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Themed Section: Novel cAMP Signalling Paradigms

REVIEW

A-kinase anchoring proteins as potential drug targets

Jessica Tröger[1], Marie C Moutty[1,2], Philipp Skroblin[1] and Enno Klussmann[1]

[1]*Max Delbrück Center for Molecular Medicine Berlin-Buch (MDC), Berlin, Germany, and*
[2]*Leibniz Institute for Molecular Pharmacology (FMP), Berlin, Germany*

Correspondence
Dr Enno Klussmann, Max-Delbrück Center for Molecular Medicine Berlin-Buch (MDC), Robert-Rössle-Strasse 10, 13125 Berlin, Germany. E-mail: enno.klussmann@mdc-berlin.de

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A-kinase anchoring proteins (AKAPs) crucially contribute to the spatial and temporal control of cellular signalling. They directly interact with a variety of protein binding partners and cellular constituents, thereby directing pools of signalling components to defined locales. In particular, AKAPs mediate compartmentalization of cAMP signalling. Alterations in AKAP expression and their interactions are associated with or cause diseases including chronic heart failure, various cancers and disorders of the immune system such as HIV. A number of cellular dysfunctions result from mutations of specific AKAPs. The link between malfunctions of single AKAP complexes and a disease makes AKAPs and their interactions interesting targets for the development of novel drugs.

LINKED ARTICLES
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Abbreviations
AKAP, A-kinase anchoring protein; AMPA, α-amino-3-hydroxy-5-methylisooxazole-4-propionic acid; AVP, arginine vasopressin; C, PKA catalytic subunit; CaM, calmodulin; CD3, cluster of differentiation; Csk, C-terminal Src kinase; CTA, cancer testis antigen; EBP50, ezrin/radixin/moesin binding protein of 50 kDa; EPAC, exchange protein activated by cAMP; ER, endoplasmic reticulum; KCNQ1, potassium voltage-gated channel, KQT-like subfamily, member 1; LQTS, long-QT syndrome; LTCC, L-type calcium channels; LTD, long-term depression; LTP, long-term potentiation; PACT, pericentrin-AKAP350 centrosomal targeting; PAG, phosphoprotein associated with glycosphingolipid-enriched microdomains; PIP2, phosphatidylinositol 4,5-bisphosphate; PKA, cAMP-dependent protein kinase or protein kinase A; PLN, phospholamban; RBD, RII binding domain; RI/RII, PKA regulatory subunit type I/II; RIAD, RI anchoring disruptor; RyR2, type 2 ryanodine receptor; sAC, soluble adenylyl cyclase; SERCA2, sarcoplasmic reticulum calcium ATPase2; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SNP, single nucleotide polymorphism; SOCE, store-operated calcium entry; SR, sarcoplasmic reticulum; SSeCKS, Src-suppressed protein C kinase substrate; TCR, T cell receptor

Introduction

Activation of a subset of GPCRs by specific extracellular ligands can trigger activation of defined cellular responses *via* the second messenger cAMP. Signal transmission by cAMP occurs through activation of downstream effector proteins including cyclic nucleotide-gated ion channels, exchange proteins activated by cAMP (Epac) and the cAMP-dependent protein kinase (PKA). Specificity of cAMP signalling is achieved by compartmentalisation through A-kinase anchoring proteins (AKAPs). AKAPs are a family of around 50 scaffolding proteins which anchor PKA and other proteins including protein kinases, protein phosphatases and phosphodiesterases to defined intracellular locations and thereby locally restrict the corresponding enzymatic activities (Figure 1; reviewed in (Pidoux and Tasken, 2010; Skroblin *et al.*, 2010; Welch *et al.*, 2010). Thus, AKAP-based protein complexes form the basis for the spatiotemporal control of cAMP signalling (Dodge-Kafka *et al.*, 2008). Individual AKAPs differ in their additional and unique characteristics, which can include intrinsic catalytic domains, interaction motifs for other proteins and targeting domains defining their subcellular localizations. Through their additional interacting domains AKAPs integrate cAMP signalling with other cellular signalling processes.

A common characteristic of AKAPs is their ability to bind PKA. PKA holoenzyme is a tetrameric complex comprising a dimer of regulatory subunits of type I or type II (RIα, RIβ, RIIα or RIIβ), and two catalytic subunits (Cα, Cβ or Cγ). Within the holoenzyme, each regulatory subunit interacts with a catalytic subunit, which is released upon binding of cAMP to the

