A-Kinase Anchoring Proteins
Getting to the Heart of the Matter

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The heart is a sophisticated organ that continuously pumps blood to ensure that oxygen and nutrients reach the brain, other organs, and peripheral tissue. The right side of the heart pumps blood to the lungs, where oxygen is taken up and carbon dioxide is removed. The left side of the heart then pumps blood to the rest of the body, where oxygen and nutrients are delivered to tissues. This cycle is sustained by the repeated contraction of cardiomyocytes, specialized muscle cells that are designed to contract and respond rapidly to physiological stimuli.

Normally, contraction of atrial and ventricular myocytes is activated by action potentials that originate in the sinoatrial node in the wall of the right atrium, often referred to as the pacemaker of the heart. Coupling of this electric signal to contraction (EC coupling) in cardiac myocytes is initiated with Ca^{2+} influx through L-type Ca^{2+} channels, which activates intracellular Ca^{2+} release via ryanodine receptors located in the sarcoplasmic reticulum (SR) and thus induces a global increase in $[Ca^{2+}]_i$ that triggers contraction.[1,2] The rate at which the sinoatrial node myocytes fire action potentials is modulated by 2 opposing nervous systems. The sympathetic nervous system uses the catecholamine hormones noradrenaline and adrenaline to increase the force and rate of atrial and ventricular contraction. In contrast, the parasympathetic nervous system releases the neurotransmitter acetylcholine to reduce action potentials from the sinoatrial node. Together, these neural systems ensure that cardiac output is matched to the physiological needs of the organism, a process that is often termed "stimulus-response coupling."

Although numerous signal-transduction cascades are operational in cardiomyocytes, G-protein–coupled receptor–signaling pathways play a prominent role. Agonists such as noradrenaline, adrenaline, angiotensin II, and endothelin-1 promote the interaction of their respective receptors with a G-protein heterotrimer comprising α-, β-, and γ-subunits.[3] This transient interaction promotes exchange of GTP for GDP on the Gα subunit and thereby activates or inhibits effector molecules and ion channels. Effector molecules, which include enzymes such as adenylate adenylyl cyclases and phospholipases, regulate the production of second messengers.[3]

Second messengers are small molecules that are mobilized or generated in response to extracellular stimuli. In the heart, Ca^{2+} and cAMP are the second messengers most frequently used by cardiac signaling pathways. They act at defined intracellular sites to initiate signaling events[4] that control excitability, contraction, and gene expression. Occupancy of β-adrenergic receptors engages the cAMP-signaling pathway to activate protein kinases, guanine nucleotide exchange factors, and ion channels.[5,6] Combinations of these cAMP-responsive enzymes modulate cardiac contraction force (inotropy), heart rate (chronotropy), and muscle relaxation (lusitropy).[7] Not surprisingly, there is a significant degree of cross talk between the Ca^{2+}-and cAMP-signaling pathways. This is achieved in part because Ca^{2+}-and cAMP-responsive proteins are often brought together in multiprotein complexes.[8] The goal of the present review is to highlight recent progress on our understanding of how anchored signaling complexes influence cardiomyocyte physiology. We will focus on cardiomyocyte A-kinase anchoring proteins (AKAPs), a family of scaffolding proteins that compartmentalize cAMP- and Ca^{2+}-responsive enzymes in proximity to preferred substrates such as ion channels, contractile proteins, Ca^{2+} pumps, and the transcriptional machinery.

