessons from PKA. Nat Rev Mol Cell Biol 13, 646–658, doi:10.1038/nrm3432 (2012). [PubMed: 22992589]
44. Zhang P, Kornev AP, Wu J & Taylor SS Discovery of Allostery in PKA Signaling. Biophys Rev 7, 227–238, doi:10.1007/s12551-015-0170-x (2015). [PubMed: 26097522]
45. Anton SE et al. Receptor-associated independent cAMP nanodomains mediate spatiotemporal specificity of GPCR signaling. Cell 185, 1130–1142 e1111, doi:10.1016/j.cell.2022.02.011 (2022). [PubMed: 35294858]
46. Zaccolo M & Pozzan T Discrete microdomains with high concentration of cAMP in stimulated rat neonatal cardiac myocytes. Science 295, 1711–1715. (2002). [PubMed: 11872839]
47. Bock A et al. Optical Mapping of cAMP Signaling at the Nanometer Scale. Cell 184, 2793, doi:10.1016/j.cell.2021.04.043 (2021). [PubMed: 33989549]
48. Turnham RE et al. An acquired scaffolding function of the DNAJ-PKAc fusion contributes to oncogenic signaling in fibrolamellar carcinoma. eLife 8, e44187, doi:10.7554/eLife.44187 (2019). [PubMed: 31063128]

49. Omar MH et al. Mislocalization of protein kinase A drives pathology in Cushing's syndrome. Cell Reports 40, 111073–111091, doi:10.1016/j.celrep.2022.111073 (2022). [PubMed: 35830806]
50. Buxton ILO & Brunton LL Compartments of cyclic AMP and protein kinase in mammalian cardiomyocytes. JBC 258, 10233–10239 (1983).
51. Theurkauf WE & Vallee RB Molecular characterization of the cAMP-dependent protein kinase bound to microtubule-associated protein 2. J. Biol. Chem 257, 3284–3290 (1982). [PubMed: 6277931]
52. Sarkar D, Erlichman J & Rubin CS Identification of a calmodulin-binding protein that co-purifies with the regulatory subunit of brain protein kinase II. J. Biol. Chem 259, 9840–9846 (1984). [PubMed: 6086653]
53. Lohmann SM, DeCamili P, Enig I & Walter U High-affinity binding of the regulatory subunit (RII) of cAMP-dependent protein kinase to microtubule-associated and other cellular proteins. Proc. Natl. Acad. Sci. U.S.A 81, 6723–6727 (1984). [PubMed: 6093118]
54. Carr DW, Hausken ZE, Fraser ID, Stofko-Hahn RE & Scott JD Association of the type II cAMP-dependent protein kinase with a human thyroid RII-anchoring protein. Cloning and characterization of the RII-binding domain. J. Biol. Chem 267, 13376–13382 (1992). [PubMed: 1618839]
55. Colledge M & Scott JD AKAPs: from structure to function. Trends Cell Biol 9, 216–221. (1999). [PubMed: 10354567]
56. Scott JD et al. Type II regulatory subunit dimerization determines the subcellular localization of the cAMP-dependent protein kinase. J. Biol. Chem 265, 21561–21566 (1990). [PubMed: 2147685]
57. Newlon MG et al. A novel mechanism of PKA anchoring revealed by solution structures of anchoring complexes. Embo J 20, 1651–1662. (2001). [PubMed: 11285229]
58. Newlon MG et al. The molecular basis for protein kinase A anchoring revealed by solution NMR. Nat. Struct. Biol 6, 222–227. (1999). [PubMed: 10074940]
59. Sarma GN et al. Structure of D-AKAP2:PKA RI complex: insights into AKAP specificity and selectivity. Structure 18, 155–166, doi:S0969–2126(10)00007–9 [pii] 10.1016/j.str.2009.12.012 (2010). [PubMed: 20159461]
60. Dahlin HR, Zheng N & Scott JD Beyond PKA: Evolutionary and structural insights that define a docking and dimerization domain superfamily. J Biol Chem 297, 100927, doi:10.1016/j.jbc.2021.100927 (2021). [PubMed: 34256050]
61. Gotz F et al. AKAP18:PKA-RIIalpha structure reveals crucial anchor points for recognition of regulatory subunits of PKA. Biochem J 473, 1881–1894, doi:10.1042/BCJ20160242 (2016). [PubMed: 27102985]
62. Carr DW et al. Identification of sperm-specific proteins that interact with A-kinase anchoring proteins in a manner similar to the type II regulatory subunit of PKA. J Biol Chem 276, 17332–17338, doi:10.1074/jbc.M011252200 (2001). [PubMed: 11278869]
63. Carr DW et al. Interaction of the regulatory subunit (RII) of cAMP-dependent protein kinase with RII-anchoring proteins occurs through an amphipathic helix binding motif. J Biol Chem 266, 14188–14192 (1991). [PubMed: 1860836]
64. Alto NM et al. Bioinformatic design of A-kinase anchoring protein-in silico: A potent and selective peptide antagonist of type II protein kinase A anchoring. Proc. Natl. Acad. Sci. U.S.A 100, 4445–4450 (2003). [PubMed: 12672969]
65. Carlson CR et al. Delineation of Type I Protein Kinase A-selective Signaling Events Using an RI Anchoring Disruptor. J Biol Chem 281, 21535–21545 (2006). [PubMed: 16728392]
66. Wang Y et al. PKA-Type I Selective Constrained Peptide Disruptors of AKAP Complexes. ACS Chem Biol 10, 1502–1510, doi:10.1021/acschembio.5b00009 (2015). [PubMed: 25765284]
67. Kennedy EJ & Scott JD Selective disruption of the AKAP signaling complexes. Methods Mol Biol 1294, 137–150, doi:10.1007/978-1-4939-2537-7_11 (2015). [PubMed: 25783883]
68. Burns-Hamuro LL et al. Designing isoform-specific peptide disruptors of protein kinase A localization. Proc. Natl. Acad. Sci. U.S.A 100, 4072–4077 (2003). [PubMed: 12646696]
69. Deak VA & Klussmann E Pharmacological Interference With Protein-protein Interactions of Akinase Anchoring Proteins as a Strategy for the Treatment of Disease. Curr Drug Targets 17, 1147–1171, doi:10.2174/1389450116666150416114247 (2016). [PubMed: 25882214]

