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

Keywords

AKAP; aquaporin; drug targets;
heart failure; PKA; small
molecules

Received

8 September 2011

Revised

5 November 2011

Accepted

16 November 2011

REVIEW

A-kinase anchoring proteins as potential drug targets

Jessica Tröger¹, Marie C Moutty^{1,2}, Philipp Skroblin¹ and
Enno Klussmann¹

¹Max Delbrück Center for Molecular Medicine Berlin-Buch (MDC), Berlin, Germany, and

²Leibniz Institute for Molecular Pharmacology (FMP), Berlin, Germany

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

This article is part of a themed section on Novel cAMP Signalling Paradigms. To view the other articles in this section visit <http://dx.doi.org/10.1111/bph.2012.166.issue-2>

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 (RI α , RI β , RII α or RII β), and two catalytic subunits (C α , C β or C γ). 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 (Hundsruker and Klusmann, 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 KCNQ₁ 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, Ca²⁺/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). AKAP18 α is predominantly anchored at the basolateral plasma membrane whereas AKAP18 β accumulates at the apical membrane of epithelial cells (Trotter *et al.*, 1999). Compared with the 81 amino acids long AKAP18 α , 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 (RyR₂) and phospholamban (PLN). These phosphorylations regulate Ca^{2+} fluxes and thereby enhance contractility. Muscle-selective AKAP, mAKAP β , directly interacts with RyR₂; this interaction appears to play a role in the phosphorylation of RyR₂ 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-RyR₂ complex is present throughout the SR or only in a perinuclear compartment; to the nuclear envelope, mAKAP is targeted through interaction with nesprin-1 α (Kapiloff *et al.*, 1999; Pare *et al.*, 2005a). In addition, mAKAP β participates in the PKA-dependent inhibition of the $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger 1 at the sarcolemma (Schulze *et al.*, 2003), leading to reduced Ca^{2+} extrusion. AKAP18 δ 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, $\text{Ca}_v1.2$ and β -adrenoceptors that are associated with caveolin 3. The complex generates a microdomain of cAMP in the vicinity of RyR₂ (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 KCNQ₁ (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 KCNQ₁, 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,9}
	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	α 1-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

^aNewhall *et al.*, 2006.^bMiki *et al.*, 2002.^cChen *et al.*, 2007.^dWirtenberger *et al.*, 2007.^eKammerer *et al.*, 2003.^fTingley *et al.*, 2007.^gNeumann *et al.*, 2009.^hWirtenberger *et al.*, 2005.ⁱMayers *et al.*, 2010.^jAppert-Collin *et al.*, 2007.^kRauch *et al.*, 2008.^lRauch, 2011.^mWillems *et al.*, 2010.ⁿHuang-Doran *et al.*, 2011.^oNumata *et al.*, 2009; 2010.^pSmith *et al.*, 2002.^qCastermans *et al.*, 2003.^rMedrihan *et al.*, 2009.^sDodge-Kafka *et al.*, 2005.^tPare *et al.*, 2005b.^uGordon *et al.*, 1992.^vAkakura *et al.*, 2008.^wSoderling *et al.*, 2003.^xLu *et al.*, 2007.^yTunquist *et al.*, 2008.^zNavedo *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 indispensable 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), AKAP18 α and AKAP18 γ (Fraser *et al.*, 1998; Lester *et al.*, 2001; Josefsen *et al.*, 2010). Their specific functions seem to be different. Overexpression of AKAP18 α in rat pancreatic β cells significantly increases glucagon-like peptide 1-mediated insulin secretion. AKAP18 γ has the opposite effect (Fraser *et al.*, 1998). Silencing studies confirmed a decrease in glucose-stimulated insulin release upon AKAP18 α depletion and an increase in the case of AKAP18 γ 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; Skroblien *et al.*, 2010). Down-regulation of SSeCKS/gravin/AKAP12 is observed in a number of tumours including radiation-induced osteosarcoma (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 occurring 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; Skroblien *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 RI α or RI β seems not