A-Kinase Anchoring Proteins

Seminal experiments in the 1950s demonstrated that hormone-mediated stimulation of cAMP synthesis by different agonists induced distinctive physiological outputs, even within the same tissue.[9] Thirty years later, it was shown that adrenergic stimulation selectively activated a pool of the cAMP-dependent protein kinase (PKA) associated with the particulate fraction of cardiomyocytes, whereas prostaglandin E_1 stimulation activated a cytosolic pool of PKA in the same cells to induce different physiological effects.[10] As more investigators pondered this concept, it became clear that cAMP was not distributed uniformly throughout the cell.[11–14] This led to the hypothesis that the opposing actions of adenylyl cyclases and phosphodiesterases (PDEs) generate intracellular gradients and compartmentalized pools of cAMP.[15,16] More recently, a genetically encoded fluorescence-based biosensor was used to measure microdomains of

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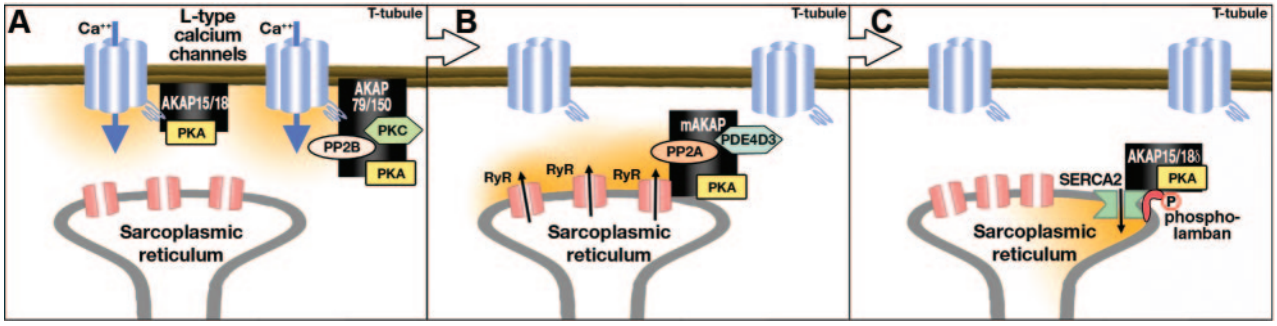

Figure 1. Schematic of the role of AKAPs in EC coupling in cardiomyocytes. A, Phase 1 of EC coupling: AKAP79/150 and the short forms of AKAP15/18 (α and β) maintain signaling complexes tethered to L-type calcium channels to enable calcium influx. B, Phase 2 of EC coupling: RyRs at the SR are bound to the mAKAP signaling complex as it responds to the increased cytosolic Ca^{2+}. mAKAP clusters PKA, PDE4D3, and PP2A to regulate the phosphorylation status of the RyR and the resultant Ca^{2+} release from the SR. C, Phase 3 of EC coupling: Active transport of calcium back into the SR via SERCA2 is regulated by phospholamban. The AKAP15/18δ long isoform brings PKA into complex with phospholamban and SERC2, where it can augment the phosphorylation of phospholamban and the reuptake of calcium into the SR.

cAMP along sarcomeric Z lines in cardiomyocytes in response to adrenergic stimulation.[17]

Although it was accepted that cAMP levels were distributed unevenly within the cell, it remained unclear exactly how PKA was retained within different subcellular compartments.[18] Soon, a variety of protein-protein interaction screens identified a set of molecules that interact with the R subunits of the PKA holoenzyme (a tetramer consisting of a regulatory [R] subunit dimer and 2 catalytic [C] subunits).[19,20] These proteins were named AKAPs in recognition of their ability to anchor PKA at defined subcellular locations.[21] A principal function of AKAPs is to position PKA and other cAMP-responsive enzymes in proximity to their substrates.[6,22,23] However, AKAPs also serve to cluster regulatory enzymes with the cAMP synthesis machinery.[24,25] For example, interactions between AKAP79/150 and the adenylyl cyclase isoforms ACV or ACVI facilitate the preferential PKA phosphorylation of the enzyme to inhibit cAMP synthesis. Such a PKA-AKAP79/150-ACV complex forms a negative-feedback loop that generates pulses of cAMP production.[24] This configuration may be particularly relevant in the pacemaker cells, because studies in ACV-knockout mice suggest that this adenylyl cyclase isoform participates in sympathetic and parasympathetic regulation of cardiac contractility.[26,27]