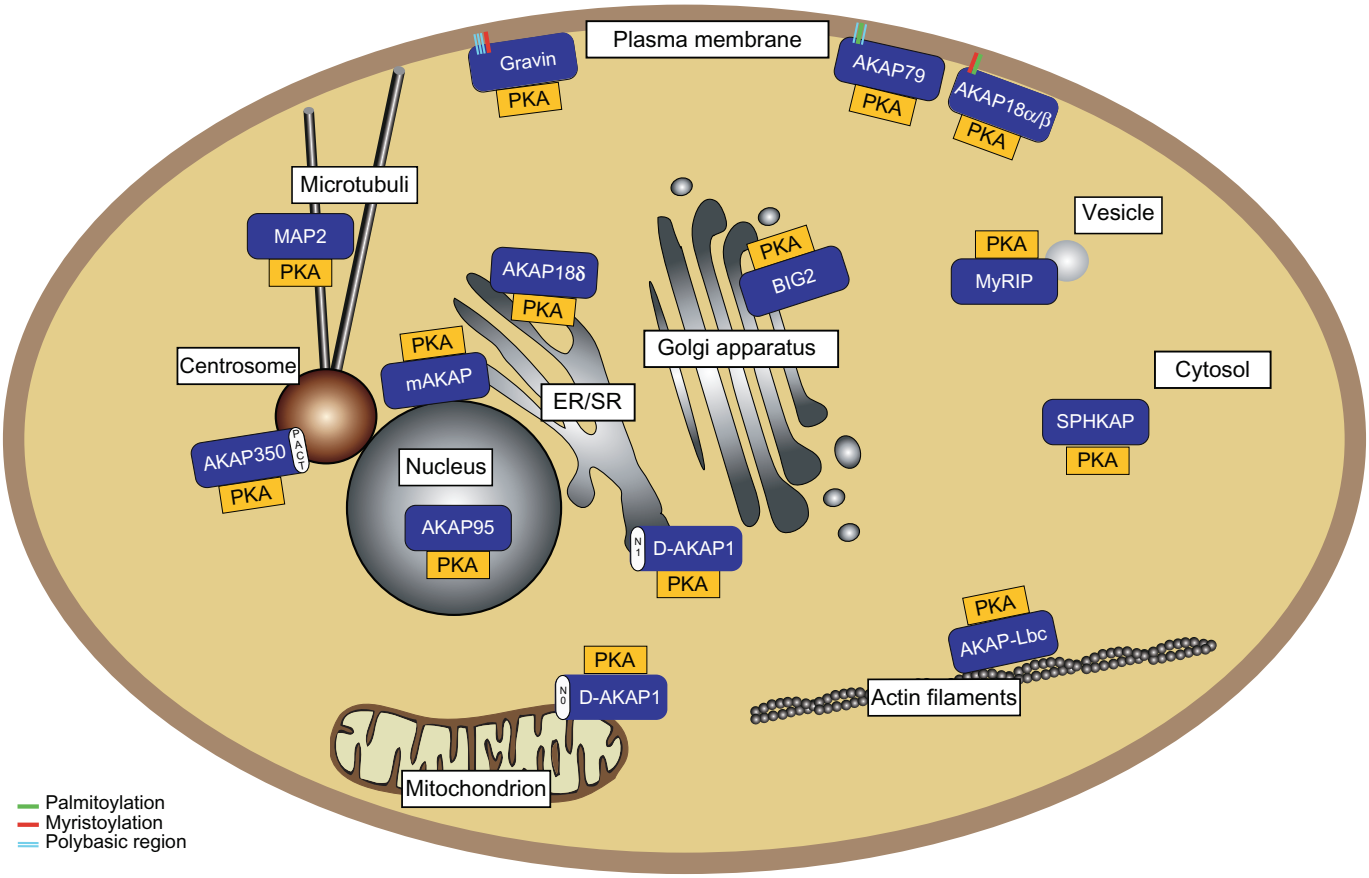

Figure 1

Distribution of AKAP-based scaffolding complexes. AKAPs target PKA and other signalling molecules to almost every cellular compartment. Some examples are shown in Figure 1. For details, see text.

regulatory subunits and thereby activated. AKAP binding is mediated by the dimerization and docking (D/D) domain formed by the dimer of R subunits. The PKA-binding domain is structurally conserved within the AKAP family, and as most AKAPs predominantly bind RII subunits, it is often termed RII binding domain. Based on their preferential binding of type I or II regulatory subunits, AKAPs are classified as RI- or RII-specific AKAPs. Of note, with sphingosine kinase type-1 interacting protein (SKIP or SPHKAP), a mammalian RI-specific AKAP has recently been identified (Kovanich *et al.*, 2010). If AKAPs can bind RI or RII, they are termed dual-specific AKAPs (Hundsrucker and Klussmann, 2008; Skroblin *et al.*, 2010).

Targeting of AKAP complexes

The specific localization of AKAPs is of fundamental importance for the generation and the coordinated control of defined cAMP signalling complexes. A variety of targeting domains direct different AKAPs to various cellular compartments, for example, the plasma membrane, mitochondria, the cytoskeleton, the sarcoplasmic reticulum (SR), the nucleus or the cytosol (Figure 1) (Tasken and Aandahl, 2004; Wong and Scott, 2004; Skroblin *et al.*, 2010).

The molecular mechanisms underlying the distribution of AKAPs are in many instances unknown. It appears that protein–protein interactions often mediate the targeting. Examples are the interactions of AKAP18δ with phospholamban, of mAKAP with Ryanodine receptors and Nesprin-1α, and of Yotiao with $KCNQ_1$ in cardiac myocytes (see below). Several AKAPs are recruited to the plasma membrane by interactions with membrane lipids. The localization of some of these AKAPs is controlled by a combination of lipid–lipid and protein–lipid or protein–protein interactions. An example is gravin (AKAP12/AKAP250), which contains a myristoylation site and three short polybasic regions mediating its localization at the cytoplasmic face of the plasma membrane. The polybasic regions bind to phosphatidylinositol 4,5-bisphosphate in the plasma membrane, whereas the myristoyl moiety of gravin is inserted into the lipid bilayer and directly anchors the protein at the plasma membrane (Malbon *et al.*, 2004). Gravin's intracellular distribution is dynamically regulated as it can be affected by calcium through binding of calmodulin (CaM). By binding to the positively charged polybasic domains, Ca^{2+}/CaM competes with membrane lipids and leads to translocation of gravin from the plasma membrane to the cytoplasm (Tao *et al.*, 2006). Additional evidence for a dynamic localization of gravin comes from a recent study with its rodent orthologue,

Src-suppressed protein C kinase substrate (SSeCKS), which relocates from the cell periphery to a perinuclear region upon activation of PKC (Lin *et al.*, 1996; Yan *et al.*, 2009). However, the underlying mechanism remains to be elucidated.

A polybasic region also defines the localization of AKAP79 (AKAP5). Additionally, it has been reported that activation of PKC or Ca^{2+}/CaM causes the release of AKAP79 from the plasma membrane (Dell'Acqua *et al.*, 1998). The interference of Ca^{2+}/CaM and activated PKC with the membrane localization of gravin and AKAP79 suggests that there might be a common mechanism by which the localization of different AKAPs is regulated. A palmitoylation of two cysteine residues in the polybasic region of AKAP79 leads to accumulation of AKAP79 in lipid rafts facilitating the regulating of store-operated calcium entry calcium channels and adenylyl cyclase 8 by this AKAP (Delint-Martinez *et al.*, 2011).

