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AKAP5 signaling complexes: focal points and functional properties

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Abstract

OBJECTIVE: Kinase Anchoring Proteins (AKAPs) have evolved to regulate the spatial and temporal organization of cellular signal transduction. As a typical member, AKAP5 which consisting of three orthologues: bovine AKAP75, rodent AKAP150 and human AKAP79, is the best known model in the anchoring and targeting properties. It is shown that AKAP5 can bind β2-adrenergic receptor, which is a member of GPCR superfamily, and orchestrate the interactions of various protein kinases, protein phosphatases and cytoskeletal element. AKAP5 is originally identified as a component of the postsynaptic density in neurons and plays a vital role in modulating neuronal activities. Subsequently, the AKAP5 complexes are also detected in other tissues and participated in various processes.

INTRODUCTION

Cellular signal transduction is one of the most attractive hotspots in life science. The substrate specificity of an enzyme, which mediates the intracellular specific phosphorylation events at particular sites, remains elusive to explain. According to relevant studies, there exists a kind of special protein within cells named anchoring protein which shows no enzyme activity, but can recuit some enzymes as well as their substrates to the subcellular structure, resulting in higher efficiency of the signal transduction (Pawson & Nash, 2003). As a diffusible intracellular second messenger, cAMP signaling is temporally and spatially restricted by one potential mechanism, the formation of A-kinase anchoring proteins (AKAPs) complexes or "signalosomes" (Jarnaess & Taskén, 2007; Smith *et al.* 2006). To date, the AKAP family has extended to over 50 structurally diverse, but functionally similar, members that are categorized by their property of co-purifying with PKA catalytic activity from tissues. Despite their diversity, there are AKAP orthologues detected in a range of species, including fission yeast, nematode worms, fruitflies, mice and humans.(Wong & Scott, 2004) Every member of the AKAP family shares certain common properties: a PKA-anchoring domain, targeting sequences, and the binding sites of other signaling molecules (Taskén & Aandahl 2004).

The PKA holoenzyme is a tetramer complex consisting of two regulatory (R) subunits, which

REVIEW ARTICLE

include four different phenotypes of RIa, RIb, RIIa and RIIb, (Newlon *et al.* 2001; Scott, 1991) and two catalytic (C) subunits. The R-subunit of PKA holoenzyme contains N-terminal docking (residues 1–23) and dimerization domains (residues 24–44) followed by an inhibitor site and two cAMP binding domains (residues 158–426) that can bind and inhibit C-subunit (Taylor *et al.* 2008). The C-subunit is released and activated upon the binding of four molecules of cAMP to the R-subunit dimer. (Newlon *et al.* 2001) All AKAPs share a common structure, an amphipathic helix of 14–18 residues with the capable of binding the N-terminal dimerization domain of the R-subunit of PKA (Carr *et al.* 1992b; Newlon *et al.* 2001). The hydrophobic face of AKAP amphipathic helix lies across the four-helix bundle formed by the R-subunit dimer, thereby allowing extensive hydrophobic interactions between both proteins (Diviani *et al.* 2000; Newlon *et al.* 1999). As far as we know, the AKAPs can not only modulate cAMP-PKA signaling pathway, but could anchor other signals (Diviani & Scott, 2001; Wong & Scott, 2004). By far, most of work has been conducted with AKAP5 (Diviani & Scott, 2001; Dodge & Scott, 2000). AKAP5 is a family consisting of three orthologues: bovine AKAP75, rodent AKAP150 and human AKAP79 (Table 1). All three proteins are highly related but only differ in their molecular weights (Dodge & Scott, 2000). In this review, we are willing to highlight the evidences from the relevant literature concerning the structural and functional properties of AKAP5.

