A-kinase anchoring proteins: protein kinase A and beyond

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Compartmentalization of kinases and phosphatases is a key determinant in the specificity of second messenger mediated signaling events. Localization of the cAMP-dependent protein kinase (PKA) and other signaling enzymes is mediated by interaction with A-kinase anchoring proteins (AKAPs). In the past year there have been many advances in our understanding of AKAPs, particularly in the field of the functional consequences of PKA anchoring.

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Abbreviations

AKAP	A-kinase anchoring protein
PKA	protein kinase A
PKC	protein kinase C
PP1	protein phosphatase-1
R	type I or type II regulatory subunit

Introduction

As the genome project approaches completion, it is becoming clear that there are more signal transduction proteins than was originally anticipated. A conservative estimate suggests that 20% of genes may encode transmembrane receptors, G protein subunits, signal-generating enzymes, protein kinases and protein phosphatases. In fact, Hunter's original prediction [1] of '1001 kinases' has been revised and estimates are now approaching 2000. With many kinase and phosphatase genes identified, the research community now is focusing on understanding how these enzymes orchestrate phosphorylation events inside cells. Much attention has been focused on the cAMP-dependent protein kinase (PKA), which becomes activated in response to cellular events that stimulate the synthesis of the second messenger, cAMP. Given that PKA is involved in numerous parallel signaling cascades, understanding the functional complexities of how the kinase is activated in the right place and at the right time inside cells is important. This specificity is achieved, in part, through the compartmentalization of PKA at different subcellular locations through interaction with A-kinase anchoring proteins (AKAPs).

AKAPs were first identified as proteins that co-purified with the PKA holoenzyme when isolated from tissues. Since then, a variety of gel overlay, interaction cloning, yeast two-hybrid and proteomic approaches have identified up to 25 unique AKAPs, some of which are members of complex gene families with numerous splice variants and isoforms (reviewed in [2]). There is no overall sequence similarity among different AKAPs; they represent a family of functionally-related molecules that are characterized by their interaction with type I or type II regulatory subunits (RI or RII) of the PKA holoenzyme. In addition to a defined R subunit binding site, AKAPs also possess unique targeting sequences that direct the PKA–AKAP complex to cellular compartments. Finally, some anchoring proteins have the ability to maintain signaling scaffolds by simultaneously associating with other kinases and phosphatases.

The PKA–AKAP interaction

Early work predicted that the R binding surface on AKAPs formed an amphipathic helix [3]. This has now been firmly established by Jennings and colleagues [4•] in NMR studies which show that the hydrophobic side chains on one face of the helix are the principal binding determinants for the interaction with the R subunit dimer. Two recent studies have significantly advanced our understanding of the AKAP binding surface on PKA. Neutron and X-ray scattering experiments have defined the quaternary structure of the type II PKA holoenzyme as an extended antiparallel dumbbell [5•], and the structure of an amino-terminal fragment of RIIα (1–44) complexed with a peptide from the human anchoring protein Ht31 has been solved by NMR [4•]. The NMR data suggest that the association is due to direct helix–helix contacts between hydrophobic residues on each protein [4•]. These findings extend earlier mapping studies which demonstrated that the extreme amino-terminus of each protomer in R subunit dimers interacts with AKAPs [6,7]. These structural data complement the findings of Carr and colleagues [8•], who have used sequence alignments of 15 AKAPs to postulate a consensus binding motif of X-(ϕ)-X-X-X-(A,S)-X-X-(ϕ2)-X-X-(ϕ2)-X-X-(A,S)-(ϕ) for interaction with the type II R subunit (where X is any amino acid, A is alanine, S is serine and ϕ is leucine, isoleucine or valine). It will be interesting to see if novel anchoring proteins can be identified by database searches using this consensus sequence.

Although most analyses of PKA anchoring have focused on AKAP interactions with the RII subunit of PKA, yeast two-hybrid analysis has identified three AKAPs that associate with the RI subunit [9–11]. Also, AKAPce is an anchoring protein from *C. elegans* that interacts with an RI-like molecule [12]. It would appear that both RI and RII interact with the amphipathic helix on the AKAP. Indeed, recent mutagenesis studies by Miki and Eddy [13•] suggest that each R subunit recognizes distinct determinants within the helical binding domain on the sperm fibrous sheath AKAP, FSC1/AKAP82. These data significantly expand the anchoring hypothesis as they suggest all PKA holoenzyme forms may be compartmentalized through association with AKAPs.

