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AKAPs: Temporal and Spatial Regulation of Intracellular Signal Transduction in the Cardiovascular System

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Abstract

The prototypical intracellular second messenger cAMP is locally controlled by multimolecular protein complexes organized by A-kinase anchoring proteins (AKAPs). AKAPs serve as scaffolds for different sets of cAMP-metabolizing enzymes that control cAMP gradients and regulate cellular responses. In addition to adenylyl cyclases and phosphodiesterases, AKAPs bind signaling enzymes and ion channels that are important regulators of cardiac contractility and pathophysiological myocyte remodeling and hypertrophy. Compartmentation increases the local concentration of cAMP signaling components, providing faster, higher fidelity regulation of cellular processes. This review series highlights the contribution of AKAPs in the heart as scaffold proteins integrating protein kinases, phosphatases and other effector molecules involved in cAMP-dependent signaling.

Keywords

Protein kinase A; A-kinase anchoring proteins; heart

The pleiotropic cyclic nucleotide cAMP is a small, diffusible second messenger important for the regulation of critical cardiac functions such as inotropy, chronotropy, lusitropy and intermediary metabolism. In addition, prolonged catecholaminergic stimulation leads to sustained cAMP signaling that induces cardiac myocyte hypertrophy and apoptosis. The synthesis and degradation of cAMP are catalyzed by adenylyl cyclases (ACs) and phosphodiesterases (PDEs), respectively. Effectors for cAMP include protein kinase A (PKA), the small G protein guanine nucleotide exchange factor Epac, and cyclic-nucleotide gated (CNG) channels. The formation of specific, localized multi-protein complexes containing various subsets of these signaling molecules defines the specialized infrastructure of cAMP signaling.

In cardiac myocytes, diverse G-protein coupled receptors that activate G_{α_s} induce adenylyl cyclase and PKA activity. However, while norepinephrine stimulation of β -adrenergic receptors is inotropic, other G_{α_s} -coupled receptors do not control contractility. Because

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different receptors regulate different cellular processes, a longstanding question in the field of signal transduction has been how different receptors that signal through the same diffusible second messenger could result in the activation of specific cellular pathways. Physical compartmentation as a mechanism conferring specificity in cAMP signal transduction was first suggested in 1977 when Corbin et al. determined that PKA existed as both soluble and particulate units in cells.¹ Upon cellular stimulation with prostaglandin E₁ (PGE₁), only the soluble fraction of PKA was activated. This result was in contrast to isoproterenol-induced stimulation of both soluble and particulate PKA. Over the years we have learned that particulate PKA is equivalent to PKA bound to AKAPs. This observation was later extended to include localized cAMP signaling within discrete areas of a cell brought about by scaffold proteins.² Today, over 50 AKAPs (including alternatively-spliced forms) have been identified that are involved in diverse cellular processes.³ These scaffold proteins regulate localized cAMP signal responses by recruiting cAMP machinery into multiprotein entities or “signalosomes” restricted to individualized compartments.

Current therapies in cardiovascular medicine tend to be focused on receptor or ion channel modulation. By inhibiting upstream molecules, currently used drugs tend to affect multiple, diverse pathways in the cardiac signaling network. For example, b-blockers have proven useful at attenuating the progression of heart failure, despite their potential to blunt sympathetic control of contractility. As our understanding of AKAP signalosomes grows, so does the potential for their use in novel therapies for cardiac disorders. The unique targeting of individual signalosomes would allow the modulation of germane processes without off-site effects, including the selective inhibition of downstream b-adrenergic pathway targets. This review series discusses the role of AKAPs in the heart in the integration of multiple signaling pathways, elucidating some of the complex protein-protein interactions within signalosomes and highlighting the potential for the development of original therapeutic approaches.

Adenylyl cyclases catalyze the synthesis of cAMP. In their review, Efendiev and Dessauer discuss AKAP-associated ACs. AC5 and AC6 are the predominant isoforms in the heart responsible for cAMP synthesis. AC5 disruption has been shown to be cardio-protective in response to pathological stress.⁴ In contrast, AC6 over-expression appears to have cardio-protective effects under stress conditions.⁵ These differences are likely due to differences in spatial distribution, as well as the local signaling environment for these distinct ACs as determined by their specific association with different AKAPs.