70. Stefan E et al. Compartmentalization of cAMP-dependent signaling by phosphodiesterase-4D is involved in the regulation of vasopressin-mediated water reabsorption in renal principal cells. J Am Soc Nephrol 18, 199–212, doi:ASN.2006020132 [pii]10.1681/ASN.2006020132 (2007). [PubMed: 17135396]
71. Rosenmund C et al. Anchoring of protein kinase A is required for modulation of AMPA/kainate receptors on hippocampal neurons. Nature 368, 853–856 (1994). [PubMed: 8159245]
72. Tavalin SJ, Westphal RS, Colledge M, Langeberg LK & Scott JD The molecular architecture of neuronal kinase/phosphatase signalling complexes. Biochem Soc Trans 27, 539–542 (1999). [PubMed: 10917637]
73. Kinderman FS et al. A dynamic mechanism for AKAP binding to RII isoforms of cAMP-dependent protein kinase. Mol Cell 24, 397–408 (2006). [PubMed: 17081990]
74. Huang LJ, Durick K, Weiner JA, Chun J & Taylor SS Identification of a novel dual specificity protein kinase A anchoring protein, D-AKAP1. J. Biol. Chem 272, 8057–8064 (1997). [PubMed: 9065479]
75. Huang LJ, Durick K, Weiner JA, Chun J & Taylor SS D-AKAP2, a novel protein kinase A anchoring protein with a putative RGS domain. Proc. Natl. Acad. Sci. USA 94, 11184–11189 (1997). [PubMed: 9326583]
76. Miki K & Eddy EM Identification of tethering domains for protein kinase A type Ialpha regulatory subunits on sperm fibrous sheath protein FSC1. J Biol Chem 273, 34384–34390 (1998). [PubMed: 9852104]
77. Miki K & Eddy EM Single amino acids determine specificity of binding of protein kinase A regulatory subunits by protein kinase A anchoring proteins [In Process Citation]. J Biol Chem 274, 29057–29062 (1999). [PubMed: 10506157]
78. Burgers PP et al. Structure of smAKAP and its regulation by PKA-mediated phosphorylation. FEBS J 283, 2132–2148, doi:10.1111/febs.13726 (2016). [PubMed: 27028580]
79. Kovanich D et al. Sphingosine kinase interacting protein is an A-kinase anchoring protein specific for type I cAMP-dependent protein kinase. Chembiochem 11, 963–971, doi:10.1002/cbic.201000058 (2010). [PubMed: 20394097]
80. Means CK et al. An entirely specific type I A-kinase anchoring protein that can sequester two molecules of protein kinase A at mitochondria. Proceedings of the National Academy of Sciences of the United States of America 108, E1227–1235, doi:10.1073/pnas.1107182108 (2011). [PubMed: 22084075]
81. Scott JD & Pawson T Cell signaling in space and time: where proteins come together and when they’re apart. Science 326, 1220–1224, doi:10.1126/science.1175668 (2009). [PubMed: 19965465]
82. Fraser ID & Scott JD Modulation of ion channels: a “current” view of AKAPs. Neuron 23, 423–426 (1999). [PubMed: 10433254]
83. Coghlan VM et al. Association of protein kinase A and protein phosphatase 2B with a common anchoring protein. Science 267, 108–112 (1995). [PubMed: 7528941]
84. Colledge M et al. Targeting of PKA to glutamate receptors through a MAGUK-AKAP complex. Neuron 27, 107–119 (2000). [PubMed: 10939335]
85. Samelson BK et al. A-kinase Anchoring Protein 79/150 Recruits Protein Kinase C to Phosphorylate Roundabout Receptors. J Biol Chem 290, 14107–14119, doi:10.1074/jbc.M115.637470 (2015). [PubMed: 25882844]
86. Klauck TM et al. Coordination of three signaling enzymes by AKAP79, a mammalian scaffold protein. Science 271, 1589–1592 (1996). [PubMed: 8599116]
87. Hoshi N, Langeberg LK & Scott JD Distinct enzyme combinations in AKAP signalling complexes permit functional diversity. Nat Cell Biol 7, 1066–1073 (2005). [PubMed: 16228013]
88. Oliveria SF, Dell’Acqua ML & Sather WA AKAP79/150 anchoring of calcineurin controls neuronal L-type Ca2+ channel activity and nuclear signaling. Neuron 55, 261–275 (2007). [PubMed: 17640527]
89. Murphy JG et al. AKAP-anchored PKA maintains neuronal L-type calcium channel activity and NFAT transcriptional signaling. Cell Rep 7, 1577–1588, doi:10.1016/j.celrep.2014.04.027 (2014). [PubMed: 24835999]

90. Hoshi N, Langeberg LK, Gould CM, Newton AC & Scott JD Interaction with AKAP79 modifies the cellular pharmacology of PKC. Mol Cell 37, 541–550, doi:S1097–2765(10)00043–2 [pii] 10.1016/j.molcel.2010.01.014 (2010). [PubMed: 20188672]

91. Tunquist BJ et al. Loss of AKAP150 perturbs distinct neuronal processes in mice. Proc Natl Acad Sci U S A 105, 12557–12562 (2008). [PubMed: 18711127]

92. Scott JD, Dessauer CW & Tasken K Creating order from chaos: cellular regulation by kinase anchoring. Annu Rev Pharmacol Toxicol 53, 187–210, doi:10.1146/annurev-pharmtox-011112-140204 (2013). [PubMed: 23043438]

93. Piggott LA, Bauman AL, Scott JD & Dessauer CW The A-kinase anchoring protein Yotiao binds and regulates adenylyl cyclase in brain. Proc Natl Acad Sci U S A 105, 13835–13840, doi:0712100105 [pii] 10.1073/pnas.0712100105 (2008). [PubMed: 18772391]

94. Kapiloff MS et al. An adenylyl cyclase-mAKAPbeta signaling complex regulates cAMP levels in cardiac myocytes. J. Biol. Chem 284, 23540–23546, doi:M109.030072 [pii] 10.1074/jbc.M109.030072 (2009). [PubMed: 19574217]

95. Li Y, Chen L, Kass RS & Dessauer CW The A-kinase anchoring protein Yotiao facilitates complex formation between adenylyl cyclase type 9 and the IKs potassium channel in heart. J Biol Chem 287, 29815–29824, doi:10.1074/jbc.M112.380568 (2012). [PubMed: 22778270]