to be affected, whereas the valine variant exhibits a threefold stronger interaction with RI α , probably causing altered sub-cellular 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 AKAP18 δ –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 (<i>in vivo</i>)	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 (<i>ex vivo</i>)	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
	AKAP18 δ -wt	AKAP–PKA	Rat neonatal cardiac myocytes	Reduced β -adrenoceptor-induced L-type Ca ²⁺ currents ⁱ
	Arg9-11-PLN	AKAP18 δ –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
Peptido-mimetic	AKAP- <i>IS</i>	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- <i>IS</i>	AKAP–PKA	INS-1 Pancreatic β -cells	Inhibition of glucagon-induced potentiation of insulin secretion ⁿ
	Superakap- <i>IS</i>	AKAP–PKA (II)	Hippocampal neurons	Attenuation of AMPA-responsive currents ^o
	Unnatural RIAD	AKAP–PKA (I)	<i>in vitro</i>	Not determined ^p
Small molecule	FMP-API-1	AKAP–PKA	Rat neonatal cardiac myocytes	Increased contractility ^q
			Rat hearts (<i>ex vivo</i>)	Increased contractility ^q

TAT-AKAD, TAT-conjugated A-kinase anchoring disruptor (PKA binding region of AKAP10); RIAD: RI-anchoring disruptor; ACTH, adrenocorticotrophic hormone; LZ, leucine zipper.

^aNewhall *et al.*, 2006.

^bMcConnell *et al.*, 2009.

^cRosenmund *et al.*, 1994.

^dSchillace *et al.*, 2009.

^eKlussmann *et al.*, 1999.

^fHenn *et al.*, 2004.

^gPatel *et al.*, 2010.

^hHulme *et al.*, 2002.

ⁱHundsruker *et al.*, 2006a.

^jLygren *et al.*, 2007.

^kCarlson *et al.*, 2006.

^lAlto *et al.*, 2003.

^mSchillace *et al.*, 2011.

ⁿFaruque *et al.*, 2009.

^oGold *et al.*, 2006.

^pTorheim *et al.*, 2009.

^qChristian *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 mAKAP β 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, 2006; Kwon *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 (Gheorghiadu *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 dilu-

tion 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.

Acknowledgements

This work was supported by grants from the Deutsche Forschungsgemeinschaft (DFG) KL1415/3-2 and KL1415/4-2, and

the GoBio program of the Bundesministerium für Bildung und Forschung (FKZ 0315516).

Conflict of interest

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

References

- Aandahl EM, Aukrust P, Skallehegg BS, Muller F, Froland SS, Hansson V *et al.* (1998). Protein kinase A type I antagonist restores immune responses of T cells from HIV-infected patients. *FASEB J* 12: 855–862.
- Aandahl EM, Aukrust P, Muller F, Hansson V, Tasken K, Froland SS (1999). Additive effects of IL-2 and protein kinase A type I antagonist on function of T cells from HIV-infected patients on HAART. *Aids* 13: F109–F114.
- Akakura S, Huang C, Nelson PJ, Foster B, Gelman IH (2008). Loss of the SSeCKS/Gravin/AKAP12 gene results in prostatic hyperplasia. *Cancer Res* 68: 5096–5103.
- Alto NM, Soderling SH, Hoshi N, Langeberg LK, Fayos R, Jennings PA *et al.* (2003). Bioinformatic design of A-kinase anchoring protein-in silico: a potent and selective peptide antagonist of type II protein kinase A anchoring. *Proc Natl Acad Sci U S A* 100: 4445–4450.
- Appert-Collin A, Cotecchia S, Nenniger-Tosato M, Pedrazzini T, Diviani D (2007). The A-kinase anchoring protein (AKAP)-Lbc-signaling complex mediates 1 adrenergic receptor-induced cardiomyocyte hypertrophy. *PNAS* 104: 10140–10145.
- Aye TT, Soni S, van Veen TA, van der Heyden MA, Cappadona S, Varro A *et al.* (2011). Reorganized PKA-AKAP associations in the failing human heart. *J Mol Cell Cardiol*. Epub ahead of print.
- Blair JE, Zannad F, Konstam MA, Cook T, Traver B, Burnett JC *et al.* (2008). Continental differences in clinical characteristics, management, and outcomes in patients hospitalized with worsening heart failure results from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) program. *J Am Coll Cardiol* 52: 1640–1648.
- Burns-Hamuro LL, Ma Y, Kammerer S, Reineke U, Self C, Cook C *et al.* (2003). Designing isoform-specific peptide disruptors of protein kinase A localization. *Proc Natl Acad Sci USA* 100: 4072–4077.
- Carlson CR, Lygren B, Berge T, Hoshi N, Wong W, Tasken K *et al.* (2006). Delineation of type I protein kinase A-selective signaling events using an RI anchoring disruptor. *J Biol Chem* 281: 21535–21545.
- Carnegie G, Soughayer J, Smith F, Pedroja B, Zhang F, Diviani D *et al.* (2008). AKAP-Lbc mobilizes a cardiac hypertrophy signaling pathway. *Mol Cell* 32: 169–179.
- Carnegie GK, Burmeister BT (2011). AKAPs that regulate cardiac remodeling. *J Cardiovasc Pharmacol* 1: 451–458.
- Carnegie GK, Means CK, Scott JD (2009). A-kinase anchoring proteins: from protein complexes to physiology and disease. *IUBMB Life* 61: 394–406.