AKAP5 SIGNALING COMPLEXES

In 1984, AKAP5 was identified for the first time as one of the AKAPs. In AKAP79, the amphipathic helix (residues 392–405) provide a hydrophobic pocket for the binding of PKA R-subunit dimers (Alto *et al.* 2002; Carnegie & Scott, 2003). As an excellent technique to demermine protein-protein interaction, surface plasmon resonance (SPR) has proven that AKAP79 binds RIIα and RIIβ approximated equally well (Herberg *et al.* 2000). More and more researches illustrate that AKAP5 family is a critical example of scaffold proteins which integrates and facilitates upstream signals with far-reaching downstream effects on cellular signal transduction. As a multivalent anchor protein, AKAP5 simultaneously binds PKA, as well as PKC, PDE4D, PP2B and calcineurin, modulates L-type voltage-dependent calcium channels, and furthermore, interacts with AMPA and NMDA receptors at postsynaptic sites (Table 1). AKAP5, as well as AKAP12, is shown binding to membrane-embedded G protein coupled receptors (GPCRs), orchestrating the interactions of various protein kinases (including tyrosine kinases), calcineurin (CaN) and cytoskeletal elements with at least one member of the superfamily of GPCRs, the prototypical β2-adrenergic receptor (Chen & Malbon, 2009; Malbon *et al.* 2004). Earlier, it is shown that AKAP5 binds both β1 and β2-adrenergic receptors in heterologous systems, which facilitates downstream signaling, as well as PKA-regulated downregulation and desensitization (Cong *et al.* 2001; Gardner *et al.* 2006).

AKAP5 is targeted to the plasma membrane through sequences that directly bind phospholipids (Dell'Acqua *et al.* 1998). The regulation of AKAPs targeting could potentially influence the actions of anchoring proteins. The membrane targeting of AKAP5 signaling complexes appears to be regulated at least in part by PKC phosphorylation (Dell'Acqua *et al.* 1998). However, it is likely that additional protein-protein interactions must also participate in microcompartmentalization of the signaling network. For instance, the interaction of AKAP79 with membrane-associated guanylate kinases (MAGUKs) could contribute to its targeting to cytoplasmic tail of NMDA receptors (Colledge *et al.* 2000). Recently, a research team uncovered a truth GPR30, or G protein-coupled estrogen receptor (GPER) forms a complex with a MAGUK and AKAP5 that constitutively inhibits cAMP production independently of Gi/o and retains receptors in the plasma membrane (Broselid *et al.* 2014). Two-thirds in the C-terminal of AKAP79 contains the structurally conserved RII-binding domain (residues 388–409) and is abundant in acidic amino acids, suggesting that any two of the three C-terminal basic regions are necessary and sufficient for submembrane targeting property of AKAP79 (Carr *et al.* 1991). In addition, the association of AKAP79 with the membrane-embedded β2-adrenergic receptor also requires some portion of intracellular, cytoplasmic loop 3 (Fraser *et al.* 2000). In neurons, AKAP79 targets PKA to dendritic compartments (Glantz *et al.* 1992; Hall *et al.* 2007) and directly interacts with ion channels (Bal *et al.* 2010; Dart, 2001; Hall *et al.* 2007), as well as several receptors, including the β-adrenergic receptor (Dai *et al.* 2009; Fraser *et al.* 2000) and glutamate receptors (Dell'Acqua *et al.* 2006; Gomez *et al.* 2002b; Snyder *et al.* 2005), as well as adenylyl cyclases (AC5 and AC6) (Bauman *et al.* 2006). Meanwhile, it is reported that AKAP79 can also interact with and regulates AC8 in pancreatic and neuronal tissue (Cong *et al.* 2001). The relevant studies collectively highlight that cellular context and the differential assembly of the AKAP5 signaling complexes plays an important role in influencing the diversity of AKAP signaling events.

FUNCTIONAL PROPERTIES OF AKAP5

AKAP5 is the prototypic member of AKAP family that was originally identified as a component of the postsynaptic densities in neurons (Carr *et al.* 1992a). Subsequently, AKAP5 is detected in an increasing number of tissues and cells (Table 1). Initially, AKAP5 was proved to regulate the neuronal activities, however, more and more studies find AKAP5 also plays a critical role in the regulation of signal transduction pathways in the cardiovascular system, gland as well as other tissues and cells.