Functional analysis of AKAP action often takes advantage of reagents that can displace PKA from anchoring proteins. Detailed biochemical analyses have demonstrated that R-subunit dimerization is necessary for PKA interaction with AKAPs and that each anchoring protein contains a reciprocal binding sequence of 14 to 18 amino acids that forms an amphipathic helix.[28,29] One of these proteins, initially called Ht31 but now known as AKAP-Lbc, contains an 18–amino acid sequence that can be used as a peptide disruptor of RII-AKAP interactions inside cells.[19] The utility of Ht31 peptide as a universal PKA-anchoring disruptor was initially demonstrated on perfusion into cultured hippocampal neurons to disrupt the location of PKA in relation to a key substrate, the AMPA-type glutamate receptor.[30] Later, it was shown that perfusion of Ht31 peptide into cardiomyocytes uncoupled cAMP-dependent regulation of the L-type calcium channel.[31] More recently, adenoviral gene transfer of Ht31 analogs into rat hearts has suggested that anchored pools of PKA contribute to ß-adrenergic stimulation of cardiomyocyte contractility.[32,33] Mislocalization of PKA alters the phosphorylation of key proteins that participate in this process, such as L-type calcium channels, the ryanodine receptors, phospholamban, and myofibrillar troponin I.[34,35] Calcium imaging and echocardiogram analyses have concluded that disruption of PKA anchoring (1) affects cardiac contractility as measured by changes in the rate of calcium transients and (2) increases the left ventricular ejection fraction and stroke volume.[33] These studies provide a compelling rationale for more mechanistic studies to assess the contribution of individual AKAP complexes in the regulation of different aspects of cardiac function under normal and pathophysiological conditions.

AKAPs Signal Cardiac Contractility

As noted above, EC coupling is the process whereby an action potential triggers a myocyte to contract. This involves a transient rise in intracellular calcium that drives contraction (reviewed by Bers[2]). From a signaling perspective, EC coupling can be considered to occur in 3 phases (Figures 1A through 1C). Phase 1 is initiated by brief openings of voltage-gated L-type Ca^{2+} channels. Small amounts of Ca^{2+} enter specialized regions of the ventricular myocyte where the junctional SR is close to the sarcolemma.[36–38] In phase 2, this localized Ca^{2+} influx triggers the synchronous activation of multiple ryanodine-sensitive Ca^{2+} channels (RyRs) in the SR to produce a global Ca^{2+} transient.[39,40] The concomitant activation of Ca^{2+}-responsive contractile proteins such as cardiac troponin C initiates contraction. Phase 3 requires termination of SR Ca^{2+} release and the transport of Ca^{2+} back into the SR through the ATP-dependent Ca^{2+} pump SERCA2 (sarcoplasmic/endoplasmic reticulum Ca^{2+} pump 2), which decreases $[Ca^{2+}]_i$ and begins myocyte relaxation. Recent evidence suggests that distinct AKAP complexes contribute to each phase of EC coupling by optimizing the phosphorylation of ion channels and contractile proteins.

The junction between the sarcolemma and the SR is decorated with local Ca^{2+} signaling complexes that contain between 10 and 25 L-type Ca^{2+} channels and approximately 100 to 200 RyRs.[2] β-adrenergic agonists stimulate PKA to

increase the amplitude of L-type Ca^{2+} currents to favor Ca^{2+} influx. The AKAP79/150 family of anchoring proteins (human AKAP79, bovine AKAP75, and murine AKAP150) facilitates this process by directing the phosphorylation of L-type Ca^{2+} channel subunits (Figure 1A).[41,42] Biochemical and electrophysiological studies initially showed that expression of recombinant AKAP79 enhanced the cAMP-dependent stimulation of L-type Cav1.2 currents.[43] AKAP79/150 also associates with the calcium/calmodulin-dependent phosphatase PP2B and a variety of calcium/phospholipid-dependent protein kinase (PKC) isoforms.[44–46] These additional AKAP79/150 binding partners are important in other aspects of cardiac myocyte function.[47]