96. Bavencoffe A et al. Persistent Electrical Activity in Primary Nociceptors after Spinal Cord Injury Is Maintained by Scaffolded Adenylyl Cyclase and Protein Kinase A and Is Associated with Altered Adenylyl Cyclase Regulation. J Neurosci 36, 1660–1668, doi:10.1523/jneurosci.0895-15.2016 (2016). [PubMed: 26843647]

97. Fraser ID et al. Assembly of an A kinase-anchoring protein-beta(2)-adrenergic receptor complex facilitates receptor phosphorylation and signaling. Curr Biol 10, 409–412 (2000). [PubMed: 10753752]

98. Tao J, Wang HY & Malbon CC Protein kinase A regulates AKAP250 (gravin) scaffold binding to the beta2-adrenergic receptor. EMBO J. 22, 6419–6429 (2003). [PubMed: 14657015]

99. Havekes R et al. Gravin orchestrates protein kinase A and beta2-adrenergic receptor signaling critical for synaptic plasticity and memory. J Neurosci 32, 18137–18149, doi:10.1523/JNEUROSCI.3612-12.2012 (2012). [PubMed: 23238728]

100. Bachmann VA et al. Gpr161 anchoring of PKA consolidates GPCR and cAMP signaling. Proc Natl Acad Sci U S A 113, 7786–7791, doi:10.1073/pnas.1608061113 (2016). [PubMed: 27357676]

101. Dodge KL et al. mAKAP assembles a protein kinase A/PDE4 phosphodiesterase cAMP signaling module. EMBO J. 20, 1921–1930. (2001). [PubMed: 11296225]

102. Dodge-Kafka KL, Langeberg L & Scott JD Compartmentation of cyclic nucleotide signaling in the heart: the role of A-kinase anchoring proteins. Circ Res 98, 993–1001 (2006). [PubMed: 16645149]

103. Carlisle Michel JJ et al. PKA phosphorylation of PDE4D3 facilitates recruitment of the mAKAP signaling complex. Biochem. J 381, 587–592 (2004). [PubMed: 15182229]

104. Michel JJ et al. Spatial restriction of PDK1 activation cascades by anchoring to mAKAPalpha. Mol Cell 20, 661–672 (2005). [PubMed: 16337591]

105. Tasken KA et al. Phosphodiesterase 4D and protein kinase a type II constitute a signaling unit in the centrosomal area. J. Biol. Chem 276, 21999–22002. (2001). [PubMed: 11285255]

106. Pidoux G & Tasken K Specificity and spatial dynamics of protein kinase A signaling organized by A-kinase-anchoring proteins. J. Mol. Endocrinol 44, 271–284, doi:JME-10–0010 [pii] 10.1677/JME-10-0010 [doi] (2010). [PubMed: 20150326]

107. Conti M et al. Cyclic AMP-specific PDE4 phosphodiesterases as critical components of cyclic AMP signaling. J. Biol. Chem 278, 5493–5496 (2003). [PubMed: 12493749]

108. Dodge-Kafka KL et al. The protein kinase A anchoring protein mAKAP coordinates two integrated cAMP effector pathways. Nature 437, 574–578 (2005). [PubMed: 16177794]

109. Krahling AM et al. CRIS-a novel cAMP-binding protein controlling spermiogenesis and the development of flagellar bending. PLoS Genet 9, e1003960, doi:10.1371/journal.pgen.1003960 (2013). [PubMed: 24339785]

110. Schillace RV, Voltz JW, Sim AT, Shenolikar S & Scott JD Multiple interactions within the AKAP220 signaling complex contribute to protein phosphatase 1 regulation. J Biol Chem 276, 12128–12134, doi:10.1074/jbc.M010398200 [doi] M010398200 [pii] (2001). [PubMed: 11152471]
111. Bajpai M et al. AKAP3 selectively binds PDE4A isoforms in bovine spermatozoa. Biol Reprod 74, 109–118, doi:10.1095/biolreprod.105.043588 (2006). [PubMed: 16177223]
112. Rahman N, Buck J & Levin LR pH sensing via bicarbonate-regulated "soluble" adenylyl cyclase (sAC). Front Physiol 4, 343, doi:10.3389/fphys.2013.00343 (2013). [PubMed: 24324443]
113. Carnegie GK & Burmeister BT A-Kinase Anchoring Proteins That Regulate Cardiac Remodeling. Journal of Cardiovascular Pharmacology 58, 451–458, doi:10.1097/fjc.0b013e31821c0220 (2011). [PubMed: 22075671]
114. Zhang J, Bal M, Bierbower S, Zaika O & Shapiro MS AKAP79/150 signal complexes in G-protein modulation of neuronal ion channels. J Neurosci 31, 7199–7211, doi:10.1523/JNEUROSCI.4446-10.2011 (2011). [PubMed: 21562284]
115. Soderling SH et al. The WRP component of the WAVE-1 complex attenuates Rac-mediated signalling. Nature Cell Biol. 4, 970–975. (2002). [PubMed: 12447388]
116. Soderling SH et al. A WAVE-1 and WRP signaling complex regulates spine density, synaptic plasticity, and memory. J. Neurosci 27, 355–365 (2007). [PubMed: 17215396]
117. Soderling SH et al. Loss of WAVE-1 causes sensorimotor retardation and reduced learning and memory in mice. Proc. Natl. Acad. Sci. U.S.A 100, 1723–1728 (2003). [PubMed: 12578964]
118. Diviani D, Osman H, Delaunay M & Kaiser S The role of A-kinase anchoring proteins in cardiac oxidative stress. Biochemical Society Transactions 47, 1341–1353, doi:10.1042/bst20190228 (2019). [PubMed: 31671182]
119. Bers DM Calcium cycling and signaling in cardiac myocytes. Annu Rev Physiol 70, 23–49, doi:10.1146/annurev.physiol.70.113006.100455 (2008). [PubMed: 17988210]
120. Fabiato A Calcium-induced release of calcium from the cardiac sarcoplasmic reticulum. Am J Physiol 245, C1–14, doi:10.1152/ajpcell.1983.245.1.C1 (1983). [PubMed: 6346892]
121. Brini M & Carafoli E Calcium pumps in health and disease. Physiol Rev 89, 1341–1378, doi:10.1152/physrev.00032.2008 (2009). [PubMed: 19789383]
122. Anderson DM et al. Widespread control of calcium signaling by a family of SERCA-inhibiting micropeptides. Sci Signal 9, ra119, doi:10.1126/scisignal.aaj1460 (2016). [PubMed: 27923914]
123. Vega AL, Yuan C, Votaw VS & Santana LF Dynamic Changes in Sarcoplasmic Reticulum Structure in Ventricular Myocytes. Journal of Biomedicine and Biotechnology 2011, 1–14, doi:10.1155/2011/382586 (2011).
124. Lou Q, Janardhan A & Efimov IR in Advances in Experimental Medicine and Biology 1145–1174 (Springer Netherlands, 2012).
125. Colombe A-S & Pidoux G Cardiac cAMP-PKA Signaling Compartmentalization in Myocardial Infarction. Cells 10, 922, doi:10.3390/cells10040922 (2021). [PubMed: 33923648]
126. Hulme JT, Westenbroek RE, Scheuer T & Catterall WA Phosphorylation of serine 1928 in the distal C-terminal domain of cardiac Cav1.2 channels during β-adrenergic regulation. Proceedings of the National Academy of Sciences 103, 16574–16579, doi:doi:10.1073/pnas.0607294103 (2006).
127. Tada M, Kirchberger MA & Katz AM Regulation of calcium transport in cardiac sarcoplasmic reticulum by cyclic AMP-dependent protein kinase. Recent Adv Stud Cardiac Struct Metab 9, 225–239 (1976). [PubMed: 176697]
128. Ha KN et al. Lethal Arg9Cys phospholamban mutation hinders Ca2+-ATPase regulation and phosphorylation by protein kinase A. Proceedings of the National Academy of Sciences 108, 2735–2740, doi:10.1073/pnas.1013987108 (2011).
129. Marx SO et al. PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. Cell 101, 365–376 (2000). [PubMed: 10830164]
130. Gao T et al. cAMP-dependent regulation of cardiac L-type Ca2+ channels requires membrane targeting of PKA and phosphorylation of channel subunits. Neuron 19, 185–196 (1997). [PubMed: 9247274]