Targeting

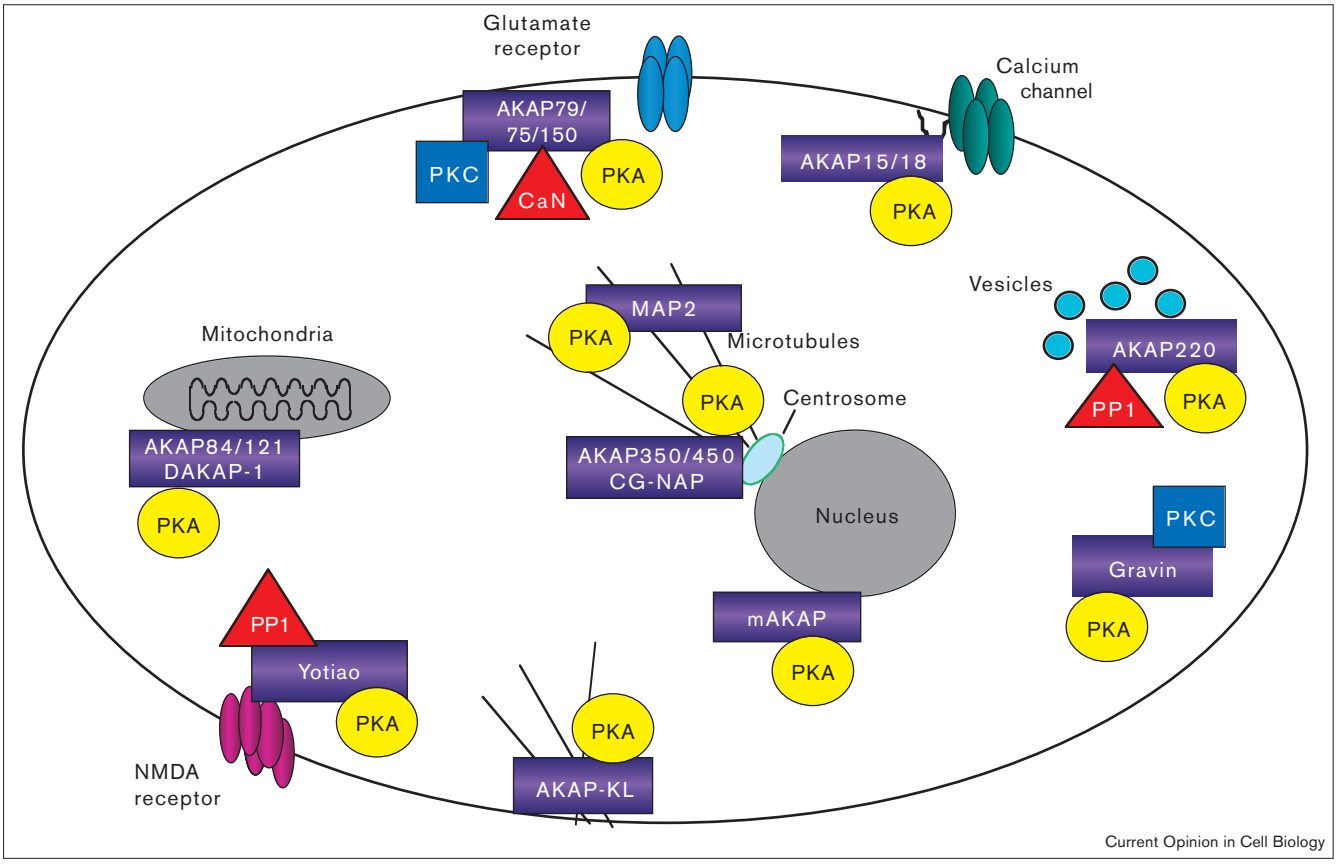
Specificity in PKA anchoring is achieved by specific targeting motifs that direct AKAPs through protein–protein interactions to structural elements, or through protein–lipid interactions to membranes. For example, the neuronal anchoring protein AKAP79 contains three non-contiguous basic regions that facilitate association with acidic phospholipids in the plasma membrane [14], AKAP15/18 is tethered to membranes via myristoylation and dual palmitoylation signals [15,16] and mAKAP, an anchoring protein selectively expressed in cardiac muscles, is targeted to the perinuclear membrane of cardiomyocytes through three 'spectrin-like' repeat sequences [17] (see Figure 1).