Tab. 1. Alternate names of AKAP5, and its distribution and binding partners.

Alternate names	Distribution [Rf.]	Location [Rf.]	Proteins in the complex [Rf.]
AKAP150 (rodent) AKAP79 (human) AKAP75 (bovine)	Brain (Hinke *et al.* 2012; Moita *et al.* 2002; Sarkar *et al.* 1984; Weisenhaus *et al.* 2010)	Plasmalemma (Dell'Acqua *et al.* 1998; Sandoz *et al.* 2006)	PKA (Protein kinase A) (Bregman *et al.* 1989; Bregman *et al.* 1991)
	Heart (Nichols *et al.* 2010)	T-tubules (Baillie *et al.* 2005)	PKC (Protein kinase C) (Brooks & Tavalin, 2010; Klauck *et al.* 1996)
	Artety (Navedo *et al.* 2008; Nieves-Cintrón *et al.* 2008)		PDE4D (phosphodiesterases) (Diering *et al.* 2014; Koçer *et al.* 2012)
	Pancreas (Hinke *et al.* 2012)		PP2B (Dell'Acqua *et al.* 2002; Hinke *et al.* 2012)
	Liver (Hinke *et al.* 2012; Sarkar *et al.* 1984)		β-adrenergic receptor (Lynch *et al.* 2005)
	Skeletal muscle (Hinke *et al.* 2012)		L-type voltage-gated Ca^{2+} channels (Gao *et al.* 1997; Navedo *et al.* 2008; Nichols *et al.* 2010)
	Uterus (Dodge *et al.* 1999a; Dodge *et al.* 1999b)		NMDA receptor (Gomez *et al.* 2002)
	Stomach (Xie & Raufman, 2001)		AMPA receptor (Brooks & Tavalin, 2010; Diering *et al.* 2014)
	Parotid (Wu *et al.* 2010)		PSD-95 (Colledge *et al.* 2000)
			SAP97 (Colledge *et al.* 2000; Tavalin *et al.* 2002)
			KCNQ channels (Bal *et al.* 2010)

This table lists three orthologues of AKAP5 in accordance with different species, and summarizes the distributions in organisms. It highlights the subcellular localization, as well as all the potential binding partners referring to studies about AKAP5 signaling complexes in different tissues and cells. AKAP, A-kinase anchoring protein; PP2B, Phosphoprotein phosphatase 2B; NMDA, N-methyl-D-aspartic acid; AMPA, α-amino-3-hydroxy-5-methyl-4- isoxazole-propionic acid; PSD-95, Postsynaptic protein of 95 kDa; SAP97, Synapse-associated protein-97; KCNQ, potassium voltage-gates channel.

Modulating neuronal activities

As a typical example, AKAP5, which is mostly reported to locate at the plasma membrane of neurons, is identified mainly distributed in the brain of rats and human, mostly in the olfactory bulb neurons, basal nuclei, cerebral cortex and other areas of the forebrain. The AKAP5 signaling complexes have plenty of vital functions which assess mainly *in vivo* using mutant mice having more physiological relevance, although in some cases the potentially confounding influence of compensatory changes may be less of a factor using acute manipulations *in vitro*. To date, three AKAP150 mutant mice lines have been generated, (Hall *et al.* 2007; Lu *et al.* 2007; Sanderson & Dell'Acqua, 2011; Tunquist *et al.* 2008) providing ample opportunities to investigate the physiological functions of this scaffolding protein. All null mice lines are viable and fertile, and all groups demonstrated that AKAP150 is the major AKAP in the brain responsible for proper anchoring of PKA or PP2B within dendritic regions. It is reported that in AKAP150 null mice, the defection of AKAP150 can lead to a disruption of synaptic plasticity and result in learning and memory defects, (Weisenhaus *et al.* 2010) as well as insensitivity of nociceptive stimuli (Jeske *et al.* 2011). AKAP150 null mice line also confirms that distinct AKAP150-enzyme complexes regulate context dependent neuronal signaling events, and that the deficits in motor coordination and strength are likely to be consistent with the expression of AKAP150 in the cerebellum (Tunquist *et al.* 2008).