131. McConnachie G, Langeberg LK & Scott JD AKAP signaling complexes: getting to the heart of the matter. Trends Mol Med 12, 317–323 (2006). [PubMed: 16809066]

132. Nichols CB et al. Sympathetic Stimulation of Adult Cardiomyocytes Requires Association of AKAP5 With a Subpopulation of L-Type Calcium Channels. Circulation Research 107, 747–756, doi:10.1161/circresaha.109.216127 (2010). [PubMed: 20671242]

133. Catterall WA Structure and Regulation of Voltage-Gated Ca2+ Channels. Annual Review of Cell and Developmental Biology 16, 521–555, doi:10.1146/annurev.cellbio.16.1.521 (2000).

134. Navedo MF & Santana LF CaV1.2 sparklets in heart and vascular smooth muscle. Journal of Molecular and Cellular Cardiology 58, 67–76, doi:10.1016/j.yjmcc.2012.11.018 (2013). [PubMed: 23220157]

135. Li X, Nooh MM & Bahouth SW Role of AKAP79/150 Protein in β1-Adrenergic Receptor Trafficking and Signaling in Mammalian Cells. Journal of Biological Chemistry 288, 33797–33812, doi:10.1074/jbc.m113.470559 (2013). [PubMed: 24121510]

136. Fraser ID et al. A novel lipid-anchored A-kinase Anchoring Protein facilitates cAMP- responsive membrane events. Embo J 17, 2261–2272 (1998). [PubMed: 9545239]

137. Gray PC, Tibbs VC, Catterall WA & Murphy BJ Identification of a 15-kDa cAMP-dependent protein kinase-anchoring protein associated with skeletal muscle L-type calcium channels. J. Biol. Chem 272, 6297–6302 (1997). [PubMed: 9045648]

138. Smith FD et al. Single nucleotide polymorphisms alter kinase anchoring and the subcellular targeting of A-kinase anchoring proteins. Proceedings of the National Academy of Sciences 115, E11465–E11474, doi:10.1073/pnas.1816614115 (2018).

139. Trotter KW et al. Alternative splicing regulates the subcellular localization of A-kinase anchoring protein 18 isoforms. J. Cell Biol 147, 1481–1492 (1999). [PubMed: 10613906]

140. J Johnson KR, Nicodemus-Johnson J, Carnegie GK & Danziger RS Molecular evolution of A-kinase anchoring protein (AKAP)-7: implications in comparative PKA compartmentalization. BMC Evol Biol 12, 125, doi:10.1186/1471-2148-12-125 (2012). [PubMed: 22834419]

141. Henn V et al. Identification of a novel A-kinase anchoring protein 18 isoform and evidence for its role in the vasopressin-induced aquaporin-2 shuttle in renal principal cells. J Biol Chem 279, 26654–26665, doi:10.1074/jbc.M312835200 (2004). [PubMed: 15037626]

142. Hulme JT, Lin TW-C, Westenbroek RE, Scheuer T & Catterall WA β-Adrenergic regulation requires direct anchoring of PKA to cardiac Cav1.2 channels via a leucine zipper interaction with A kinase-anchoring protein 15. Proceedings of the National Academy of Sciences 100, 13093–13098, doi:10.1073/pnas.2135335100 (2003).

143. Hulme JT, Ahn M, Hauschka SD, Scheuer T & Catterall WA A novel leucine zipper targets AKAP15 and cyclic AMP-dependent protein kinase to the C terminus of the skeletal muscle Ca(2+) channel and modulates its function. J. Biol. Chem 277, 4079–4087 (2002). [PubMed: 11733497]

144. Cserne Szappanos H et al. Identification of a novel cAMP dependent protein kinase A phosphorylation site on the human cardiac calcium channel. Scientific Reports 7, doi:10.1038/s41598-017-15087-0 (2017).