Recent studies illustrate that targeting can be regulated through alternative splicing of AKAP genes. For example, three study groups have independently cloned a family of anchoring proteins, called CG-NAP or AKAP350/450, that tether PKA to centrosomes [18•,19,20]. Although most of these gene products are localized to centrosomes and midbody or the Golgi, another splice variant, yotiao, uses a distinct targeting motif to bind directly to the NMDA receptor in neurons [21••]. Similarly, Taylor and colleagues [22•] have shown that distinct targeting sequences are located within the amino-terminal regions of the dual-specificity anchoring protein, DAKAP-1, and that these sequences localize splice variants to either mitochondria or the endoplasmic reticulum. Given the diversity of AKAP targeting mechanisms, an interesting question is whether this targeting is regulated. For example, Rubin and colleagues [23] have suggested that the *Drosophila* DAKAP200 is targeted to both membrane and cytoskeleton through myristoylation and polybasic domains, respectively, in a manner similar to the MARCKS protein [23]. The cytoskeletal targeting of DAKAP200 is regulated through protein kinase C (PKC) phosphorylation of the polybasic region [24•]. Thus, it seems possible that a variety of regulatory mechanisms for the targeting of other anchoring proteins will be elucidated soon.

Multivalent scaffolds

Perhaps the most interesting property of AKAPs is their simultaneous anchoring of other kinases and phosphatases (reviewed in [25]). The first example of such an AKAP that binds multiple enzymes was AKAP79, which interacts with PKA, PKC and the calcium/calmodulin-dependent phosphatase, PP2B [26]. Functional studies from a variety of laboratories have suggested that AKAP79 maintains these enzymes at sites close to the plasma membrane in order to coordinately regulate the phosphorylation state and

Figure 1



A schematic representation of the subcellular localization of various AKAPs. A selection of AKAPs discussed in this article and their binding partners are presented.

activity of transmembrane proteins such as ion channels (reviewed in [27]). In the past year, other multivalent anchoring proteins have been identified. For example, AKAP220 has been shown to maintain a scaffold of both PKA and protein phosphatase-1 (PP1) [28] and yotiao acts as an adapter protein to complex PKA and PP1 with the NR1A-containing subtype of the NMDA receptor [21••]. Ono and colleagues [18•] have shown that the centrosomal and Golgi-specific anchoring protein, CG-NAP, not only binds PKA and PP1, but also has binding sites for the Rho-dependent kinase, the nerve growth factor (NGF)-activated protein kinase PKN, and the heterotrimeric phosphatase PP2A. These data suggest that CG-NAP serves as a scaffolding protein that has the capability to assemble different combinations of kinases and phosphatases at centrosomes or Golgi. AKAPs that bind to multiple signaling molecules may nucleate a variety of combinations of enzymes at specific subcellular locations.

Furthermore, regulation of anchored enzyme activity is emerging as an important property of AKAP complexes. For example, the catalytic subunit of PKA is inactive when bound to AKAPs and association of PKC with gravin or AKAP79 maintains the enzyme in an inactive state [29]. In contrast, examples are emerging for the upregulation of phosphatase activity by AKAPs. The type I phosphatase, PP1, is active when bound to yotiao, keeping the activity of the NMDA ion channel low [21••]. With the discovery of many AKAPs that bind to multiple signaling enzymes, it will be important to determine the activity of each enzyme when bound to the anchoring protein. In addition, future studies also should focus on characterizing these protein complexes to determine whether one enzyme influences the activity of other bound enzymes.