Recent studies suggest that AKAP79/150 has multiple regulatory roles in the cardiovascular system. For example, AKAP79/150-associated pools of PKCα have been implicated in the induction of persistent Ca^{2+} sparklets, local Ca^{2+} signals produced by recurrent openings of L-type Ca^{2+} channels in arterial myocytes that enhance vascular tone (Figure 1A).[48] Arterial myocytes isolated from AKAP150-knockout mice do not generate persistent Ca^{2+} sparklets. Furthermore, AKAP150$^{-/-}$ mice are naturally hypotensive and do not develop angiotensin II–induced hypertension.[48] Collectively, these results suggest that local modulation of L-type Ca^{2+} channels by AKAP150-targeted pools of PKA, PKCα, and PP2B may control different aspects of Ca^{2+} influx that contribute to cardiac EC coupling, vascular tone, and changes in blood pressure.

Another AKAP also modulates cardiac L-type Ca^{2+} channels. Alternate splicing of the AKAP15/18 gene yields several isoforms that reside in distinct subcellular locations.[49] The α- and β-isoforms of AKAP15/18 are found at the plasma membrane in complex with L-type Ca^{2+} channels.[50,51] Lipid modification of 3 residues in the extreme amino terminus of the anchoring protein is required for association with the inner face of the plasma membrane, whereas a leucine zipper–like motif in the carboxyl terminus interacts with the cytoplasmic domain of the L-type Ca^{2+} channel.[50,52] This arrangement ensures that an anchored pool of PKA is optimally positioned and available to phosphorylate the channel (Figure 1A). Experimental support for this notion has been provided by electrophysiological analysis showing that expression of a targeting-defective mutant of AKAP15/18α that lacks the sites of lipid modification reduces the rate of cAMP-dependent stimulation of L-type Ca^{2+} currents.[50] Complementary studies have shown that peptide-mediated disruption of the AKAP15/18α-channel interaction with a leucine zipper peptide mimetic has similar effects on myocyte L-type Ca^{2+} currents (Figure 1A).[52] A leucine zipper–like motif has also been identified in AKAP79/150 (Figure 1A).[53] Thus, it would appear that cardiac myocytes use AKAP15/18α or AKAP79/150 to modulate the entry of extracellular Ca^{2+} through L-type calcium channels.[54,55] Although both anchoring proteins appear equally adept at coordinating cAMP-signaling events that initiate EC coupling by virtue of their ability to anchor PKA, AKAP79/150 has the capacity to recruit additional binding partners such as PKCs and the phosphatase PP2B into its channel-associated complex.[56,57] In addition, PP2B may interact directly with cardiac L-type Ca^{2+} channels, because phosphatase-binding sites have been mapped to the cytoplasmic regions of the α_1-1.2 subunit of the channel.[58] The formation of these more sophisticated multiprotein signaling complexes that are mediated by AKAP79/150 may permit the more precise transmission of second-messenger signals to this Ca^{2+} channel. Another advantage of the formation of more sophisticated AKAP signaling complexes in proximity to Ca^{2+} channels is that it may permit integration of cAMP and calcium/phospholipid signals at this intracellular locus.