145. Hofmann F, Flockerzi V, Kahl S & Wegener JW L-Type CaV1.2 Calcium Channels: From In Vitro Findings to In Vivo Function. Physiological Reviews 94, 303–326, doi:10.1152/physrev.00016.2013 (2014). [PubMed: 24382889]

146. Kumari N, Gaur H & Bhargava A Cardiac voltage gated calcium channels and their regulation by β-adrenergic signaling. Life Sciences 194, 139–149, doi:10.1016/j.lfs.2017.12.033 (2018). [PubMed: 29288765]

147. Fuller MD, Emrick MA, Sadilek M, Scheuer T & Catterall WA Molecular Mechanism of Calcium Channel Regulation in the Fight-or-Flight Response. Science Signaling 3, ra70–ra70, doi:doi:10.1126/scisignal.2001152 (2010). [PubMed: 20876873]

148. Fu Y, Westenbroek RE, Scheuer T & Catterall WA Phosphorylation sites required for regulation of cardiac calcium channels in the fight-or-flight response. Proceedings of the National Academy of Sciences 110, 19621–19626, doi:doi:10.1073/pnas.1319421110 (2013).

149. Fu Y, Westenbroek RE, Scheuer T & Catterall WA Basal and β;-adrenergic regulation of the cardiac calcium channel Cav1.2 requires phosphorylation of serine 1700. Proceedings of the National Academy of Sciences 111, 16598–16603, doi:doi:10.1073/pnas.1419129111 (2014).

150. Weiss S, Oz S, Benmocha A & Dascal N Regulation of Cardiac L-Type Ca2+ Channel Cav1.2 Via the β-Adrenergic-cAMP-Protein Kinase A Pathway. Circulation Research 113, 617–631, doi:10.1161/circresaha.113.301781 (2013). [PubMed: 23948586]

151. Liu G et al. Mechanism of adrenergic CaV1.2 stimulation revealed by proximity proteomics. Nature 577, 695–700, doi:10.1038/s41586-020-1947-z (2020) [PubMed: 31969708]

152. Lygren B et al. AKAP complex regulates Ca2+ re-uptake into heart sarcoplasmic reticulum. EMBO Rep 8, 1061–1067 (2007). [PubMed: 17901878]

153. Carlson CR et al. AKAP18δ Anchors and Regulates CaMKII Activity at Phospholamban-SERCA2 and RYR. Circulation Research 130, 27–44, doi:10.1161/circresaha.120.317976 (2022). [PubMed: 34814703]

154. Gonano LA & Vila Petroff M AKAP18δ Puts CaMKII in the Right Place at the Right Time: Implications for Cardiac Ca2+ Handling. Circulation Research 130, 45–47, doi:10.1161/circresaha.121.320537 (2022). [PubMed: 34995136]

155. Nauert JB, Klauck TM, Langeberg LK & Scott JD Gravin, an autoantigen recognized by serum from myasthenia gravis patients, is a kinase scaffold protein. Curr. Biol 7, 52–62. (1997). [PubMed: 9000000]

156. Shih M, Lin F, Scott JD, Wang HY & Malbon CC Dynamic complexes of beta2-adrenergic receptors with protein kinases and phosphatases and the role of gravin. J. Biol. Chem 274, 1588–1595 (1999). [PubMed: 9880537]

157. Li Z et al. Force development and intracellular Ca2+ in intact cardiac muscles from gravin mutant mice. European Journal of Pharmacology 807, 117–126, doi:10.1016/j.ejphar.2017.04.020 (2017). [PubMed: 28428008]

158. Guillory AN et al. Enhanced Cardiac Function in Gravin Mutant Mice Involves Alterations in the β-Adrenergic Receptor Signaling Cascade. PLoS ONE 8, e74784, doi:10.1371/journal.pone.0074784 (2013). [PubMed: 24058627]

159. Chen L, Kurokawa J & Kass RS Phosphorylation of the A-kinase-anchoring protein Yotiao contributes to protein kinase A regulation of a heart potassium channel. J Biol Chem 280, 31347–31352 (2005). [PubMed: 16002409]

160. Wakatsuki T, Schlessinger J & Elson EL The biochemical response of the heart to hypertension and exercise. Trends Biochem Sci 29, 609–617, doi:10.1016/j.tibs.2004.09.002 (2004). [PubMed: 15501680]

161. Carnegie GK et al. AKAP-Lbc mobilizes a cardiac hypertrophy signaling pathway. Mol Cell 32, 169–179 (2008). [PubMed: 18951085]

162. Appert-Collin A, Cotecchia S, Nenniger-Tosato M, Pedrazzini T & Diviani D The A-kinase anchoring protein (AKAP)-Lbc-signaling complex mediates alpha1 adrenergic receptor-induced cardiomyocyte hypertrophy. Proc. Natl. Acad. Sci. U.S.A 104, 10140–10145 (2007). [PubMed: 17537920]

163. Diviani D, Soderling J & Scott JD AKAP-Lbc anchors protein kinase A and nucleates Galpha 12-selective Rho-mediated stress fiber formation. J. Biol. Chem 276, 44247–44257. (2001). [PubMed: 11546812]

164. Cariolato L, Cavin S & Diviani D A-kinase anchoring protein (AKAP)-Lbc anchors a PKN-based signaling complex involved in alpha1-adrenergic receptor-induced p38 activation. J Biol Chem 286, 7925–7937, doi:10.1074/jbc.M110.185645 (2011). [PubMed: 21224381]

165. Takimoto E & Kass DA Role of Oxidative Stress in Cardiac Hypertrophy and Remodeling. Hypertension 49, 241–248, doi:10.1161/01.hyp.0000254415.31362.a7 (2007). [PubMed: 17190878]

166. Ramachandra CJA et al. Oxidative stress in cardiac hypertrophy: From molecular mechanisms to novel therapeutic targets. Free Radical Biology and Medicine 166, 297–312, doi:10.1016/j.freeradbiomed.2021.02.040 (2021). [PubMed: 33675957]