Several AKAPs are targeted to the plasma membrane through myristoyl and palmitoyl modifications, including the short isoforms α and β of AKAP18 (Fraser *et al.*, 1998; Trotter *et al.*, 1999). AKAP18α is predominantly anchored at the basolateral plasma membrane whereas AKAP18β accumulates at the apical membrane of epithelial cells (Trotter *et al.*, 1999). Compared with the 81 amino acids long AKAP18α, the β isoform contains an insertion of 23 amino acids C-terminally of residue 17. Whether this difference is responsible for the differential targeting is not understood.

Another well-characterized targeting domain has been described for D-AKAP1. An N-terminal splice variant of this AKAP (N0) localises to the mitochondrial outer membrane, whereas a longer form (N1) that has a 33 amino acid insertion within the N-terminal region of N0 is found at the smooth and the rough membrane of the endoplasmic reticulum (ER) (Huang *et al.*, 1999). Targeting of both isoforms to their destinations depends on the same motif, a bi-functional helix surrounded by hydrophobic amino acid residues (Ma and Taylor, 2002). A single residue in D-AKAP1 (Asp31) seems to be critical for a subcellular switch turning the mitochondrial targeting signal into a bipartite ER targeting signal without destroying the mitochondrial targeting signal (Ma and Taylor, 2008).

The centrosomal AKAPs pericentrin and AKAP350 are both recruited to their destination by the same protein interaction module, the pericentrin-AKAP350 centrosomal targeting domain (Diviani *et al.*, 2000; Gillingham and Munro, 2000). Although this 90 amino acids spanning domain is well conserved and has been shown to interact with CaM, the recruiting mechanism probably does not involve CaM. However, this has not been clarified yet (Gillingham and Munro, 2000).

Despite the few unveiled targeting mechanisms, for the majority of AKAPs the mechanisms underlying their intracellular distribution are not understood. Elucidation of these targeting mechanisms will help to understand the regulation and physiological functions of individual AKAP signalling complexes.

Physiological relevance of AKAPs in health and disease

Tight spatial and temporal regulation of cAMP signalling is of fundamental importance for many physiological processes. This is particularly evident as altered cAMP signalling is associated with or causes a variety of pathological cellular responses involved in endocrinological, nephrological, neurodegenerative, cardiovascular and immune diseases and several types of cancer (Table 1). In many instances, the diseases do not involve changes in global cAMP/PKA signalling, but often involve malfunctions of specific AKAP complexes.

AKAPs in cardiac physiology and pathophysiology

In the heart, AKAP complexes participate in the regulation of a variety of processes, for example, sympathetic modulation of excitation-contraction coupling (reviewed (Carnegie *et al.*, 2009; Mauban *et al.*, 2009; Scott and Santana, 2010; Skroblin *et al.*, 2010; Carnegie and Burmeister, 2011; Diviani *et al.*, 2011; Kritzer *et al.*, 2011). β-adrenoceptor activation on the surface of cardiac myocytes leads to a PKA-catalyzed phosphorylation of a variety of substrates, among them L-type Ca^{2+} channels, type 2 ryanodine receptors (RyR_2) and phospholamban (PLN). These phosphorylations regulate Ca^{2+} fluxes and thereby enhance contractility. Muscle-selective AKAP, mAKAPβ, directly interacts with RyR_2; this interaction appears to play a role in the phosphorylation of RyR_2 by PKA and thereby in the enhancement of the Ca^{2+} efflux from the SR into the cytosol (Marx *et al.*, 2000; 2001; Kapiloff *et al.*, 2001). However, it is unclear whether the mAKAP-RyR_2 complex is present throughout the SR or only in a perinuclear compartment; to the nuclear envelope, mAKAP is targeted through interaction with nesprin-1α (Kapiloff *et al.*, 1999; Pare *et al.*, 2005a). In addition, mAKAPβ participates in the PKA-dependent inhibition of the Na^+/Ca^{2+} exchanger 1 at the sarcolemma (Schulze *et al.*, 2003), leading to reduced Ca^{2+} extrusion. AKAP18δ directly interacts with PLN, facilitates the phosphorylation of PLN by PKA and thereby stimulates the dissociation of PLN from the sarcoplasmic reticulum Ca^{2+} ATPase 2. This, in turn, results in enhanced calcium re-uptake into the SR (Lygren *et al.*, 2007). AKAP5 participates in the control of the sympathetic regulation of the amplitude and rate of decay of Ca^{2+} transients in cardiac myocytes, apparently through a signalling complex containing AKAP5, adenylyl cyclase 5/6, PKA, PP2B, $Ca_v1.2$ and β-adrenoceptors that are associated with caveolin 3. The complex generates a microdomain of cAMP in the vicinity of RyR_2 (Nichols *et al.*, 2010). The AKAP9 isoform Yotiao modulates cardiac repolarization via its interaction with PKA and control of the PKA phosphorylation of the voltage gated potassium channel $KCNQ_1$ (Kurokawa *et al.*, 2004).