The second phase of EC coupling begins when openings of L-type Ca^{2+} channels cause a local increase of $[Ca^{2+}]_i$ from 100 nmol/L to approximately 10 to 20 μmol/L, which activates nearby RyRs to release Ca^{2+} from the SR (Figure 1B). Planar bilayer work suggests that phosphorylation of the RyR by PKA increases the sensitivity of the channel to Ca^{2+} and accelerates the kinetics of adaptation.[59] In the intact cell, PKA is recruited to the RyR complex by the muscle-selective anchoring protein (mAKAP).[60–63] mAKAP is a multivalent anchoring protein that brings PKA and the cAMP-metabolizing enzyme phosphodiesterase PDE4D3 to the RyR.[64–66] The clustering of a cAMP-metabolizing enzyme with PKA limits the availability of cAMP to ensure that kinase activation is transient (Figure 1B).[64] Furthermore, the phosphorylation state of the RyR is constantly monitored by the mAKAP-associated phosphatase PP2A.[60] Loss of anchored PDE4D3 and hyperactivation of the anchored PKA may correlate with the onset of "leaky" channels found in certain models of exercise-induced cardiac arrhythmias and heart failure.[67–69] However, an equally plausible explanation is that compensatory changes in calcium content of the SR make the RyR leaky during arrhythmias. These latter events could be critical in determining whether abnormal calcium waves and sparks are propagated.[70]

The third phase of EC coupling involves active transport of Ca^{2+} back into the lumen of the SR to initiate myocyte relaxation (Figure 1C). The SERCA2 pump and its modulator protein, phospholamban, control this process.[71–73] Monomeric phospholamban is a 52–amino acid protein that represses SERCA2. However, β-adrenergic stimulation favors PKA phosphorylation of phospholamban. This promotes its pentamerization and the derepression of SERCA2.[72,74,75] Precise regulation of this system is achieved in part because all of the components are organized into a supramolecular complex that consists of the SERCA2, phospholamban, PKA, and a high-molecular-weight isoform of AKAP15/18.[76,77] Elegant biochemical and imaging studies show that disruption of PKA interaction with the AKAP15/18δ isoform interferes with the phosphorylation of phospholamban (Figure 1C). This prevents the release of phospholamban from SERCA2 to blunt Ca^{2+} reuptake and myocyte relaxation.[76] Reversible control of the cAMP response may be provided by an anchored pool of type 4 PDE, which is believed to associate with AKAP15/18δ.[78,79]

AKAP Signaling Under Pathophysiological Conditions

Adverse genetic profiles and unfavorable environmental factors contribute to the origin of many cardiac disorders.

Because AKAPs orchestrate signaling events that modulate cardiac contractility, it appears reasonable that defects in anchoring protein genes or pathophysiological changes in AKAP signaling complexes may underlie certain heart diseases. Several recent reports now support this notion.

Sudden death due to arrhythmia kills more than 400 000 people a year in the United States and many more throughout the world. As a result, there is a concerted international effort to identify genes that regulate heart rhythm. Several independent findings point toward a role for dual-function anchoring proteins (d-AKAP-2) in heart rhythm control. A genetic screen of single-nucleotide polymorphisms in DNA pools of 6500 age-stratified healthy European, Asian, and American individuals detected an amino acid change from Ile to Val at position 646 in d-AKAP-2 (AKAP10).[80] Individuals harboring the d-AKAP-2 646Val variant often exhibited a decrease in the length of the PR interval on ECGs (the time from the onset of atrial depolarization to the beginning of ventricular depolarization). In vitro biochemical analyses of the d-AKAP-2 646Val variant suggested that this amino acid substitution in the PKA-anchoring domain of the protein enhanced its affinity for the type 1 PKA holoenzyme 3-fold.[81] Although a mechanistic connection between these 2 observations remains unclear, d-AKAP-2 mutant mice expressing a truncated form of d-AKAP-2 that are unable to anchor PKA develop cardiac arrhythmias and die prematurely.[82] Furthermore, cultured myocytes isolated from these mice were reported to display an increased contractile response to cholinergic signals.[82]