- Carrera A, Gerton GL, Moss SB (1994). The major fibrous sheath polypeptide of mouse sperm: structural and functional similarities to the A-kinase anchoring proteins. *Dev Biol* 165: 272–284.
- Castermans D, Wilquet V, Parthoens E, Huysmans C, Steyaert J, Swinnen L *et al.* (2003). The neurobeachin gene is disrupted by a translocation in a patient with idiopathic autism. *J Med Genet* 40: 352–356.
- Chen HH, Schrier RW (2006). Pathophysiology of volume overload in acute heart failure syndromes. *Am J Med* 119 (Suppl. 1): S11–S16.
- Chen L, Marquardt ML, Tester DJ, Sampson KJ, Ackerman MJ, Kass RS (2007). Mutation of an A-kinase-anchoring protein causes long-QT syndrome. *Proc Natl Acad Sci U S A* 104: 20990–20995.
- Chiriva-Internati M, Ferrari R, Yu Y, Hamrick C, Gagliano N, Grizzi F *et al.* (2008). AKAP-4: a novel cancer testis antigen for multiple myeloma. *Br J Haematol* 140: 465–468.
- Chiriva-Internati M, Yu Y, Mirandola L, D'Cunha N, Hardwicke F, Cannon MJ *et al.* (2011). Identification of AKAP-4 as a new cancer/testis antigen for detection and immunotherapy of prostate cancer. *Prostate* 72: 12–23.
- Christian F, Szaszak M, Friedl S, Drewianka S, Lorenz D, Goncalves A *et al.* (2011). Small molecule AKAP-protein kinase A (PKA) interaction disruptors that activate PKA interfere with compartmentalized cAMP signaling in cardiac myocytes. *J Biol Chem* 286: 9079–9096.
- Colas P (2008). High-throughput screening assays to discover small-molecule inhibitors of protein interactions. *Curr Drug Discov Technol* 5: 190–199.
- Cornez I, Tasken K (2010). Spatiotemporal control of cyclic AMP immunomodulation through the PKA-Csk inhibitory pathway is achieved by anchoring to an Ezrin-EBP50-PAG scaffold in effector T cells. *FEBS Lett* 584: 2681–2688.
- Daino K, Roch-Lefevre S, Ugolin N, Altmeyer-Morel S, Guilly MN, Chevillard S (2009). Silencing of Cited2 and Akap12 genes in radiation-induced rat osteosarcomas. *Biochem Biophys Res Commun* 390: 654–658.
- Delint-Martinez I, Willoughby D, Hammond GV, Ayling LJ, Cooper DM (2011). Palmitoylation targets AKAP79 to lipid rafts and promotes its regulation of the calcium sensitive adenylyl cyclase type 8. *J Biol Chem* 286: 32962–32975.
- Dell'Acqua ML, Faux MC, Thorburn J, Thorburn A, Scott JD (1998). Membrane-targeting sequences on AKAP79 bind phosphatidylinositol-4, 5-bisphosphate. *EMBO J* 17: 2246–2260.
- Diviani D, Langeberg LK, Doxsey SJ, Scott JD (2000). Pericentrin anchors protein kinase A at the centrosome through a newly identified RII-binding domain. *Curr Biol* 10: 417–420.
- Diviani D, Sonderling J, Scott JD (2001). AKAP-Lbc anchors protein kinase A and nucleates α 12-selective rho-mediated stress fiber formation. *J Biol Chem* 276: 44247–44257.
- Diviani D, Dodge-Kafka KL, Li J, Kapiloff MS (2011). A-kinase anchoring proteins-scaffolding proteins in the heart. *Am J Physiol Heart Circ Physiol* 301: H1742–H1753.
- Dodge-Kafka KL, Soughayer J, Pare GC, Carlisle Michel JJ, Langeberg LK, Kapiloff MS *et al.* (2005). The protein kinase A anchoring protein mAKAP coordinates two integrated cAMP effector pathways. *Nature* 437: 574–578.
- Dodge-Kafka KL, Bauman A, Kapiloff MS (2008). A-kinase anchoring proteins as the basis for cAMP signaling. *Handb Exp Pharmacol* 186: 3–14.
- Esposito P, Piotti G, Bianzina S, Malul Y, Dal Canton A (2011). The syndrome of inappropriate antidiuresis: pathophysiology, clinical management and new therapeutic options. *Nephron Clin Pract* 119: c62–c73.
- Faruque OM, Le-Nguyen D, Lajoix AD, Vives E, Petit P, Bataille D *et al.* (2009). Cell-permeable peptide-based disruption of endogenous PKA-AKAP complexes: a tool for studying the molecular roles of AKAP-mediated PKA subcellular anchoring. *Am J Physiol Cell Physiol* 296: C306–C316.
- Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P (2007). Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 18: 581–592.
- Frank B, Wiestler M, Kropp S, Hemminki K, Spurdle AB, Sutter C *et al.* (2008). Association of a common AKAP9 variant with breast cancer risk: a collaborative analysis. *J Natl Cancer Inst* 100: 437–442.
- Fraser ID, Tavalin SJ, Lester LB, Langeberg LK, Westphal AM, Dean RA *et al.* (1998). A novel lipid-anchored A-kinase anchoring protein facilitates cAMP-responsive membrane events. *EMBO J* 17: 2261–2272.
- Gelman IH (2002). The role of SSeCKS/gravin/AKAP12 scaffolding proteins in the spatiotemporal control of signaling pathways in oncogenesis and development. *Front Biosci* 7: d1782–d1797.
- Gheorghiadu M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K *et al.* (2007). Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA* 297: 1332–1343.
- Gillingham AK, Munro S (2000). The PACT domain, a conserved centrosomal targeting motif in the coiled-coil proteins AKAP450 and pericentrin. *EMBO Rep* 1: 524–529.
- Gold MG, Lygren B, Dokurno P, Hoshi N, McConnachie G, Tasken K *et al.* (2006). Molecular basis of AKAP specificity for PKA regulatory subunits. *Mol Cell* 24: 383–395.
- Gordon T, Grove B, Loftus JC, O'Toole T, McMillan R, Lindstrom J *et al.* (1992). Molecular cloning and preliminary characterization of a novel cytoplasmic antigen recognized by myasthenia gravis sera. *J Clin Invest* 90: 992–999.
- Henn V, Edemir B, Stefan E, Wiesner B, Lorenz D, Theilig F *et al.* (2004). Identification of a novel A-kinase anchoring protein 18 isoform and evidence for its role in the vasopressin-induced aquaporin-2 shuttle in renal principal cells. *J Biol Chem* 279: 26654–26665.
- Hofmann B, Nishanian P, Nguyen T, Insixiangmay P, Fahey JL (1993). Human immunodeficiency virus proteins induce the inhibitory cAMP/protein kinase A pathway in normal lymphocytes. *Proc Natl Acad Sci USA* 90: 6676–6680.
- Huang LJ, Wang L, Ma Y, Durick K, Perkins G, Deerinck TJ *et al.* (1999). NH2-Terminal targeting motifs direct dual specificity A-kinase-anchoring protein 1 (D-AKAP1) to either mitochondria or endoplasmic reticulum. *J Cell Biol* 145: 951–959.
- Huang-Doran I, Bicknell LS, Finucane FM, Rocha N, Porter KM, Tung YC *et al.* (2011). Genetic defects in human pericentrin are associated with severe insulin resistance and diabetes. *Diabetes* 60: 925–935.
- Hughes L, Wingate J, Griffith R, Aitken RJ (2007). Modelling and measuring redox cycling and cytotoxicity of quinones. *Drug Metab Lett* 1: 245–253.