D36 mice line is another mutant harboring a knock-in mutation generated by introducing a premature stop codon that results in the deletion of the last 36 amino acids from the C terminus of the AKAP150 protein. This truncated protein fully eliminates PKA anchoring by AKAP150 (Lu *et al.* 2007). D36 mice together with AKAP150 null mice show abnormally increased numbers of dendritic spines *in vivo* and increased numbers of functional excitatory synapses in acute hippocampal slices. Both the changes are apparent in the early postnatal and juvenile stages, but do not persist into adulthood (Lu *et al.* 2011). In the light of electrophysiological and behavioral analysis, D36 mice develop deficits in both synaptic plasticity and operant learning (Weisenhaus *et al.* 2010). D36 as well as AKAP150 null mice have more frequent and larger inhibitory synaptic events in acute brain slices from juveniles, suggesting a compensatory change to counteract increased excitatory synaptic function. All these studies point to the importance of the balancing kinase, PKA, in AKAP5 signaling network. However, phosphorylation of GluA1 on Ser-845 is strongly reduced (by 70%) under basal conditions in AKAP5 KO mice but not at all in D36 mice, in which the PKA binding site of AKAP5 has been deleted without affecting AC association with GluA1. In parallel, long term potentiation is only modestly affected in acute forebrain slices from D36

mice but completely abrogated in AKAP5 KO mice. This study uncovers the truth that AC anchoring by AKAP5 is critical for postsynaptic signaling via cAMP and PKA (Zhang *et al.* 2013).

However, a surprising finding from multiple studies indicates that deficits in synaptic plasticity and behavioral phenotypes are generally more severe in D36 mice compared with the constitutive null mice (Lu *et al.* 2007; Weisenhaus *et al.* 2010). For instance, D36 mice develop impaired long-term potentiation in young adult and impaired long-term depression in juvenile, however, no deficits in either form of long-term plasticity are detected in the null mice (Tunquist *et al.* 2008). What's more, it is in D36 mice but not in null mice detected impaired reversal learning. These unique deficits in the D36 mice may partially be explained by the mechanism that AKAP5 constitutively anchors both PKA and PP2B at synapses, thus, incorporating mutant D36 that retains PP2B binding at the PSD may profoundly alter the signaling balance more potently in D36 mice than in the AKAP150 null mice. The deficiency of PKA binding to AKAP5 also appears to cover the reported binding site for L-type calcium channels in the distal C-terminal portion of AKAP150 (Oliveria *et al.* 2007). Recently, two independent laboratories claim that AKAP150ΔPP2B mutant mice have been established (Sanderson & Dell'Acqua, 2011). AKAP150ΔPP2B mutant mice are deleted the 21-bp sequence that encodes a 'PIxIxIT' motif locating between residues 655 and 661 of AKAP150, to eliminate PP2B anchoring by AKAP150, hence a term AKAPΔPIX mice (Hinke *et al.* 2012). Thus, it will be of great interest for measuring the detailed characterization of these mutant mice against D36 mice.