167. Van Der Pol A, Van Gilst WH, Voors AA & Van Der Meer P Treating oxidative stress in heart failure: past, present and future. European Journal of Heart Failure 21, 425–435, doi:10.1002/ejhf.1320 (2019). [PubMed: 30338885]
168. Taglieri DM et al. The C-terminus of the long AKAP13 isoform (AKAP-Lbc) is critical for development of compensatory cardiac hypertrophy. J Mol Cell Cardiol 66, 27–40, doi:10.1016/j.yjmcc.2013.10.010 (2014). [PubMed: 24161911]
169. Czachor A, Failla A, Lockey R & Kolliputi N Pivotal role of AKAP121 in mitochondrial physiology. American Journal of Physiology-Cell Physiology 310, C625–C628, doi:10.1152/ajpcell.00292.2015 (2016). [PubMed: 26825124]
170. Gabrovsek L et al. A-kinase-anchoring protein 1 (dAKAP1)-based signaling complexes coordinate local protein synthesis at the mitochondrial surface. Journal of Biological Chemistry 295, 10749–10765, doi:10.1074/jbc.ra120.013454 (2020). [PubMed: 32482893]
171. Abrenica B, AlShaaban M & Czubryt MP The A-kinase anchor protein AKAP121 is a negative regulator of cardiomyocyte hypertrophy. J Mol Cell Cardiol 46, 674–681, doi:10.1016/j.yjmcc.2009.01.018 (2009). [PubMed: 19358331]
172. Perrino C et al. AKAP121 downregulation impairs protective cAMP signals, promotes mitochondrial dysfunction, and increases oxidative stress. Cardiovascular Research 88, 101–110, doi:10.1093/cvr/cvq155 (2010). [PubMed: 20511238]
173. Lin RY, Moss SB & Rubin CS Characterization of S-AKAP84, a novel developmentally regulated A kinase anchor protein of male germ cells. J Biol Chem 270, 27804–27811, doi:10.1074/jbc.270.46.27804 (1995). [PubMed: 7499250]
174. Kim H et al. Fine-tuning of Drp1/Fis1 availability by AKAP121/Siah2 regulates mitochondrial adaptation to hypoxia. Mol Cell 44, 532–544, oi:10.1016/j.molcel.2011.08.045 (2011). [PubMed: 22099302]
175. McCartney S, Little BM, Langeberg LK & Scott JD Cloning and characterization of A-kinase anchor protein 100 (AKAP100): a protein that targets A-kinase to the sarcoplasmic reticulum. J. Biol. Chem 270, 9327–9333 (1995). [PubMed: 7721854]
176. Pare GC, Easlick JL, Mislow JM, McNally EM & Kapiloff MS Nesprin-1alpha contributes to the targeting of mAKAP to the cardiac myocyte nuclear envelope. Exp Cell Res 303, 388–399 (2005). [PubMed: 15652351]
177. Kapiloff MS, Schillace RV, Westphal AM & Scott JD mAKAP: an A-kinase anchoring protein targeted to the nuclear membrane of differentiated myocytes. J. Cell Sci 112, 2725–2736 (1999). [PubMed: 10413680]
178. Kapiloff MS, Jackson N & Airhart N mAKAP and the ryanodine receptor are part of a multi-component signaling complex on the cardiomyocyte nuclear envelope. J Cell Sci 114, 3167–3176. (2001). [PubMed: 11590243]
179. Passariello CL, Li J, Dodge-Kafka K & Kapiloff MS mAKAP—A Master Scaffold for Cardiac Remodeling. Journal of Cardiovascular Pharmacology 65, 218–225, doi:10.1097/fjc.0000000000000206 (2015). [PubMed: 25551320]
180. Pare GC et al. The mAKAP complex participates in the induction of cardiac myocyte hypertrophy by adrenergic receptor signaling. J Cell Sci 118, 5637–5646 (2005). [PubMed: 16306226]
181. Ruehr ML et al. Targeting of protein kinase A by muscle A kinase-anchoring protein (mAKAP) regulates phosphorylation and function of the skeletal muscle ryanodine receptor. J Biol Chem 278, 24831–24836 (2003). [PubMed: 12709444]
182. Paruchuri S & Thodeti CK Form follows function: polymorphisms in mAKAP alter cardiac cAMP/PKA signaling. American Journal of Physiology-Heart and Circulatory Physiology 315, H626–H628, doi:10.1152/ajpheart.00248.2018 (2018). [PubMed: 29727216]
183. Kritzer MD et al. The scaffold protein muscle A-kinase anchoring protein beta orchestrates cardiac myocyte hypertrophic signaling required for the development of heart failure. Circ Heart Fail 7, 663–672, doi:10.1161/circheartfailure.114.001266 (2014). [PubMed: 24812305]
184. Li J et al. The mAKAPbeta scaffold regulates cardiac myocyte hypertrophy via recruitment of activated calcineurin. J Mol Cell Cardiol 48, 387–394, doi:10.1016/j.yjmcc.2009.10.023 (2010). [PubMed: 19883655]

185. Li J, Vargas MAX, Kapiloff MS & Dodge-Kafka KL Regulation of MEF2 transcriptional activity by calcineurin/mAKAP complexes. Experimental Cell Research 319, 447–454, doi:10.1016/j.yexcr.2012.12.016 (2013). [PubMed: 23261540]

186. Zhang L et al. Phospholipase Cε Hydrolyzes Perinuclear Phosphatidylinositol 4-Phosphate to Regulate Cardiac Hypertrophy. Cell 153, 216–227, doi:10.1016/j.cell.2013.02.047 (2013). [PubMed: 23540699]

187. Wong W, Goehring AS, Kapiloff MS, Langeberg LK & Scott JD mAKAP compartmentalizes oxygen-dependent control of HIF-1alpha. Sci Signal 1, ra18, doi:1/51/ra18 [pii] 10.1126/scisignal.2000026 (2008). [PubMed: 19109240]

188. Neumann SA et al. AKAP10 (I646V) functional polymorphism predicts heart rate and heart rate variability in apparently healthy, middle-aged European-Americans. Psychophysiology 46, 466–472 (2009). [PubMed: 19496216]

189. Bucko PJ et al. Subcellular drug targeting illuminates local kinase action. Elife 8, doi:10.7554/eLife.52220 (2019).

