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A-Kinase Anchoring Protein (AKAP)

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Synonyms

A kinase (PRKA) anchor protein; A-kinase anchoring protein (AKAP); AKAP

Historical Background

Classical physiological experiments identified cAMP as a diffusible intracellular secondary messenger capable of activating cAMP-dependent protein kinase (PKA). These studies defined hormone- and location-specific patterns of PKA activation, suggesting that PKA signaling was compartmentalized. For example, in perfused rat cardiomyocytes, adrenergic stimulation selectively activates a pool of PKA isolated from certain fractions, while prostanoids predominately activate cytosolic PKA (Scott et al. 2013).

The first AKAP to be identified, microtubule-associated protein 2 (MAP2), was copurified with the PKA regulatory subunit subtype II (RII) from rat brain extracts. Over 50 additional AKAP family members have subsequently been identified (Fraser and Scott 1999). AKAPs are structurally diverse and share little primary sequence similarity, but are functionally similar and are classified by their ability to copurify with PKA catalytic activity from tissues (Langeberg and Scott 2015).

Properties of AKAPs

As depicted in Fig. 1, all AKAPs share the following common properties:

1. Conserved PKA anchoring domain: AKAPs contain a 14–18 residue amphipathic helix which interacts with the N-terminal docking/dimerization (D/D) domain of the regulatory (R) subunit of PKA. Most identified AKAPs exhibit high-affinity binding to RII. Several AKAPs interact with RI, or are dual-affinity (binding RI or RII), and these interactions are typically 10–100-fold lower affinity than for RII (Huang et al. 1997; Means et al. 2011).
2. Localization signal: AKAPs compartmentalize signaling complexes through targeted interactions at specific subcellular locations. This is achieved either through targeting domains or differential targeting of splice variants through additional modification (e.g., AKAP18-α and β isoforms are targeted to the plasma membrane via myristoyl and dual palmitoyl groups).

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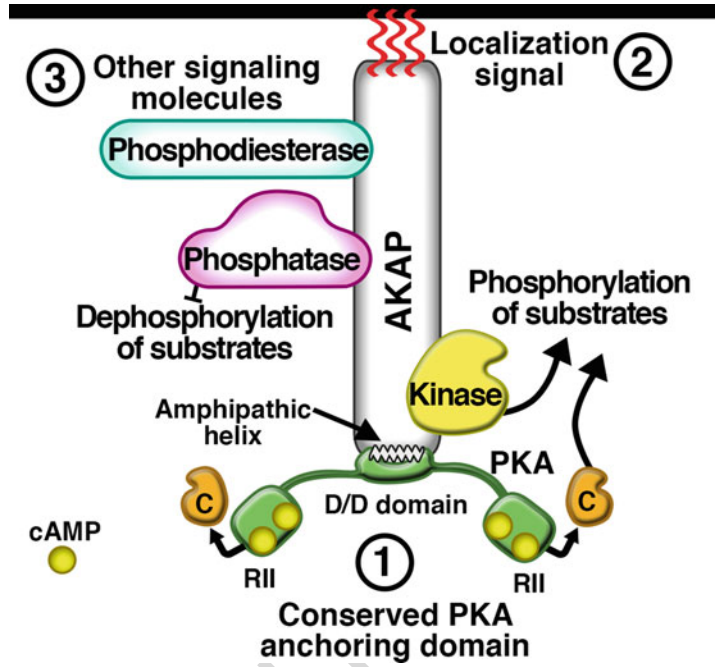

A-Kinase Anchoring Protein (AKAP), Fig. 1 Properties of AKAPs. AKAPs regulate the subcellular localization of PKA, generating substrate specificity for PKA. All AKAPs possess three properties: (1) A conserved PKA anchoring domain; (2) Localization signals to direct AKAP complexes to subcellular locations; (3) Interaction with other signaling molecules, including phosphodiesterases, phosphatases, and kinases

3. Ability to form complexes with other signaling molecules: AKAPs directly couple upstream cAMP signaling (e.g., G-coupled protein receptor (GPCR) activation of adenylyl cyclase) with both signaling terminators (e.g., protein phosphatases, phosphodiesterases) and other elements of signaling pathways (e.g., protein kinases, small GTPases, GTPase activating proteins (GAPs)/Guanine nucleotide exchange factors (GEFs) (reviewed in Wong and Scott 2004).

A hallmark of AKAPs is the ability to simultaneously associate with several binding partners to form multimeric signaling complexes. This confers the ability to facilitate rapid and efficient signal transmission in a local environment through spatial integration of constituents of different signaling pathways.