Long-QT syndrome is a rare congenital heart condition that can result in sudden death as a consequence of exercise- or excitement-induced arrhythmia. This condition occurs because of the delayed repolarization of myocyte membranes. This prolongs the duration of the ventricular action potential and thus is diagnosed as a lengthening of the QT interval. Myocyte repolarization requires the movement of potassium ions out of the cell. Consequently, the most common type of long-QT syndrome (LQT1) is associated with mutations in the KCNQ1 subunit of a potassium channel.[83] The anchoring protein Yotiao associates with a variety of ion channels, including the KCNQ1 subunit responsible for I_{Ks} currents that shape cardiac action potential duration in response to β-adrenergic agonists.[84] The primary function of Yotiao is to facilitate phosphorylation of Ser27 on KCNQ1 to modulate ion channel activity; however, anchored PKA also phosphorylates serine 43 on Yotiao to enhance cAMP-dependent activation of I_{Ks}.[85,86] Inherited mutations in another region of Yotiao (S1570L) that reduce the interaction between KCNQ1 suppress cAMP-induced phosphorylation of the I_{Ks} channel. The functional consequence of the S1570L mutation in mice is delayed repolarization of the ventricular action potential, a recognized symptom of LQT1 (Figure 2A).[87] Taken together, these findings suggest that spatial organization of the cAMP-signaling enzymes by Yotiao is important to orchestrate ion channel activity during myocyte repolarization.[88] More recent evidence suggests that the phosphodiesterase PDE4D3, a negative regulator of anchored PKA, is also present in the Yotiao signaling complex (Figure 2A). Electrophysiological studies have shown that pharmacological inhibition of anchored PDE activity enhances cAMP-dependent stimulation of I_{Ks}.[89] In this context, the recruitment of a PDE4D3 constrains the local availability of cAMP to more precisely regulate the anchored pool of PKA.

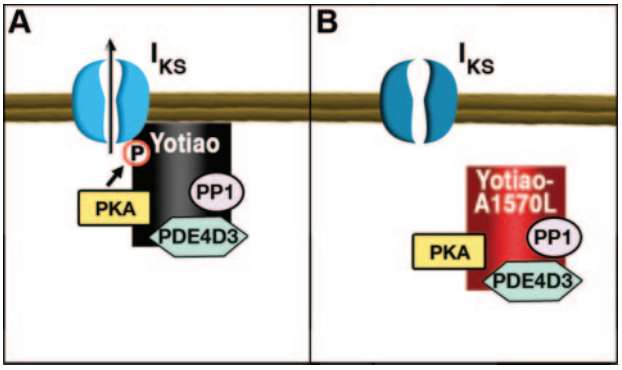

Figure 2. Schematic of Yotiao and I_{Ks} currents. A, In myocytes, Yotiao associates with the KCNQ1 subunit of the I_{Ks} potassium channel. Anchored PKA phosphorylation of Yotiao enhances activation of the channel. B, The S1570L Yotiao mutant has reduced interaction with KCNQ1 and delayed repolarization of ventricular action potential.

Another means to vary the modulation of signaling scaffolds may be to induce time-dependent changes in the composition or amount of AKAP complexes. There have been recent reports suggesting that temporal changes in AKAP complexes can occur, either in response to sudden physiochemical changes in the environment or more gradually as a cellular adaptation to stress. For example, activation of β-adrenergic receptors during periods of cardiac stress initially improves cardiac output by increasing heart rate and contractility; however, chronic mobilization of the same signaling pathway ultimately harms the heart.[90]

Elevated catecholamines in the heart evoke transcriptional activation of the myocyte enhancer factor pathway to induce a cellular response known as pathological myocardial hypertrophy.[91,92] This initiates a developmental gene reprogramming paradigm known as the fetal gene response.[93,94] A clearer picture of how individual steps in this hypertrophic signaling pathway are linked is beginning to emerge. The anchoring protein AKAP-Lbc is one of the genes upregulated in hypertrophic myocytes and functions as a scaffolding protein for PKA and PKC to mediate activation of a third enzyme, protein kinase D (PKD1; Figure 3A).[95] A combination of cellular and live-cell imaging approaches supports a model in which AKAP-Lbc facilitates activation of protein kinase D, which in turn phosphorylates the histone deacetylase HDAC5 to promote its nuclear export. Finally, the concomitant reduction in nuclear histone deacetylase activity favors myocyte enhancer factor-2 transcription and the onset of cardiac hypertrophy.[96] Although most of the study was conducted in neonatal rat cardiomyocytes, further support for this concept was provided by analysis of human heart tissue samples obtained after death from individuals who exhibited hypertrophic cardiomyopathy, which showed that AKAP-Lbc mRNA increased 2±0.5-fold over normal age-matched patient control subjects.[96] Because myocardial hypertrophy is extremely common, affecting 14% to 18% of the general adult population, further investigation of the AKAP-Lbc/