190. Bucko PJ et al. Gravin-associated kinase signaling networks coordinate gamma-tubulin organization at mitotic spindle poles. J Biol Chem 295, 13784–13797, doi:10.1074/jbc.RA120.014791 (2020). [PubMed: 32732289]

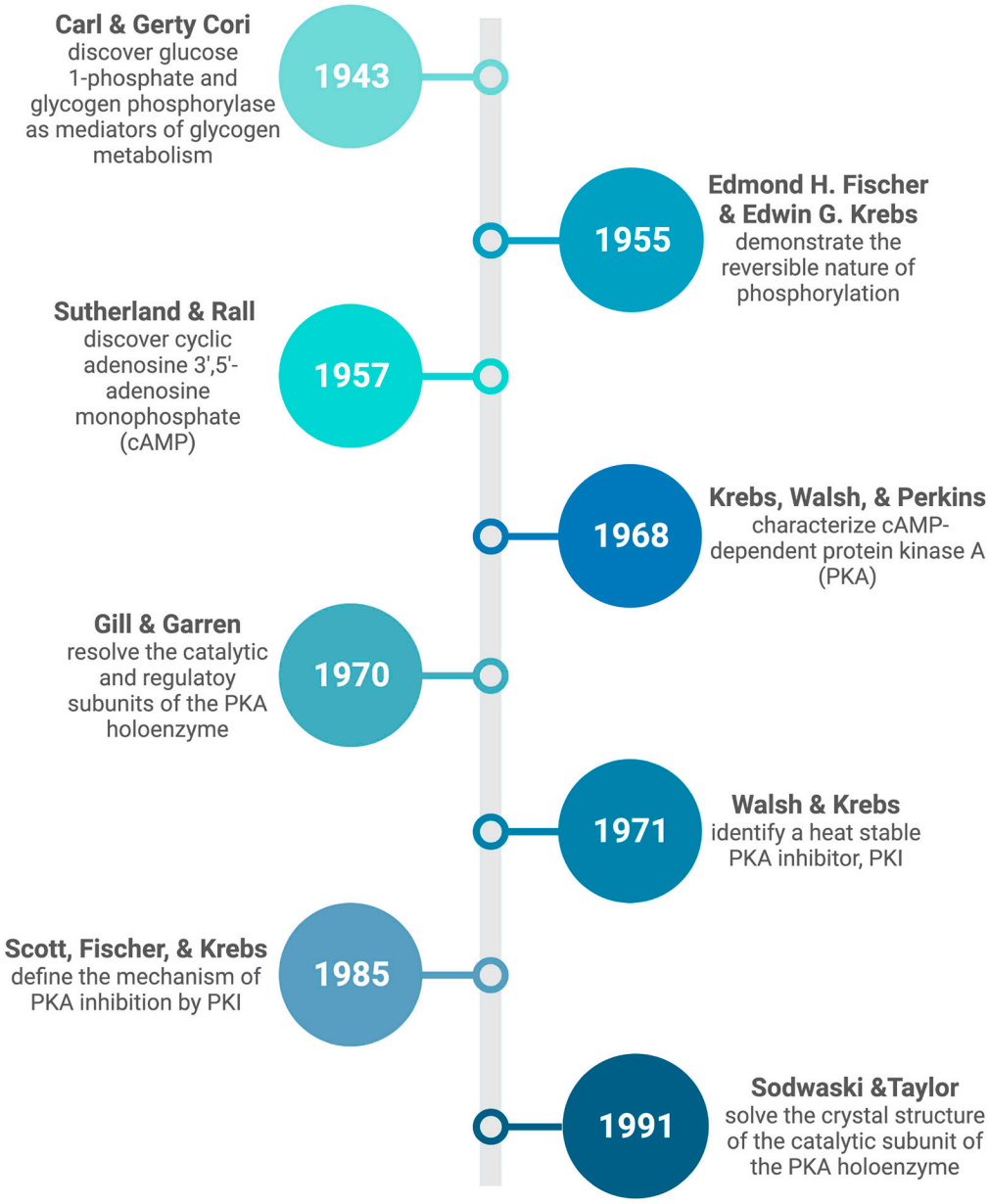

Figure 1: Timeline of key discoveries pertaining to cAMP responsive phosphorylation.
(Figure created in Biorender)