Direct evidence for the involvement of distinct AKAPs in cardiac diseases comes from genetic polymorphisms and knockout studies. A single nucleotide polymorphism (SNP) in Yotiao, S1570L, reduces its interaction with $KCNQ_1$, thereby altering the repolarization of cardiac myocytes in the human heart and causes long-QT syndrome (Chen *et al.*, 2007). An SNP in the PKA-binding domain of D-AKAP2 (AKAP10), I646V, can cause shortening of the PR interval of the cardiac cycle (Kammerer *et al.*, 2003), elevated resting heart rate and diminished heart rate variability (Tingley *et al.*, 2007; Neumann *et al.*, 2009), which are markers that predict an increased risk of sudden cardiac death. In line with this, mutant mice lacking the last 51 amino acids of the D-AKAP2

Table 1

Disease relevance of AKAPs

AKAP	Modification	Associated disease
D-AKAP1 (AKAP1)	Gene knockout in mice	Female infertility and defects in oocyte meiosis[a]
AKAP82 (AKAP4)	Gene knockout in mice	Male infertility and defects in sperm motility[b]
Yotiao (AKAP9)	Genetic polymorphism Ser1570Lys	Long Q-T syndrome, cardiac arrhythmias[c]
D-AKAP2 (AKAP10)	Genetic polymorphism Ile646Val	Familial breast cancer[d]
		Long P-R interval in electrocardiography[e]
		Increased basal heart rate,[f] reduced heart rate variability[f,g]
	Gene truncation in mice	Cardiac arrhythmia[f]
AKAP-Lbc (AKAP13)	Genetic polymorphism Lys526Gln	Familial breast cancer[h]
	Knockout in mice	Defective cardiac development, death by cardiac arrest[i]
	Down-regulation by shRNA	α1-adrenergic receptor-induced cardiac hypertrophy[j]
Pericentrin	Genetic loss of function mutations	Microcephalic osteodysplastic primordial dwarfism type II[k,l,m], along with insulin resistance and diabetes[n]
	Genetic polymorphism	Schizophrenia, major depressive disorder[o]
Neurobeachin	Gene disruption or partial deletion	Autism[p,q]
	Gene knockout in mice	Perturbed synaptic function, perinatal death[r]
mAKAP (AKAP6)	Down-regulation by shRNA	Cytokine-and GPCR-induced cardiac hypertrophy[s,t]
Gravin (AKAP12)	Autoantibody against gravin	Autoimmune disease myasthenia gravis[u]
	Gene knockout in mice	Prostate hyperplasia[v]
WAVE-1	Gene knockout in mice	Sensorimotor retardation, deficits in learning and memory[w]
AKAP150 (AKAP79) (AKAP5)	Gene knockout in mice	Altered synaptic transmission and memory retention, deficient motor coordination and strength[x,y]
		Decreased myogenic tone[z]

[a]Newhall *et al.*, 2006.
[b]Miki *et al.*, 2002.
[c]Chen *et al.*, 2007.
[d]Wirtenberger *et al.*, 2007.
[e]Kammerer *et al.*, 2003.
[f]Tingley *et al.*, 2007.
[g]Neumann *et al.*, 2009.
[h]Wirtenberger *et al.*, 2005.
[i]Mayers *et al.*, 2010.
[j]Appert-Collin *et al.*, 2007.
[k]Rauch *et al.*, 2008.
[l]Rauch, 2011.
[m]Willems *et al.*, 2010.
[n]Huang-Doran *et al.*, 2011.
[o]Numata *et al.*, 2009; 2010.
[p]Smith *et al.*, 2002.
[q]Castermans *et al.*, 2003.
[r]Medrihan *et al.*, 2009.
[s]Dodge-Kafka *et al.*, 2005.
[t]Pare *et al.*, 2005b.
[u]Gordon *et al.*, 1992.
[v]Akakura *et al.*, 2008.
[w]Soderling *et al.*, 2003.
[x]Lu *et al.*, 2007.
[y]Tunquist *et al.*, 2008.
[z]Navedo *et al.*, 2008.

gene display cardiac arrhythmia and die prematurely (Tingley *et al.*, 2007).

Dysregulation of AKAPs and their interactions are also associated with chronic heart failure (Movsesian and Bristow, 2005; Mauban *et al.*, 2009; Diviani *et al.*, 2011; Kritzer *et al.*, 2011). Aye *et al.* found in human failing hearts an increase in the interaction between PKA and the AKAPs SPHKAP and AKAP2 (sixfold each), AKAP18 (more than twofold) and MAP2 (12-fold), whereas the authors revealed decreases in the interactions of PKA with AKAP1 by 50% and with Yotiao by 15% of the normal level (Aye *et al.*, 2011).

AKAPs in neurological diseases

Neurological disorders including Alzheimer's disease, seizure, mental retardation and drug addiction are usually accompanied by perturbations in the plasticity of excitatory glutamatergic synapses, that is, the inability to modulate the strength of synaptic transmission. In the hippocampus, two forms of altered synaptic strength have been intensively studied, long-term potentiation and long-term depression (LTD) (Martin and Morris, 2002). Two major players involved in these changes are the glutamate receptors, NMDA and AMPA receptors (reviewed in Soderling and Derkach, 2000). Phosphorylation by PKA and other kinases modulates the activity of glutamate receptors and thereby the depolarization of the post-synaptic neurons.

The most prominent AKAP involved in regulation of synaptic plasticity is AKAP5 (AKAP79/150), which contributes to NMDA receptor-mediated LTD (Jurado *et al.*, 2010). AKAP5-deficient mice showed altered synaptic transmission and exhibited deficiencies in neuronal processes including motor coordination (Tunquist *et al.*, 2008). Mice expressing an AKAP5 mutant that lacks the PKA binding domain showed even stronger defects in synaptic plasticity and learning processes (Weisenhaus *et al.*, 2010).

AKAPs in the reproductive system

Several AKAPs are expressed in the male and female reproductive systems (Luconi *et al.*, 2011). Investigations have particularly focused on the roles of D-AKAP1, WAVE1, AKAP3 and AKAP4 in reproduction.