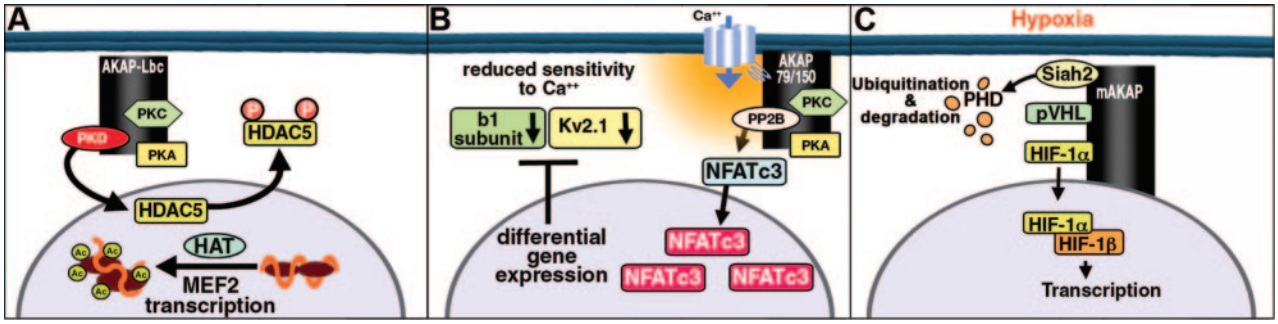

Figure 3. Schematic of the role of AKAPs in transcriptional regulation in the heart. A, An upregulation of AKAP-Lbc facilitates PKD activation and phosphorylation of HDAC5, which leads to transcriptional activation of the myocyte enhancer factor (MEF) pathway and the onset of hypertrophy. B, Calcium-mediated activation of AKAP150-targeted PP2B leads to dephosphorylation of NFATc3 in arterial myocytes. Dephosphorylated NFATc3 accumulates in the nucleus, where it leads to decreased gene expression of channel subunits. C, mAKAP organizes ubiquitin E3 ligases that managed the stability of the transcription factor HIF-1α. During hypoxia, HIF-1α translocated to the nucleus initiates transcription of proangiogenic, metabolic, and antiapoptotic genes that promote cell survival during hypoxia.

PKD/HDAC5 pathway is warranted to establish whether AKAP-Lbc is a valid biomarker for hypertrophic cardiomyopathy.

AKAP79/150 may also be involved in pathophysiological changes of gene expression that occur in vascular smooth muscle during the development of hypertension.[97] In these cells, activation of PKCα induces persistent Ca^{2+} sparklets, producing an increase in local Ca^{2+} influx that activates nearby AKAP150-targeted PP2B. On activation, PP2B dephosphorylates NFATc3, which allows this transcription factor to translocate into the nucleus of arterial myocytes, where it modulates gene expression (Figure 3B). AKAP79/150-associated phosphatase PP2B and NFATc3 activity levels are low in arterial smooth muscle under physiological conditions because of low levels of persistent Ca^{2+} sparklet activity; however, in hypertension, elevated PKCα activity increases persistent Ca^{2+} sparklet activity, thereby increasing PP2B activity and consequently the NFATc3 nuclear import rate, which leads to high nuclear accumulation of this transcription factor. This in turn leads to downregulation of the b1 subunit of the large-conductance, Ca^{2+}-activated K^+ channel and the Kv2.1 channel subunit in arterial myocytes.[98,99] When these findings are considered in light of evidence that abnormalities in the AKAP79/150-associated PKC contribute to the onset of hypertension, it appears reasonable to speculate that an anchored pool of PP2B may work via a distinct mechanism to counteract this process.