- Hughes LM, Griffith R, Carey A, Butler T, Donne SW, Beagley KW *et al.* (2009). The spermstatic and microbicidal actions of quinones and maleimides: toward a dual-purpose contraceptive agent. *Mol Pharmacol* 76: 113–124.
- Hulme JT, Ahn M, Hauschka SD, Scheuer T, Catterall WA (2002). A novel leucine zipper targets AKAP15 and cyclic AMP-dependent protein kinase to the C terminus of the skeletal muscle Ca²⁺ channel and modulates its function. *J Biol Chem* 277: 4079–4087.
- Hundsrucker C, Klusmann E (2008). Direct AKAP-mediated protein-protein interactions as potential drug targets. *Handb Exp Pharmacol* 186: 483–503.
- Hundsrucker C, Krause G, Beyermann M, Prinz A, Zimmermann B, Diekmann O *et al.* (2006a). High-affinity AKAP7delta-protein kinase A interaction yields novel protein kinase A-anchoring disruptor peptides. *Biochem J* 396: 297–306.
- Hundsrucker C, Rosenthal W, Klusmann E (2006b). Peptides for disruption of PKA anchoring. *Biochem Soc Trans* 34: 472–473.
- Josefsen K, Lee YC, Thams P, Efendic S, Nielsen JH (2010). AKAP 18 alpha and gamma have opposing effects on insulin release in INS-1E cells. *FEBS Lett* 584: 81–85.
- Jurado S, Biou V, Malenka RC (2010). A calcineurin/AKAP complex is required for NMDA receptor-dependent long-term depression. *Nat Neurosci* 13: 1053–1055.
- Kammerer S, Burns-Hamuro LL, Ma Y, Hamon SC, Canaves JM, Shi MM *et al.* (2003). Amino acid variant in the kinase binding domain of dual-specific A kinase-anchoring protein 2: a disease susceptibility polymorphism. *Proc Natl Acad Sci U S A* 100: 4066–4071.
- Kapiloff MS, Schillace RV, Westphal AM, Scott JD (1999). mAKAP: an A-kinase anchoring protein targeted to the nuclear membrane of differentiated myocytes. *J Cell Sci* 112: 2725–2736.
- Kapiloff MS, Jackson N, Airhart N (2001). mAKAP and the ryanodine receptor are part of a multi-component signaling complex on the cardiomyocyte nuclear envelope. *J Cell Sci* 114: 3167–3176.
- Kinderman FS, Kim C, von Daake S, Ma Y, Pham BQ, Spraggon G *et al.* (2006). A dynamic mechanism for AKAP binding to RII isoforms of cAMP-dependent protein kinase. *Mol Cell* 24: 397–408.
- King LS, Kozono D, Agre P (2004). From structure to disease: the evolving tale of aquaporin biology. *Nat Rev Mol Cell Biol* 5: 687–698.
- Klusmann E, Rosenthal W (2008). Protein-protein interactions as new drug targets. Preface. *Handb Exp Pharmacol* 186: v–vi.
- Klusmann E, Maric K, Wiesner B, Beyermann M, Rosenthal W (1999). Protein kinase A anchoring proteins are required for vasopressin-mediated translocation of aquaporin-2 into cell membranes of renal principal cells. *J Biol Chem* 274: 4934–4938.
- Konstam MA, Gheorghade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K *et al.* (2007). Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 297: 1319–1331.
- Kovanich D, van der Heyden MA, Aye TT, van Veen TA, Heck AJ, Scholten A (2010). Sphingosine kinase interacting protein is an A-kinase anchoring protein specific for type I cAMP-dependent protein kinase. *Chembiochem* 11: 963–971.
- Kritzer MD, Li J, Dodge-Kafka K, Kapiloff MS (2011). AKAPs: the architectural underpinnings of local cAMP signaling. *J Mol Cell Cardiol*. Epub ahead of print.