The maturation of oocytes is controlled by AKAP–PKA interactions. They participate in the maintenance of meiotic arrest (Newhall *et al.*, 2006). The resumption of oocyte maturation has been suggested to involve AKAP1 (Webb *et al.*, 2008). Knockout studies in mice revealed that the complete absence of AKAP1 leads to infertility of females with maturation defective ovaries, whereas the fertility of male animals was not affected (Newhall *et al.*, 2006). During fertilization of the oocyte, WAVE1 re-localizes to the nuclear envelope, which is accompanied by redistribution of PKA type II and the tyrosine kinase Abl (Rawe *et al.*, 2004b). Alterations in the localization of WAVE1 perturb the normal progression of fertilization (Rawe *et al.*, 2004a), which might represent a possible link to the early developmental defects in flies observed upon mutations in the WAVE/Scar gene (Miki and Takenawa, 2003).

In males, AKAP–PKA interactions are crucial for sperm motility (Vijayaraghavan *et al.*, 1997). AKAPs involved in this process are the sperm-specific AKAP3 and AKAP4, both located in the fibrous sheath (Carrera *et al.*, 1994; Vijayaraghavan *et al.*, 1999). Evidence for a role of AKAP4 in sperm motility was provided by gene knockout in mice, which resulted in reduced motility of sperm and infertile male animals (Miki *et al.*, 2002). In line, the abundance of AKAP4 correlates with sperm motility (Moretti *et al.*, 2007). Though the presence of AKAP4 seems indispensible for sperm motility and thus the process of fertilization, the underlying mechanisms are still unclear. Evidence for the involvement of AKAP3 in the regulation of sperm motility comes from studies analysing the stimulating effect of bicarbonate (Luconi *et al.*, 2004). Bicarbonate activates soluble adenylyl cyclase and thereby triggers a signalling cascade, which evokes tyrosine phosphorylation of AKAP3 resulting in enhanced anchoring of PKA by AKAP3.

AKAPs in the immune system

The activation of T cells by the T cell receptor (TCR) is an important step in cellular immune responses (reviewed by Mosenden and Tasken, 2011). PKA type I, the predominant variant in these cells, is anchored in lipid rafts by the dual-specific AKAP ezrin (Ruppelt *et al.*, 2007). Ezrin anchors PKA in close proximity to the TCR/CD3 complex (Skalhegg *et al.*, 1994). Activation of PKA by cAMP suppresses T cell replication and maintains T cells in a resting state. The underlying mechanism involves phosphorylation of the C-terminal Src kinase (Csk) by PKA, which increases Csk activity, inhibiting activity of downstream Src kinases and ultimately preventing T cell activation (Vang *et al.*, 2001). Ezrin forms a protein complex containing PKA, ezrin/radixin/moesin binding protein of 50 kDa, phosphoprotein associated with glycosphingolipid-enriched microdomains and Csk suggesting a tight spatiotemporal control of PKA signalling in this context (Cornez and Tasken, 2010).

HIV-1 infection has been associated with increased levels of cAMP and enhanced activation of PKA (Hofmann *et al.*, 1993). Studies on immune responses in HIV patients revealed that increased activation of PKA type I contributes to T cell dysfunction (Aandahl *et al.*, 1998), and inhibition of PKA had beneficial effects on T cell proliferation (Aandahl *et al.*, 1999). In a murine AIDS model, specific disruption of AKAP-PKA type I complexes with the RI-anchoring disruptor peptide RIAD causes resistance of T cells to retrovirus-induced immunodeficiency (Mosenden *et al.*, 2011) which is most likely evoked by perturbations in the PKA/ezrin/Csk pathway. Besides ezrin, D-AKAP1 is also involved in the progression of HIV infection. D-AKAP1 binds HIV reverse transcriptase and, in the manner of a cofactor, supports reverse transcription during HIV infection (Lemay *et al.*, 2008). However, more detailed studies are required to fully understand the functional role of this AKAP in HIV progression.

AKAPs in insulin secretion and glucose metabolism

Diabetes mellitus is a disease caused by insulin deficiency (type I diabetes) or by an initial insulin resistance and consequent insufficient insulin secretion (type II diabetes). This leads to impaired glucose metabolism and, ultimately, to *diabetes mellitus*, which may be associated with diabetic nephropathy, polyneuropathy, retinopathy, and cardiovascular complica-

tions including atherosclerosis and heart failure. The important role of pancreatic AKAPs in insulin secretion became obvious through the finding that inhibition of AKAP–PKA interactions with the PKA anchoring disruptor Ht31 diminished insulin secretion from a rat insulinoma cell line and isolated rat pancreatic islets (Lester *et al.*, 1997). AKAPs involved in insulin release are AKAP150 (AKAP5), AKAP18α and AKAP18γ (Fraser *et al.*, 1998; Lester *et al.*, 2001; Josefsen *et al.*, 2010). Their specific functions seem to be different. Overexpression of AKAP18α in rat pancreatic β cells significantly increases glucagon-like peptide 1-mediated insulin secretion. AKAP18γ has the opposite effect (Fraser *et al.*, 1998). Silencing studies confirmed a decrease in glucose-stimulated insulin release upon AKAP18α depletion and an increase in the case of AKAP18γ depletion. This is consistent with their respective regulations by glucose (Josefsen *et al.*, 2010). AKAP150 interacts with PKA and calcineurin (protein phosphatase 2B), whereby it coordinates the reversible phosphorylation of PKA targets involved in insulin exocytosis (Lester *et al.*, 2001). AKAP150 interacts with the GTPase IQGAP1, which is involved in the control of the cytoskeleton (Nauert *et al.*, 2003). This interaction may play a role in the transport of insulin-bearing vesicles. Hence, pharmacological targeting of specific AKAP–PKA complexes has the potential for the development of new medication for the treatment of *diabetes mellitus*. However, this example also highlights the necessity of specifically targeting defined AKAP–PKA pools rather than global interference with these interactions.