Functional consequences of PKA anchoring

Although much is now understood about the molecular organization of AKAPs, the most important questions revolve around the *in vivo* function of each signaling complex. Heterologous expression of AKAP79, AKAP15/18 and AKAP-KL have implicated these anchoring proteins in modulation of ion channels through directing pools of kinases and phosphatases close to particular channel subunits (reviewed in [27]). To date, perhaps the most sophisticated mechanism of channel modulation is yotiao, an anchoring protein that directly interacts with the NR1A subunit of the NMDA receptor ion channel in neurons. Biochemical and electrophysiological studies suggest that yotiao simultaneously binds to both PKA and PP1 in order to modulate NMDA receptor activity [21••] (Figure 2a). The phosphatase is bound to yotiao in its active state, and electrophysiological experiments suggest that PP1 limits the channel activity until PKA becomes active through the generation of cAMP. PKA activation leads to phosphorylation of the NMDA receptor and a concomitant increase in ion flow. Thus, yotiao serves as a scaffold protein that physically attaches both enzymes to their substrate.

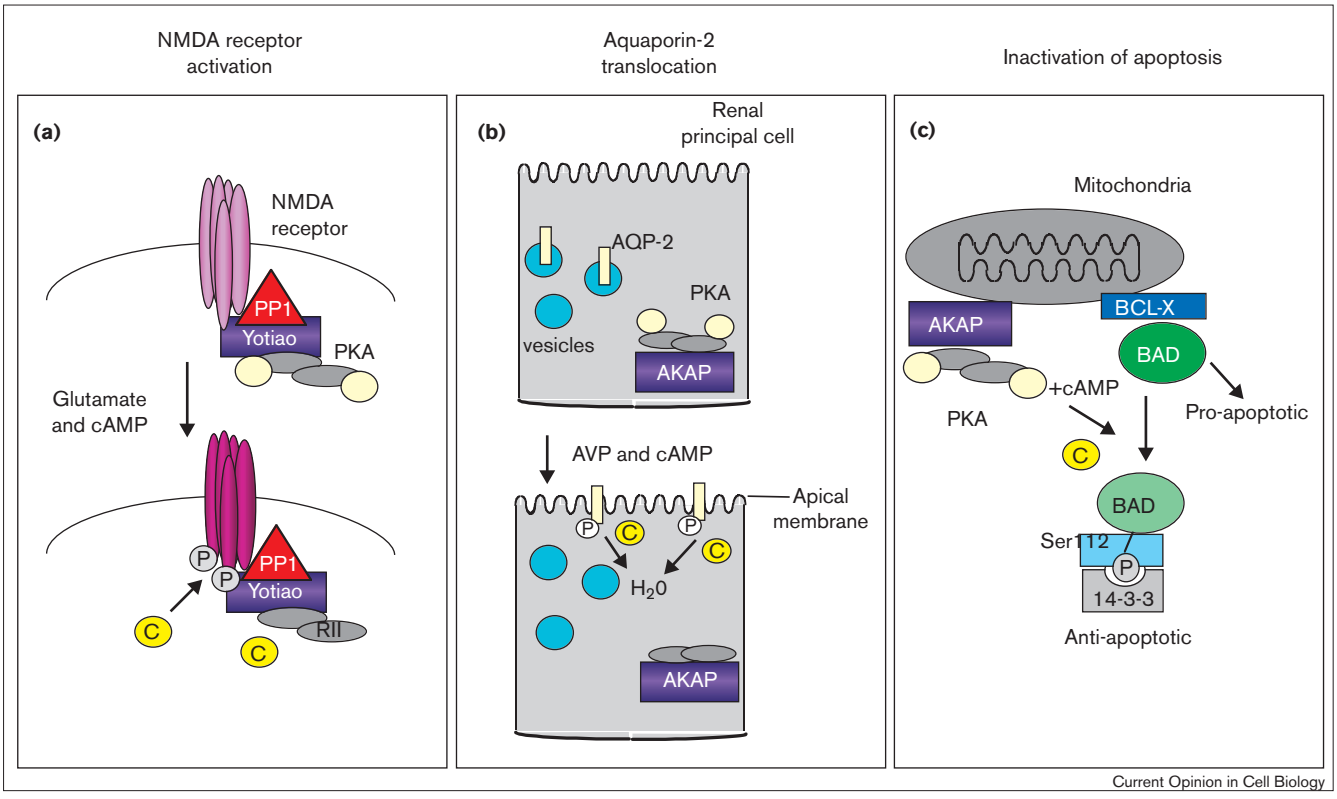
AKAPs also have been proposed to facilitate the intracellular action of specific hormones. PKA anchoring in pancreatic beta cells is required for effective insulin secretion in response to the hormone glucagon-like peptide-1. Glucagon-like peptide-1-mediated insulin secretion in primary cultures of pancreatic islets and in clonal beta cells is blocked if PKA-anchoring is disrupted [30]. Also, the antidiuretic peptide arginine-vasopressin utilizes the cAMP signaling pathway to induce the phosphorylation and translocation of aquaporin-2 water channels in the kidney. Rosenthal and colleagues [31••] have shown that channel translocation in primary cultures of renal duct cells is blocked by application of peptides that antagonize PKA–AKAP interactions (Figure 2b). Although the identity of the AKAP that is responsible for this effect is unknown, this elegant study illustrates a situation in which not only the activity of PKA is important, but also its tethering to specific subcellular compartments. Recent evidence suggests that hormonal changes may regulate AKAP scaffold composition. For example, Sanborn and co-workers [32,33] demonstrated that levels of PKA and PP2B bound to AKAP79 varied during pregnancy, leading to changes in the regulation of phosphatidylinositide turnover.