- Kurokawa J, Motoike HK, Rao J, Kass RS (2004). Regulatory actions of the A-kinase anchoring protein Yotiao on a heart potassium channel downstream of PKA phosphorylation. *Proc Natl Acad Sci U S A* 101: 16374–16378.
- Kwon TH, Nielsen J, Moller HB, Fenton RA, Nielsen S, Frokiaer J (2009). Aquaporins in the kidney. *Handb Exp Pharmacol* 190: 95–132.
- Lemay J, Maidou-Peindara P, Cancio R, Ennifar E, Coadou G, Maga G *et al.* (2008). AKAP149 binds to HIV-1 reverse transcriptase and is involved in the reverse transcription. *J Mol Biol* 383: 783–796.
- Lester LB, Langeberg LK, Scott JD (1997). Anchoring of protein kinase A facilitates hormone-mediated insulin secretion. *Proc Natl Acad Sci USA* 94: 14942–14947.
- Lester LB, Faux MC, Nauert JB, Scott JD (2001). Targeted protein kinase A and PP-2B regulate insulin secretion through reversible phosphorylation. *Endocrinology* 142: 1218–1227.
- Lezoualc’h F, Metrich M, Hmitou I, Duquesnes N, Morel E (2008). Small GTP-binding proteins and their regulators in cardiac hypertrophy. *J Mol Cell Cardiol* 44: 623–632.
- Li J, Negro A, Lopez J, Bauman AL, Henson E, Dodge-Kafka K *et al.* (2010). The mAKAPbeta scaffold regulates cardiac myocyte hypertrophy via recruitment of activated calcineurin. *J Mol Cell Cardiol* 48: 387–394.
- Lin X, Gelman IH (1997). Reexpression of the major protein kinase C substrate, SSeCKS, suppresses v-src-induced morphological transformation and tumorigenesis. *Cancer Res* 57: 2304–2312.
- Lin X, Tomblin E, Nelson PJ, Ross M, Gelman IH (1996). A novel src- and ras-suppressed protein kinase C substrate associated with cytoskeletal architecture. *J Biol Chem* 271: 28430–28438.
- Liu W, Guan M, Su B, Li J, Ma W, Liu C *et al.* (2010). Rapid determination of AKAP12 promoter methylation levels in peripheral blood using methylation-sensitive high resolution melting (MS-HRM) analysis: application in colorectal cancer. *Clin Chim Acta* 411: 940–946.
- Lu Y, Allen M, Halt AR, Weisenhaus M, Dallapiazza RF, Hall DD *et al.* (2007). Age-dependent requirement of AKAP150-anchored PKA and GluR2-lacking AMPA receptors in LTP. *EMBO J* 26: 4879–4890.
- Luconi M, Carloni V, Marra F, Ferruzzi P, Forti G, Baldi E (2004). Increased phosphorylation of AKAP by inhibition of phosphatidylinositol 3-kinase enhances human sperm motility through tail recruitment of protein kinase A. *J Cell Sci* 117: 1235–1246.
- Luconi M, Cantini G, Baldi E, Forti G (2011). Role of a-kinase anchoring proteins (AKAPs) in reproduction. *Front Biosci* 16: 1315–1330.
- Lygren B, Tasken K (2008). The potential use of AKAP18delta as a drug target in heart failure patients. *Expert Opin Biol Ther* 8: 1099–1108.
- Lygren B, Carlson CR, Santamaria K, Lissandron V, McSorley T, Litzenberg J *et al.* (2007). AKAP complex regulates Ca²⁺ re-uptake into heart sarcoplasmic reticulum. *EMBO Rep* 8: 1061–1067.
- Ma Y, Taylor S (2002). A 15-residue bifunctional element in D-AKAP1 is required for both endoplasmic reticulum and mitochondrial targeting. *J Biol Chem* 277: 27328–27336.
- Ma Y, Taylor SS (2008). A molecular switch for targeting between endoplasmic reticulum (ER) and mitochondria: conversion of a mitochondria-targeting element into an ER-targeting signal in DAKAP1. *J Biol Chem* 283: 11743–11751.