AKAP5 may play a role in regulating human neuronal activity. AKAP5 has numerous cellular binding/interaction partners, which are prominently involved either in glutamatergic, noradrenergic, serotonergic or dopaminergic neurotransmission. Most of them are altered in bipolar disorder (Bernstein *et al.* 2013). A study of CNVs in bipolar disorder and schizophrenia cases that map to locicontaining brain-expressed genes, proves AKAP5 is included in neuronal function (Wilson *et al.* 2006). The increased copy number of AKAP5 is confirmed in a single bipolar-disorder sample. Another cohort of 60 samples, including 15 bipolar disorder, 15 schizophrenia, 15 major depression, and 15 healthy control, is directly tested for CNVs at the identified loci by quantitative PCR. Subsequently, a similar study questions the reliability of the high-throughput methodology and provides evidences that the prior study might have generated false-positive CNV results (Sutrala *et al.* 2007). However, recent research proves AKAP5 and its interaction partners might be the potential targets for therapeutic interventions in the treatment of BD (bipolar disorder) (Bernstein *et al.* 2013). A latest study reveals that, in healthy young human participants, a functional genetic polymorphism of the AKAP5 gene, Pro100Leu affects anger control and physical aggressive behavior. AKAP5 Pro100Leu effects on emotion processing might be task-dependent with Pro homozygotes showing lower control of emotional interference (Richter *et al.* 2013).

Modulation of cardiovascular system

AKAP5-organized signaling module plays a vital role in cardiac remodeling , especially in sympathetic stimulation of the calcium transient in adult heart cells (Nichols *et al.* 2010; Li *et al.* 2014). Knockdown of AKAP79/150 in cardiac myocytes inhibited the recycling of the β1-AR and increased β1-AR-mediated production of cyclic AMP, which indicates that AKAP79/150 might be cardioprotective via its key role in regulating the signaling intensity of cardiacβ1-AR (Li *et al.* 2013). Due to its consensus PxIxIT calcineurin-binding domain as a potent inhibitor of calcineurin activity, AKAP5 functions in the cardiac literature. As a calcineurin-binding peptides, expression of the AKAP5 site inhibits NFAT (nuclear transcription factor)-dependent myocyte hypertrophy (De Windt *et al.* 2001). Dittmer *et al.* show that inhibition of PKA activity or binding to AKAP5 impairs CDI (Ca^{2+}-dependent inactivation) of Cav1.2 (Dittmer *et al.* 2014). Furthermore, it is demonstrated that AKAP5 also mediates the association of $\beta_{1/2}$-adrenergic receptors, AC5/6, PKAII and a caveolin-3-associated sub-population of Cav1.2 L-type Ca^{2+} channels in cardiac myocytes, facilitating the selective PKA phosphorylation of that pool of ion channels in response to β-adrenergic stimulation. Although the overall stimulated influx of Ca^{2+} through L-type Ca^{2+} channels remained intact, β-adrenergic stimulation of Ca^{2+} transients is absent in cardiac myocytes from AKAP5 knock-out mice. However, in myocytes isolated from an AKAP5 knock-in mouse which is lack of the AKAP5-PKA binding domain, β-adrenergic stimulation of Ca^{2+} transients is normal ,which suggests that overall Ca^{2+} transients depend on the scaffold, but not PKA-phosphorylation of Cav1.2 (Nichols *et al.* 2010).

AKAP5 complexes participate in regulating the entry of extracellular Ca^{2+} through L-type calcium channels in arterial myocytes. Association of AKAP5 and PKCα modulates the induction of persistent Ca^{2+} sparklets, which are local Ca^{2+} signals produced by recurrent openings of L-type Ca^{2+} channels in arterial myocytes that enhance arterial tone (Navedo *et al.* 2008). During the development of hypertension, AKAP5 may also participate in regulating gene expression in the vascular smooth muscle. According to the study, activated PKCα stimulates persistent Ca^{2+} sparklets and an increase in local Ca^{2+} influx that activates AKAP5-targeted PP2B,.The activated PP2B, therefore, dephosphorylates NFATc3 to allow for the gene expression modulated by transcription factor (Navedo *et al.* 2008). In the research, AKAP5-knockout mice lack persistent Ca^{2+} sparklets, and exists lower arterial wall intracellular calcium as well as decreased myogenic tone, resulting in

hypotensive instead of angiotensin II-induced hypertension (Navedo *et al.* 2008). In cases of hypertension, there exists a persistent increase of Ca^{2+} sparklet activity owning to an upregulation of PKCα activity, which elevates PP2B activity and NFATc3-mediated transcription (Navedo & Hell, 2014; Nieves-Cintron *et al.* 2008).