AKAPs in cancer

Differential regulation of AKAPs is involved in a variety of human cancers. One example is gravin. It is a tumour suppressor protein involved in the regulation of the cell cycle and cell migration (Gelman, 2002; Skroblin *et al.*, 2010). Down-regulation of SSeCKS/gravin/AKAP12 is observed in a number of tumours including radiation-induced osteoblastoma (Daino *et al.*, 2009), breast (Perou *et al.*, 2000), ovary (Welsh *et al.*, 2001) and prostate cancer (Xia *et al.*, 2001). Accordingly, re-expression of SSeCKS in prostate cancer cells was shown to suppress tumorigenesis (Lin and Gelman, 1997) and to cause inhibition of metastasis (Su *et al.*, 2010). A likely explanation for reduced expression of gravin orthologues is hypermethylation of the promotor region of AKAP12 occuring in a variety of human cancers (Liu *et al.*, 2010; Wu *et al.*, 2011). In Addition, the AKAP12 gene is located in a hot spot region, which is deleted in prostate, breast and ovary cancers (Wan *et al.*, 1999; Xia *et al.*, 2001; Skroblin *et al.*, 2010).

AKAP4 (also termed AKAP82) is a testis-specific AKAP (Turner *et al.*, 2001), with a pivotal role in sperm motility and thus male fertility (Miki *et al.*, 2002; Moretti *et al.*, 2007). Recently, AKAP4 has been classified as a cancer testis antigen (CTA), which is strongly expressed in multiple myeloma (Chiriva-Internati *et al.*, 2008).

SNPs of several AKAPs are associated with an increased risk for the development of breast cancer [including AKAP9 (Frank *et al.*, 2008), AKAP-Lbc (Wirtenberger *et al.*, 2005) and D-AKAP2 (Wirtenberger *et al.*, 2007)]. The SNP A2073G in D-AKAP2 results in the amino acid substitution I646V, which is located in the PKA-binding domain of the protein. This substitution alters PKA binding in an isoform-specific manner (Kammerer *et al.*, 2003): the binding of RIIα or RIIβ seems not to be affected, whereas the valine variant exhibits a threefold stronger interaction with RIα, probably causing altered subcellular distribution of PKA type I.

AKAP-dependent signalling complexes as potential therapeutic targets

The involvement of AKAPs and their interactions in numerous cellular processes and their dysregulation in diseases make AKAP complexes potential drug targets, in particular AKAP–PKA interactions. Interventions could be achieved by down-regulation of specific AKAPs with RNAi as well as by selective inhibition of AKAP-dependent protein-protein interactions. For example, disruption of AKAP–PKA interactions has been carried out by the use of peptides derived from PKA-binding domains of known AKAPs (Table 2). However, due to the conservation in the binding modes between different AKAPs and the different PKA isoforms, such peptides did not gain a higher specificity than differentiating between type I and type II PKA. A further drawback of peptide inhibitors is their limited applicability in biological systems due to a relatively short half-life and limited cell permeability. Attractive alternatives to inhibitory peptides are peptidomimetics and small molecule inhibitors. At comparable specificities, such agents can attain higher stability than peptides. We have recently introduced the first small molecule disruptor of AKAP–PKA interactions, FMP-API-1. However, this molecule requires further optimization as it not only targets AKAP–PKA interactions but also activates PKA (Christian *et al.*, 2011). A further possibility to interfere with protein–protein interactions is the covalent chemical modification of proteins. An example is the alkylation of AKAP3 and AKAP4 that disrupts PKA-dependent signalling in human spermatozoa (Hughes *et al.*, 2009). However, the restricted specificity of this method clearly limits the range of its biological application.

In addition to AKAP–PKA interactions, other AKAP-dependent protein–protein interactions are disease relevant and are thus also potential drug targets, for example, the AKAP18δ-PLN interaction (Table 2) (Lygren and Tasken, 2008). A few selected examples are discussed below and illustrate the potential of AKAPs and their interactions as drug targets.

AKAP-dependent protein–protein interactions in chronic heart failure

Chronic heart failure is a disease with a huge unmet medical need. A major challenge is the discovery of novel and safer drugs with fewer side effects that provide long-term benefits for the patients. As mentioned previously, AKAP-dependent protein–protein interactions play key roles in the control of the β-adrenoceptor-induced increase in cardiac contractility. The β-adrenoceptor-dependent pathway provides several potential targets for interference. Recent attempts to interfere with AKAP–PKA interactions using PKA anchoring disruptor peptides in cultured cardiac myocytes, isolated hearts and in rodent models did not yield completely consistent results but overall suggested that the net effect of the peptides is an enhancement of cardiac myocyte contractility (McConnell

Table 2

Functional consequences of disrupting AKAP-dependent protein–protein interactions

Type	Name	Target	Model system	Physiological effect
Peptide	Ht-31	AKAP–PKA	Mouse oocytes	Stimulation of oocyte maturation[a]
			Rat hearts (*in vivo*)	Increased β-AR-stimulated contractility[b]
			Hippocampal neurons	Reduced AMPA/kainate channel currents[c]
			CD4(+) T cells	Reduced antigen presentation, inhibition of TNF-α and IL-10 production[d]
	S-Ht31	AKAP–PKA	Renal inner medullary collecting duct (IMCD) cells	Inhibition of forskolin-stimulated AQP-2 translocation[e,f]
	TAT-AKAD	AKAP–PKA	Cardiac myocytes	Reduced contractility[g]
			Mouse hearts (*ex vivo*)	Negative effect on chronotropy, inotropy and lusitropy[g]
	AKAP15-LZ	AKAP18 – L-type Ca^{2+} channel	Mouse skeletal muscle cells (MM14, DZ1A)	Inhibition of voltage-dependent potentiation of L-type Ca^{2+} channel[h]
	AKAP18δ-wt	AKAP–PKA	Rat neonatal cardiac myocytes	Reduced β-adrenoceptor-induced L-type Ca^{2+} currents[i]
	Arg9-11-PLN	AKAP18δ–PLN	Rat neonatal and adult cardiac myocytes	Reduced adrenoceptor-induced Ca^{2+} reuptake into the SR[j]
	RIAD-Arg11	AKAP–PKA (I)	T cells	Uncoupling of cAMP-mediated inhibition of T-cell function[k]
			Mouse Y1 adrenocortical cells	Reduced ACTH-stimulated progesterone production[k]
	AKAP-*IS*	AKAP–PKA	HEK293 cells	Attenuation of GluR1 (AMPA receptor subunit) currents[l]
			CD4(+) T cells, KG-1 dendritic progenitor cells	Reduced antigen presentation[d,m]
	TAT-AKAP-*IS*	AKAP–PKA	INS-1 Pancreatic β-cells	Inhibition of glucagon-induced potentiation of insulin secretion[n]
	Superakap-*IS*	AKAP–PKA (II)	Hippocampal neurons	Attenuation of AMPA-responsive currents[o]
Peptido-mimetic	Unnatural RIAD	AKAP–PKA (I)	*in vitro*	Not determined[p]
Small molecule	FMP-API-1	AKAP–PKA	Rat neonatal cardiac myocytes	Increased contractility[q]
			Rat hearts (*ex vivo*)	Increased contractility[q]