While ACs initiate cAMP signaling, PDEs terminate it.⁶ Delving into the components of signalosomes that are critical for cAMP metabolism, Stangherlin et al. discuss the AKAP-anchored PDE superfamily of enzymes that attenuate cAMP signaling. Spatial transmission of cAMP signaling does not occur as a result of a global increase in total cAMP levels throughout the cell, but rather in response to the elevation of cAMP levels in discrete compartments. The local concentration of cAMP affects the activation state of PKA and other cAMP effectors, and the interplay between PDE and ACs sets the threshold for signaling. By creating areas of cAMP rarefaction, PDEs provide the functional compartmentation necessary to elicit localized cAMP-dependent PKA activation. The discovery of PDEs came closely after identifying cAMP as a signaling molecule.^{7,8} PDE isoforms contain a high degree of sequence and structural similarity and confound the development of therapies directly targeting these proteins. As subcellular targeting of ACs and PDEs is achieved by protein-protein interactions through specific domains, newer therapeutic strategies based on the disruption of AC and PDE recruitment to AKAPs require a detailed understanding of the organization of these macromolecular signaling complexes.

PKA-dependent phosphorylation through cAMP signaling is an important determinant in the progression of a signaling response. Equally important is the presence of phosphatases within anchored multimolecular complexes for the maintenance of the dynamic range of signaling pathways. Redden and Dodge-Kafka introduce the emerging role of AKAP-associated phosphatases in response to cAMP-dependent stimulation. Unregulated kinase activity has detrimental effects on overall signaling levels and can rapidly lead to a disease state. The primary role of phosphatases is to oppose kinase function and re-establish basal signaling, and AKAP-associated phosphatases regulate kinase activity in a spatial and temporal manner. Protein phosphatases 1, 2A and 2B (calcineurin) are the three main phosphatases in myocytes. Anchoring to scaffold proteins allows these ubiquitously expressed enzymes to exert localized effects on cardiac ion channels like L-type calcium channels and the ryanodine receptor and transcription factors like NFAT. Importantly, activation of phosphatase activity can result in cardiac hypertrophy, as well as uncoupling of cardiac contractility.

Turning to the cellular processes regulated by AKAP complexes, Carnegie and Burmeister discuss the role of AKAPs in excitation-contraction coupling, sarcomeric regulation and the induction of pathological hypertrophy. The authors discuss individual AKAP complexes and their critical importance for the maintenance of spatiotemporal control of cardiac signaling pathways. They describe how disruption of specific anchoring domains on AKAPs affects not only signalosome assembly, but also deregulates localized signaling events.

Finally, Greenwald and Saucerman review the principles of computational modeling that may explain how AKAP complexes affect signaling dynamics. The organization of multiple signaling components into cohesive AKAP-anchored units permits local integration of signals in response to diverse upstream stimuli (inputs) and affecting different downstream effectors (outputs). Computational models can help us understand the complex networks of signaling cascades in ways traditional experimental and intuition alone do not suffice. The authors discuss the network motifs that are established by AKAP scaffolds for signal responses, including feedback and feedforward loops that affect adaptation and sensitivity. Such models will aid in the development of hypotheses driving future studies in intracellular signal transduction.

Overall, this review series elaborates how AKAPs provide the architectural infrastructure for intracellular signal transduction pathways in the cell. Defining cellular compartments for the localized control of signaling is a hallmark characteristic of AKAPs enabling high fidelity, efficient communication between signaling and effector proteins through specific protein-protein interactions. The pleiotropic properties of many signaling proteins is problematic for the development of specific drug therapies. Instead, the disruption of specific protein-protein interactions may provide a therapeutic index greater than the use of active site enzyme inhibitors. Ongoing research about scaffold proteins will allow the development of such novel therapeutic strategies for the future treatment of cardiovascular diseases, including heart failure.

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