Like all organs, the heart needs a constant supply of oxygen-rich blood. A system of arteries and veins supplies the myocardium with oxygen-rich blood and then returns oxygen-depleted blood to the right atrium. As a result, the concentration of cellular oxygen is maintained within a narrow range (termed "normoxia"). A key cellular response to a state of reduced oxygen tension (hypoxia) involves the induction of genes by the transcription factor known as hypoxia-inducible factor 1α (HIF-1α).[100] Under normoxic conditions, HIF-1α is kept low through its ubiquitin-mediated proteasomal degradation. The half-life of HIF-1α under normoxic conditions has been calculated to be approximately 5 minutes.[101] However, if the oxygen supply suddenly drops, myocytes enter a hypoxic state, and the continual destruction of HIF-1α halts instantly (Figure 3C). This allows the protein to form a stable heterodimeric complex with the HIF-1β subunit to initiate transcription of proangiogenic, metabolic, and antiapoptotic genes to promote cell survival in response to a sudden ischemic event.[102–104] Accordingly, the accumulation of HIF-1α is an early marker of myocardial infarction.[105]

Although the molecular mechanisms underlying the destruction or maintenance of HIF-1α are well defined,[106] the subcellular organization of the factors that regulate these processes has not been investigated. It has recently been shown that mAKAP organizes ubiquitin E3 ligases that manage the stability of HIF-1α and optimally position it close to its site of action inside the nucleus.[107] Functional experiments in cardiomyocytes showed that depletion of mAKAP or disruption of its targeting to the perinuclear region altered the stability of HIF-1α and transcriptional activation of genes associated with hypoxia.[107] Compartmentalization of oxygen-sensitive signaling components may influence the fidelity and magnitude of the hypoxic response (Figure 3C). These findings infer a link between hypoxia and hypertrophic signaling pathways. Indeed, mAKAP may provide such a link, because the abundance of mAKAP is increased in response to hypertrophic stimuli.[61] Further support for this notion comes from evidence that mAKAP anchors 2 signaling enzymes that act sequentially to influence cardiomyocyte hypertrophy and the stability of HIF-1α. One of these, the cAMP-responsive guanine nucleotide exchange factor Epac-1, is the upstream element in a signaling pathway that modulates the activity of extracellular signal–regulated kinase 5 (ERK5), a protein kinase that augments the hypertrophic response and influences the stability of HIF-1α.[65,108,109] Thus, certain mAKAP complexes may create cellular microenvironments in which cAMP signals can feed into oxygen-responsive transcriptional activation pathways.

Cardiomyocytes are exquisitely adapted to facilitate rapid changes in heart rate in response to sympathetic and parasympathetic nervous impulses. AKAPs are central to this process because they position protein kinases, phosphatases, and PDEs in proximity to selected substrates. The material discussed in the present article draws attention to the importance of anchored enzyme activity in the spatial and temporal synchronization of persistent intracellular process such as

cardiac contractility. However, recent evidence suggests that the anchoring proteins themselves may play a more active role in the regulation of cardiac contractility than merely functioning as scaffolding proteins. For example, Yotiao binding to I_{Ks} channels is believed to evoke allosteric changes that increase the magnitude of I_{Ks} currents,[88] and interaction with AKAP15/18δ is believed to enhance the phospholamban rate of multimerization.[77] Finally, anchoring proteins such as AKAP-Lbc and mAKAP interface with the protein acetylation and ubiquitination machinery, respectively, to evoke changes in transcriptional activation pathways.[96,107] These latter observations imply that AKAPs not only contribute to the bidirectional control of second-messenger phosphorylation events but also shape broader aspects of cardiovascular physiology and pathophysiology.

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