AKAP Nomenclature

Many AKAPs are named according to their apparent molecular mass as determined by migration in SDS polyacrylamide gel electrophoresis (SDS-PAGE) (e.g., AKAP79 protein migrates at ~79 kDa, with a molecular mass of ~49 kDa). Some AKAPs were found to be fragments or smaller transcripts of larger genes and renamed (e.g., muscle-specific mAKAP was first designated AKAP100). Other AKAPs were first identified in other contexts and retained their original names (e.g., Gravin (AKAP250) was identified as an autoantigen in the sera of myasthenia gravis patients (Nauert et al. 1997).

In nucleotide and protein database nomenclature, some AKAPs are referred to by their gene names; for example, bovine AKAP75, human AKAP79, and murine AKAP150 all refer to the products of the *AKAP5* gene (Brandon et al. 2003; Tunquist et al. 2008). Furthermore, AKAP nomenclature is complicated by alternative splicing, which results in multiple isoforms from the same AKAP gene. For example, the *AKAP9* gene has six known splice variants including Yotiao, AKAP350, AKAP450, and centrosome- and Golgi-localized PKN-associated protein (CG-NAP).

Functions of AKAPs

AKAPs have been implicated in diverse physiological processes, including reproduction and development, learning and memory, cardiac function, and diseases such as cancer and diabetes.

AKAPs: Reproduction and Development

Multiple AKAPs function in oogenesis and spermatogenesis, including multiple splice variants of *AKAP1*. D-AKAP1 anchoring of type II PKA is required for progression through meiosis II in oocytes (Newhall et al. 2006). Likewise, S-AKAP84 anchoring of type II PKA is required for mitochondrial trafficking in developing spermatids. Gravin (*AKAP12*) has also been implicated in embryogenesis as it plays a role in regulating cell migration through inhibition of a Rho/ROCK/myosin II pathway.

AKAPs: Learning and Memory

One of the first identified roles for AKAPs was the synchronization of synaptic signaling events that underlie learning and memory. AKAP79 regulates synaptic plasticity through coordinating PKA, PKC, and PP2B/calcineurin signaling at the postsynaptic membrane in response to phosphorylation of ion channel subunits (e.g., AMPA receptor) (Snyder et al. 2005; Tunquist et al. 2008; Zhang et al. 2016). Moreover, AKAP79 can coordinate multiple channel types (M-type K+, L-type Ca^{2+}, or TRPV1 channels) and G protein-coupled receptors simultaneously to assemble multichannel supercomplexes (Snyder et al. 2005; Tunquist et al. 2008; Zhang et al. 2016).

The AKAP known as Wiskott-Aldrich syndrome, verprolin-homology domain containing protein (WAVE) also has defined neuronal functions. WAVE-1 is expressed in the central nervous system and organizes different protein networks involved in actin assembly and synaptic plasticity. WAVE-1 knockout mice display defects in hippocampal learning and memory (Soderling et al. 2003). WAVE-1 exists in a variety of multiprotein complexes, thus underscoring the ability of AKAPs to spatiotemporally localize alternate signaling pathways depending on the physiological context.

AKAPs: The Immune System

Prostaglandin E_2 (PGE2) and other ligands are potent inducers of cAMP, which in T-cells activates PKA to inhibit TCR-induced T-cell proliferation (Mosenden and Tasken 2011). Type I PKA is the predominant isoform involved in immunomodulation. It has been shown that the AKAP ezrin targets type I PKA to TCR-CD3 complexes present at lipid rafts in T cells to facilitate the phosphorylation of the tyrosine kinase Csk. This in turn negatively regulates the activity of tyrosine kinase Lck and thereby downregulates T-cell receptor activation.

Cardiac AKAPs

A number of "cardiac" AKAPs have been identified in the heart and their roles in regulating cardiovascular function have been among the most explored. In the heart, AKAPs scaffold a wide range of enzymes that underlie fundamental processes such as cardiac development, hypertrophy, contractility, and cardiac rhythm. For example, AKAP-Lbc (*AKAP13*) regulates signaling of cAMP and the small GTPase Rho to initiate proper cardiomyocyte development (Carnegie et al. 2008). In addition, AKAP-Lbc interacts with PKA, PKC, PKD, and with the guanine nucleotide exchange factor for Rho to coordinate hypertrophic signals (Carnegie et al. 2008). While AKAP-Lbc-mediated activation of PKD underlies cardiac hypertrophy, AKAP-Lbc targeted PKA signaling prevents the activation of hypertrophy-promoting Rho (Diviani et al. 2004).

The muscle-specific A-kinase anchoring protein, mAKAP (*AKAP6*), also has been implicated in hypertrophic responses through its regulation of ERK5 and PP2B (calcineurin) signaling. In addition, mAKAP has been proposed to mediate

heart contractibility by coordinating PKA activity at L-type Ca^{2+} channels and ryanodine receptors (RyR), although the underlying mechanism remains elusive (Lehnart and Marks 2006). Some think that the flow of Ca^{2+} current through L-type Ca^{2+} channels activates RyRs and initiates further Ca^{2+} release from the sarcoplasmic reticulum. Phosphorylation of RyR by mAKAP-bound PKA increases Ca^{2+} permeability allowing the heart cells to contract.