Modulating glucose homeostasis

Glucose homeostasis is maintained by the intake, production, utilization and storage of this essential nutrient. Serum glucose levels decrease in response to insulin whereas counter regulatory hormones such as glucagon, adrenaline, cortisol and growth hormone reverse this response. Stimulus-secretion coupling with insulin release from β-cells is a multistep process: Ca^{2+} influx triggers fusion of insulin granules with the cell membrane and this can be modulated by calmodulin, phospholipid or cAMP-dependent protein kinases (Bratanova-Tochkova *et al.* 2002; Hiriart & Aguilar-Bryan, 2008). As early as 1997, Lester found that anchored PKA augmented GLP-1 mediated insulin secretion (Lester *et al.* 1997). Subsequent research indicates that AKAP5 signaling network contributes to stimulus-secretion coupling with insulin release. AKAP5-tethered PKA and PP2B govern the phosphorylation-dependent modulation of voltage-gated L-type Ca^{2+} currents, partly because this anchoring protein binds directly to the cytoplasmic tail of the channel. (Oliveria *et al.* 2007) Fluo-4 imaging experiments show that ablation of AKAP150 perturbs glucose-induced intracellular calcium flux. This interruption in local Ca^{2+} influx is accompanied by perturbation of submembrane oscillations of cAMP levels that are crucial for insulin releasing (Dyachok *et al.* 2008; Idevall-Hagren *et al.* 2010; Tian *et al.* 2011). Recently, it is reported that AKAP150 coordinates Ca^{2+} and cAMP-stimulated insulin secretion from β-cells ,and that AKAP150 null mice exhibit enhanced insulin sensitivity, thus, anchored signaling events that facilitate insulin secretion and glucose homeostasis may be set by AKAP150 associated phosphatase activity (Hinke *et al.* 2012).

Other functions

Apart from the above functions, AKAP5 also expresses in other tissue and functions in some ways. The physiological importance of AKAP79 signaling complex has been demonstrated in the rat uterus, where PKA acts via the inhibition of phospholipase C (PLC) activity as a known uterine relaxan. Dodge found that PKA associated with the plasma membrane via binding to an AKAP, presumably AKAP79.(Dodge *et al.* 1999a) Given that enhanced activation of Akt is a recognized hallmark of increased insulin action,(Whiteman *et al.* 2002) and that AMPK is considered to be the metabolic master-switch controlling target tissue responsiveness to insulin,(Kahn *et al.* 2005) AKAP150 knockout mice show elevated insulin sensitivity in skeletal muscle