Another approach to address the function of AKAPs is to search for specific AKAPs that participate in a known cAMP-responsive pathway. For instance, it has been known for some time that cAMP inhibits apoptosis in cells deprived of certain survival factors [34]. In a search for the kinases that phosphorylate the pro-apoptotic factor, BAD, Korsmeyer and co-workers [35••] identified an anchored pool of PKA at the mitochondria, presumably through association with the mitochondrial anchoring protein SAKAP84/D-AKAP1 (Figure 2c). PKA phosphorylation of Ser112 on BAD is a cell survival signal that provides a recognition site for the multifunctional adapter protein 14–3–3. Binding of 14–3–3 prevents apoptosis by blocking BAD association with pro-apoptotic factors. Disruption of PKA anchoring prevents BAD phosphorylation leading to the onset of mitochondrial dysfunction and other apoptotic events [35••].

Conclusions and perspectives

Although there is considerable information about the molecular interactions of AKAPs, several fundamental questions remain unanswered. For instance, it is clear that multiple AKAPs are targeted to the same subcellular compartment. This raises the question of whether there are redundancies in PKA anchoring or if individual anchoring proteins precisely direct their kinases and phosphatases to individual substrates. Curiously, both situations may exist. The physical association of the yotiao signaling complex with the NMDA receptor suggests that there are instances of precise compartmentalization of signaling enzymes with their substrates. In contrast, AKAP15/18, AKAP79 and MAP2B all have been implicated in the compartmentalization of PKA with the same target protein, L-type

Figure 2



Three examples of how AKAP-mediated targeting of signal transduction enzymes affects specific cellular processes. **(a)** Yotiao-mediated tethering of PKA and PP1 to the NMDA receptor in neurons [21••]. **(b)** Anchored pools of PKA facilitate aquaporin (AQP)-2 translocation and phosphorylation in the principal cells of the renal collecting duct [31••]. **(c)** A pool of PKA anchored to the mitochondria mediates cAMP-responsive phosphorylation of the pro-apoptotic factor BAD. Phosphorylation of serine112 permits BAD association with the adapter protein 14–3–3 to favor anti-apoptotic events [35••].

calcium channels, in a variety of cellular models [15,36–38]. In addition, AKAP15/18 also functionally couples to neuronal sodium channels [39] and AKAP79 has been implicated in the modulation of AMPA/kainate receptors [40]. Further analysis of AKAPs in whole animals is necessary to delineate their function more precisely. Temporal regulation also may prove to play a role in regulating AKAP function, although this mechanism has not yet been explored in detail. Binding of certain enzymes to the same AKAP scaffold may be mutually exclusive or may be regulated by other factors. In other words, a given AKAP may bind to only a subset of its potential interacting partners at any given time in a particular cell. This is likely to be the case for AKAP79, for which the list of binding partners continue to expand. One possibility is that the composition of localized signaling scaffolds may be tailored to influence the phosphorylation status of individual substrates within a local cellular environment.

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