AKAP79 (*AKAP5*) likewise coordinates L-type Ca^{2+} channel activity and plays a role in regulating cardiac rhythm. By serving as a platform for PKA and PKCα activity at Cav1.2, AKAP79 mediates the open and closed conformations of the calcium channel (Hoshi et al. 2010; Navedo et al. 2010). Similarly, AKAP18 has been shown to influence and interact with Cav1.2. In another context, this AKAP can influence Ca^{2+} reuptake by bringing together PKA and phospholamban, a critical regulator of the sarcoplasmic reticulum Ca^{2+} – ATPase (SERCA).

Cardiac rhythm can also be regulated through the targeting of PKA, PP1, and PDE4D3 to slowly activating cardiac potassium channel I_{Ks} via Yotiao (*AKAP9*) (Li et al. 2012). The I_{Ks} channel is required for the repolarization of the ventricular action potential in the heart so coordination of enzyme signaling at this receptor is crucial for maintaining a rhythmic heartbeat (Li et al. 2012).

AKAPs and Disease

Mutations in *PCNT*, which encodes for the AKAP pericentrin cause Seckel syndrome, a disease marked by defective ATR-dependent DNA damage signaling accompanied by a reduction of brain and body size. Other SNPs have been identified in a variety of AKAPs and correspond to emergence of disease phenotypes associated with cardiomyopathies, cancer, and diabetes.

Cardiomyopathies

Mutations in Yotiao are found in patients that suffer from the congenital disorder known as long-QT syndrome (LQTS). LQTS is characterized by a prolonged QT interval on an ECG and is often accompanied by ventricular tachyarrhythmias, which may result in cardiac arrest. The S1570 L mutation in the I_{Ks} alpha subunit binding domain of Yotiao results in reduced cAMP-induced phosphorylation of the channel and causes a delayed repolarization of the ventricular action potential in cardiac cells (Chen et al. 2007).

Cancer

Gravin (*AKAP12*), which is downregulated in a number of cancer cell lines as well as human cancer tissues, maps to 6q24–25.2, a deletion hotspot in prostate, breast, and ovarian cancers (Gelman 2012). Furthermore, expression of Gravin inhibits cancer cell invasiveness through its suppression of PKC-Raf/MEK/ERK pathway signaling. In addition, it binds to and coordinates signaling of Aurora A and Plk1 kinases, two proteins that are highly upregulated in cancer (Canton et al. 2012; Hehnly et al. 2015). AKAP-Lbc also plays a role in coordinating signaling proteins that become dysregulated during cancer. It has been shown to regulate MAPK signaling through its interactions with KSR and various Raf isoforms (Smith et al. 2010).

Diabetes

Phosphorylation of β-cell proteins through AKAP79-anchored PKA and PP2B activity is important for regulating insulin secretion. AKAP150-null mice (murine version of AKAP79) have decreases in glucose-stimulated Ca^{2+} entry and cAMP production as well as impaired insulin secretion (Hinke et al. 2012). Similarly, AKAP18α or γ have been described to regulate glucose-stimulated insulin secretion.

Summary

The AKAP family of proteins represents a versatile class of signal organizing proteins that bring together different combinations of signaling effectors. As the study of these proteins has progressed, it has become clear that this scaffolding function is key to maintain signaling homeostasis. This is achieved in part by the combinatorial assembly of distinct subsets of anchored enzymes in a

context-specific manner (Wong and Scott 2004). Single particle EM analyses reveal that the preferential and processive recruitment of signaling enzymes is possible because AKAP complexes contain regions of intrinsic disorder and consequently can adopt a range of conformations (Smith et al. 2013).

Another emerging theme is the notion that pathological states that effect AKAP action perturb local signaling mechanisms. This is particularly evident in the retina, where loss of PKA anchoring to AKAP2 prevents appropriate phosphorylation of the aquaporin 0 (AQP0) water channel. The clinical consequence of perturbing this local phosphorylation event is the rapid onset of cortical cataract, a permanent change in ocular lens transparency (Gold et al. 2012). A variation on this theme occurs in the kidney, where another anchoring protein AKAP220 coordinates the location of PKA and PP1 in proximity to the aquaporin 2 (AQP2) water channel. Mouse knockout studies reveal that loss of AKAP220 leads to accumulation of AQP2 at the apical plasma membrane and reduces urine-diluting capacity during overhydration (Whiting et al. 2016). This phenotype may also be clinically relevant, as accumulation of AQP2 at the apical membrane is the desired therapeutic outcome when treating patients with certain renal disorders including nephrogenic diabetes insipidus. In conclusion, AKAPs exquisitely coordinate local signaling in essential processes that underlie a variety of physiological states.

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