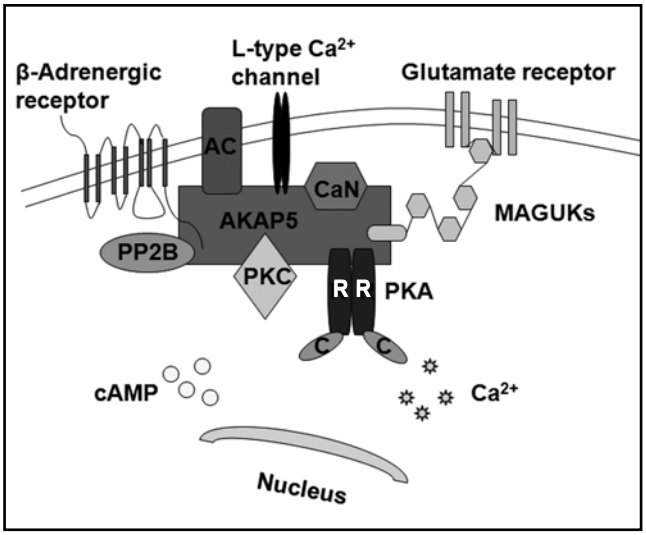

Fig. 1. Schematic diagram of AKAP5 signaling complexes in excitable cells. AKAP5 proves multivalent docking sites for PKA, PKC, PP2B and other signaling molecules ,and constitutively associates with β-adrenergic receptor (Chen & Malbon 2009; Wang *et al.* 2006). In sympathetic regulation of excitation–contraction coupling, AKAP5 can regulate the L-type Ca^{2+} channel and interact with CaN, resulting in intracellular Ca^{2+} fluctuation (Kritzer *et al.* 2012). The interaction of AKAP5 with MAGUKs could contribute to its targeting to cytoplasmic tail of glutamate receptors (Colledge *et al.* 2000).

(Hinke *et al.* 2012). It is proved that disruption of the AKAP150-PKA linkage impairs cAMP-mediated pepsinogen secretion and cross talk between signaling pathways (Xie & Raufman, 2001). In mouse parotid acini, Wu detected the contribution of AKAP5 in amylase secretion (Wu *et al.* 2010). AKAP5 is also detected in liver, however , by now its functions have not been discovered (Hinke *et al.* 2012; Sarkar *et al.* 1984). The latest research indicates AKAP-PKA plays a role in the anti-inflammatory effects of fenoterol in ASM cells, and that the decrease in expression of AKAP5 and AKAP12 in response to cigarette smoke and in COPD patient lungs, which suggests that cigarette smoke-induced changes in AKAP5 and AKAP12 in COPD patients may affect efficacy of pharmacotherapy (Poppinga *et al.* 2015).

CONCLUSIONS AND PERSPECTIVES

In recent years, an increasing number of new evidences have deepened our understanding of AKAP signaling networks and their complexity. According to the original model, there were only two properties of AKAP family, that is, a PKA binding domain and a targeting domain. However, the discovery that AKAP5 associated with other signaling enzymes forced a reevaluation of the functional properties of AKAPs (Faux & Scott, 1996). The AKAP5 model has evolved to encompass the growing facets of AKAPs signaling (example: Figure 1). Now, new research on AKAP5 will once

again change the understanding on these multifaceted proteins to include the formation of multiunit signaling complexes comprising of both upstream activators and downstream targets (Colledge *et al.* 2000; Fraser *et al.* 2000).

AKAPs are potential to assemble signaling complexes through association with multiple enzymes and binding partners. This intriguing idea is illustrated by AKAP5, which anchors and targets to multiple intracellular molecules (Dodge & Scott, 2000; Wong & Scott, 2004) (Table 1). It has been shown that β-Adrenergic stimulation of PKA regulates synaptic ion channels which associate with MAGUKs (Kornau *et al.* 1995; Raman *et al.* 1996). There are more and more evidences proving the vital role of AKAP5 in synaptic transduction and cardiovascular pathophysiology processes, therefore, undoubtedly future studies will focus on the possibility of similar complexes formed in other tissues, since AKAP5 displays a broad range of expression.

Distinct gene knockout mice are developed to explore the physiological importance of AKAPs. To date, there are three AKAP150 mutant mice lines having been generated (Hall DD *et al.* 2007; Lu Y *et al.* 2007; Tunquist BJ *et al.* 2008; Sanderson JL *et al.* 2011). Since the association of AKAP5 with the RII subunit of PKA, calcineurin and many other signaling molecules has been implicated in both neuronal activity and cardiovascular system (example: Figure 1), it is conceivable that these mice demonstrate deficiencies in cerebral and cardiovascular function. AKAP150 also expresses in liver, but has no function (Hinke *et al.* 2012). As for the significant role in cellular signaling transduction, it is likely that the application of new techniques will uncover further understanding about AKAP5 and further examples in which relocalization and turnover of AKAP complexes have an essential role in specifying the spatial and temporal organization of signaling events.

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