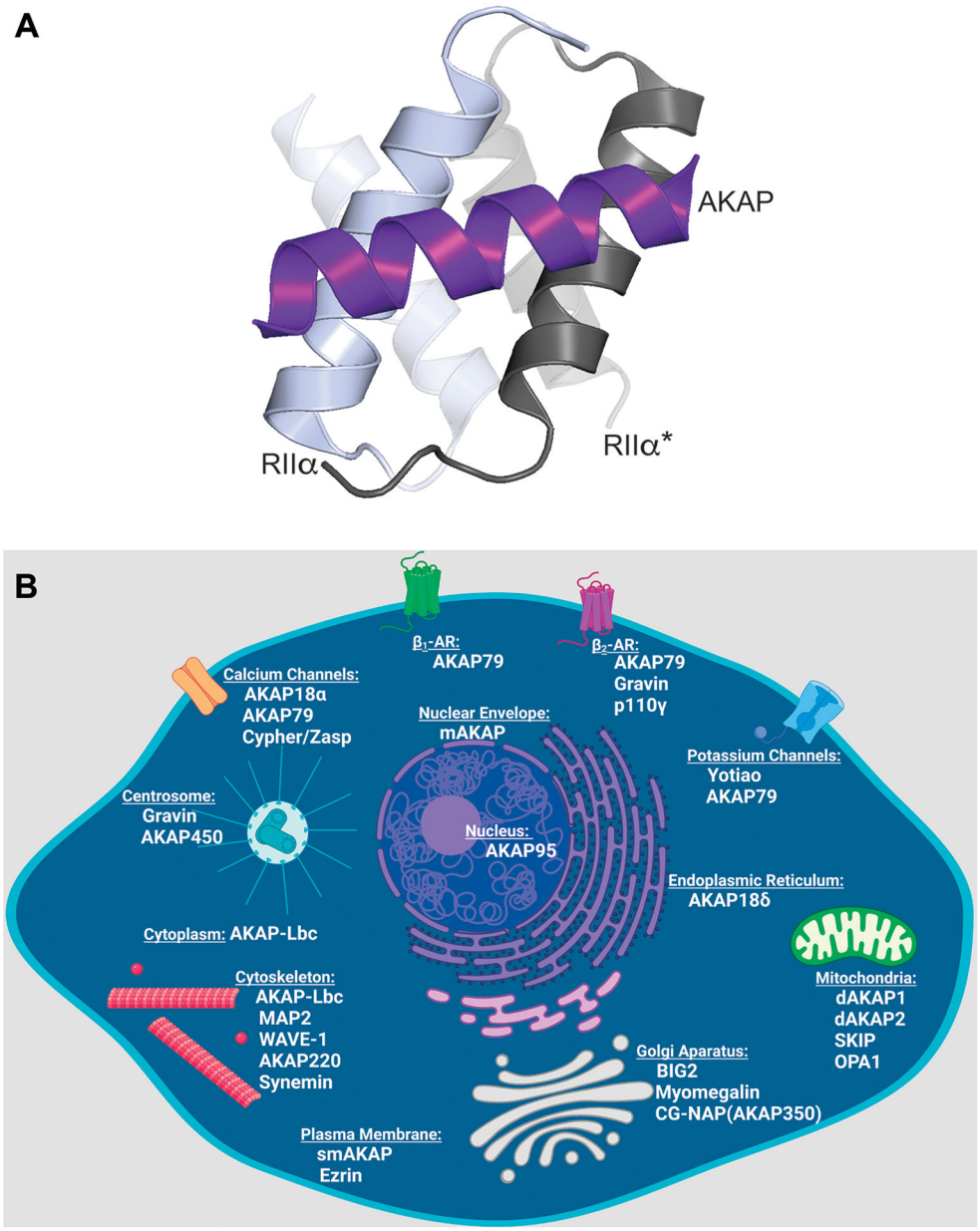

Figure 2: AKAPs localize PKA to a variety of intracellular locations.

A) Structural model of the AKAP amphipathic helix (purple) in complex with the docking and dimerization domain of RIIα. Both protomers of the RII dimer are depicted in shades of grey. Model made using PYMOL 2.5 and structures from the protein database with accession number 2izx. B) Schematic of a cell indicating the locations of compartment-specific AKAPs (schematic created in Biorender).

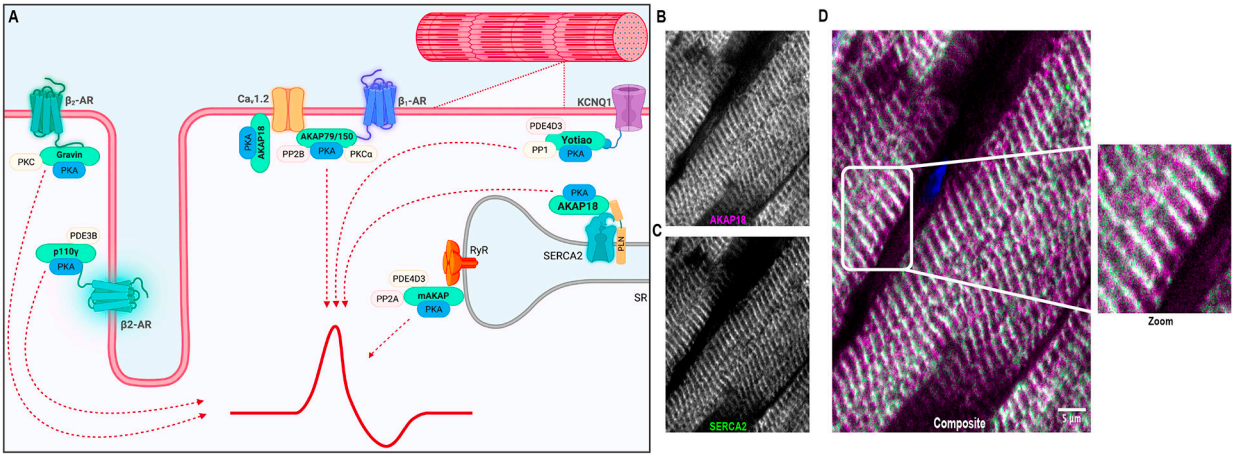

Figure 3: AKAPs coordinate excitation-contraction coupling.

A) Schematic (created in Biorender) depicting AKAP regulation of channel activity, ion flow, contraction, and relaxation of cells. B-D) Confocal images depicting the localization of AKAP18 with SERCA2 ATPase at the Z bands (see zoom panel) within normal human heart (paraffin embedded tissue sections).

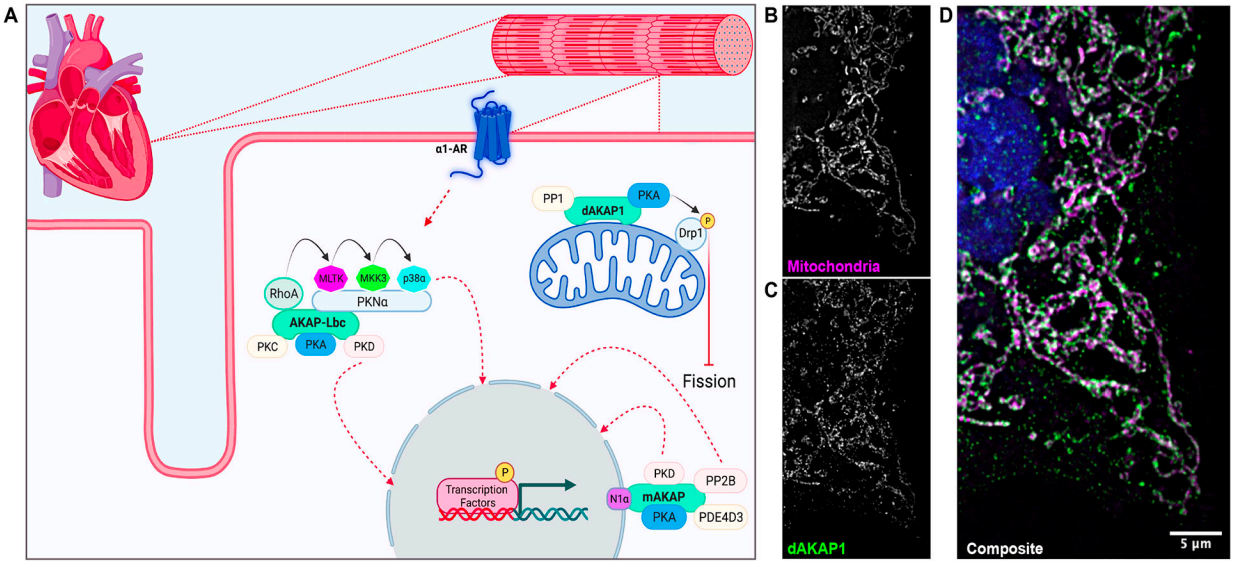

Figure 4: AKAPs mediate the heart's hypertrophic response.

A) Schematic (created in Biorender) depicting AKAP regulation of hypertrophic gene expression, reactive oxygen species generation, and mitochondrial morphology. B-D) Three-dimensional structured illumination microscopy shows the localization of dAKAP1 to the mitochondria of U2OS cells.