TAT-AKAD, TAT-conjugated A-kinase anchoring disruptor (PKA binding region of AKAP10); RIAD: RI-anchoring disruptor; ACTH, adrenocorticotropic hormone; LZ, leucine zipper.
[a]Newhall *et al.*, 2006.
[b]McConnell *et al.*, 2009.
[c]Rosenmund *et al.*, 1994.
[d]Schillace *et al.*, 2009.
[e]Klussmann *et al.*, 1999.
[f]Henn *et al.*, 2004.
[g]Patel *et al.*, 2010.
[h]Hulme *et al.*, 2002.
[i]Hundsrucker *et al.*, 2006a.
[j]Lygren *et al.*, 2007.
[k]Carlson *et al.*, 2006.
[l]Alto *et al.*, 2003.
[m]Schillace *et al.*, 2011.
[n]Faruque *et al.*, 2009.
[o]Gold *et al.*, 2006.
[p]Torheim *et al.*, 2009.
[q]Christian *et al.*, 2011.

et al., 2009; Patel *et al.*, 2010). Similarly, the small molecule inhibitor of AKAP–PKA interactions, FMP-API-1, enhances the contractility of isolated cardiac myocytes and isolated rat hearts (Christian *et al.*, 2011). However, the observed FMP-API-1-induced increase in contractility is most likely also due to its stimulatory effect on PKA activity.

Targeting cardiac hypertrophy. Cardiac hypertrophy is an intermediate state during the development of chronic heart failure. Main characteristics are hypertrophic growth along with remodelling of cytoskeletal proteins and re-expression of fetal genes. Two AKAPs, mAKAP and AKAP-Lbc, are apparently involved in the development of cardiac hypertrophy (Appert-Collin *et al.*, 2007; Negro *et al.*, 2008; Diviani *et al.*, 2011). AKAP-Lbc is the scaffold for several proteins including RhoA (Diviani *et al.*, 2001) and Ras/Raf/ERK (Smith *et al.*, 2010). Low molecular weight GTPases are key players in cytoskeletal dynamics (Sit and Manser, 2011) and are involved in the development of cardiac hypertrophy (Lezoualc'h *et al.*, 2008). AKAP-Lbc is up-regulated in response to hypertrophic stimuli and enhances the signal transmission through several GPCRs coordinating distinct downstream signalling pathways including the RhoA and PKD/HDAC5/MEF2 paths that elicit the fetal gene response (Carnegie *et al.*, 2008).

The mAKAPβ scaffolding complex comprises PKA as well as the phosphatase calcineurin, which regulates the transcription factor NFAT that is associated with hypertrophic gene expression (Li *et al.*, 2010). mAKAP is also up-regulated in hypertrophic cardiac myocytes. Disruption of mAKAP/PKA binding suppresses mAKAP-mediated hypertrophic responses in cardiac myocytes (Pare *et al.*, 2005b).

Therefore, an attractive pharmacological approach for the treatment of cardiac hypertrophy is the disruption of AKAP-Lbc- and/or mAKAP-based protein complexes.

Targeting excessive water reabsorption. Heart failure and also the syndrome of inappropriate antidiuretic hormone secretion (SIADH) are associated with elevated levels of arginine vasopressin (AVP). AVP binds to vasopressin V2 receptors (V2R) and thereby induces the redistribution of the water channel aquaporin-2 (AQP2) from intracellular vesicles into the plasma membrane of renal collecting duct principal cells (Schrier and Cadnapaphornchai, 2003; King *et al.*, 2004; Chen and Schrier, 2006Kwon *et al.*, 2009; Nedvetsky *et al.*, 2009). Elevated AVP causes predominant localization of AQP2 in the plasma membrane enhancing reabsorption of water from primary urine. V2R antagonists, the vaptans, block the pathway and are approved for the treatment of SIADH. Unfortunately, this approach failed to provide benefits for chronic heart failure patients [EVEREST trial (Gheorghiade *et al.*, 2007; Konstam *et al.*, 2007; Miyazaki *et al.*, 2007; Blair *et al.*, 2008; O'Connor *et al.*, 2010)].

AKAP–PKA interactions are essential for the AVP-induced redistribution of AQP2 (Klussmann *et al.*, 1999; Szaszak *et al.*, 2008). Interfering with these interactions might be an alternative approach to reduce the amount of AQP2 in the plasma membrane and thereby to decrease the excessive AVP-induced water reabsorption in chronic heart failure and SIADH.

Enhanced water reabsorption and accompanying lower plasma osmolality, hyponatremia and impaired urinary dilution are characteristics for the syndrome of inappropriate antidiuresis (reviewed in Esposito *et al.*, 2011). Typical for this disorder is the absence of a renal disease or any identifiable non-osmotic stimulus known to release the anti-diuretic hormone (AVP). As discussed previously, AKAP–PKA interactions might also be an interesting target in this scenario to reduce the AVP-dependent uptake of water by preventing the predominant localization of AQP2 in the plasma membrane.

AKAPs as targets for novel contraceptives

AKAP3 and AKAP4 (Miki *et al.*, 2002; Luconi *et al.*, 2004) are crucial for the motility of sperm, which make them indispensable for male fertility (see above). Thus, interfering with the function of these AKAPs in sperm may be a possibility for the development of novel contraceptives (reviewed in Suri, 2005). Indeed, the work of Hughes demonstrates that quinoid compounds cause selective alkylation of AKAP3 and AKAP4, disrupt PKA signalling and ultimately lead to the suppression of sperm movement (Hughes *et al.*, 2009). A disadvantage of such quinones is their toxicity (Hughes *et al.*, 2007), which could be circumvented by the development of new derivatives with similar beneficial effects but lower toxicity. Besides their spermatostatic effect, these molecules have a bactericidal activity on *Chlamydiaceae*. Therefore, such substances would be dual-purpose contraceptives. They prevent pregnancy and protect against sexually transmitted diseases.

AKAP4 as potential new target in immunotherapies against cancer

Besides its pivotal role in sperm motility (Miki *et al.*, 2002) the dual-specific AKAP4 also plays a critical role in cancer. AKAP4 is CTA in two types of cancer, the B-cell malignancy multiple myeloma (Chiriva-Internati *et al.*, 2008) and prostate cancer (Chiriva-Internati *et al.*, 2011). CTAs are strongly immunogenic tumour-associated antigens, whose expression is typically limited to germ line and cancer cells (Scanlan *et al.*, 2004). Due to these characteristics, CTAs represent a highly attractive class of antigens for immunotherapy approaches for the treatment of cancer. The detection of anti-AKAP4 immunoglobulins in sera of multiple myeloma patients (Chiriva-Internati *et al.*, 2008) indicates the possible use of AKAP4 as a tumour biomarker. Chiriva-Internati *et al.* succeeded in generating AKAP4-specific cytotoxic T lymphocyte responses, which led to the selective killing of prostate cancer cells (Chiriva-Internati *et al.*, 2011). Collectively, these observations make AKAP4 a promising target for immunotherapy/tumour vaccination against prostate cancer, one of the major tumours in men (Ferlay *et al.*, 2007).

Outlook

AKAP-based multi-protein complexes are present in almost every compartment of a cell (Figure 1). AKAP-dependent protein–protein interactions crucially contribute to the coordination of cellular signalling in a spatially and temporally defined manner (Dodge-Kafka *et al.*, 2008; Carnegie *et al.*, 2009; Mauban *et al.*, 2009; Pidoux and Tasken, 2010; Skroblin *et al.*, 2010; Diviani *et al.*, 2011; Kritzer *et al.*, 2011). Dysregulation of a number of AKAPs and/or their protein-protein

interactions is associated with or causes diseases. Thus, AKAP complexes represent interesting targets for the development of new therapeutics.

Due to their specificity and diversity intracellular protein–protein interactions are attractive drug targets (Wells and McClendon, 2007; Klussmann and Rosenthal, 2008). The inhibition of protein–protein interactions in defined cellular compartments permits a highly selective pharmacological interference with defined, local cellular processes. Such an approach should not affect whole cell functions as it occurs upon treatment with drugs targeting, for example, receptors, ion channels and pumps or enzyme activities, that is, proteins often involved in the control of multiple downstream processes. Thus, targeting disease-relevant AKAP-dependent protein–protein interactions is a novel pharmacological concept that may lead to a novel class of safer and more effective drugs, most of all, for the treatment of diseases with an unmet medical need.

The use of global inhibitors of AKAP–PKA interactions, in particular in cardiac myocytes and β-cells, has highlighted the necessity to specifically target the interactions of defined AKAPs with PKA. This is highly unlikely to be achieved by targeting the interacting surfaces as they are conserved. Required are agents such as small molecules or peptidomimetics that allosterically bind to single AKAPs and thereby affect local pools of PKA. As opposed to the PKA binding domains, other protein–protein interaction domains are unique to each AKAP. Hence, the disease-relevant ones such as those of AKAP-Lbc that mediate cardiac myocyte hypertrophy are also potential targets for pharmacotherapy.

Present data on solution structures of AKAP peptides and the D/D domain of the regulatory subunit of PKA comprising the binding side of both molecules (Newlon *et al.*, 1999; 2001; Gold *et al.*, 2006; Kinderman *et al.*, 2006) together with knowledge of the contribution of single amino acids to these interactions (e.g. Alto *et al.*, 2003; Burns-Hamuro *et al.*, 2003; Hundsrucker *et al.*, 2006b; Hundsrucker and Klussmann, 2008) offer the opportunity to study the details of this binding and to structurally design non-peptidic small molecule antagonists for global inhibition of AKAP–PKA complexes. Further attempts, and most likely novel approaches, to obtain structural information on the flexible and modular AKAPs are needed to gain detailed insight into the molecular determinants of AKAP-dependent protein–protein interactions. For the identification of disruptors of disease-relevant AKAP-dependent protein–protein interactions, high-throughput screening is an alternative strategy (Colas, 2008). FMP-API-1 is a first small molecule inhibitor of AKAP–PKA interactions identified in such a screening approach (Christian *et al.*, 2011). As the molecule also activates PKA, more specific inhibitors of AKAP–PKA interactions are required. In the future, the development of specific modulators of disease-relevant AKAP-dependent protein–protein interactions is highly desirable in order to validate such interactions as drug targets.

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Conflict of interest

The authors declare that they do not have conflicts of interest.

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