- Malbon CC, Tao J, Shumay E, Wang HY (2004). AKAP (A-kinase anchoring protein) domains: beads of structure-function on the necklace of G-protein signalling. *Biochem Soc Trans* 32: 861–864.
- Martin SJ, Morris RG (2002). New life in an old idea: the synaptic plasticity and memory hypothesis revisited. *Hippocampus* 12: 609–636.
- Marx SO, Reiken S, Hisamatsu Y, Jayaraman T, Burkhoff D, Rosemblyt N *et al.* (2000). PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. *Cell* 101: 365–376.
- Marx SO, Reiken S, Hisamatsu Y, Gaburjakova M, Gaburjakova J, Yang YM *et al.* (2001). Phosphorylation-dependent regulation of ryanodine receptors: a novel role for leucine/isoleucine zippers. *J Cell Biol* 153: 699–708.
- Mauban JRH, O'Donnell M, Warriar S, Manni S, Bond M (2009). AKAP-scaffolding proteins and regulation of cardiac physiology. *Physiology* 24: 78–87.
- Mayers CM, Wadell J, McLean K, Venere M, Malik M, Shibata T *et al.* (2010). The rho guanine nucleotide exchange factor AKAP13 (BRX) is essential for cardiac development in mice. *J Biol Chem* 285: 12344–12354.
- McConnell BK, Popovic Z, Mal N, Lee K, Bautista J, Forudi F *et al.* (2009). Disruption of protein kinase A interaction with A-kinase-anchoring proteins in the heart *in vivo*: effects on cardiac contractility, protein kinase A phosphorylation, and troponin I proteolysis. *J Biol Chem* 284: 1583–1592.
- Medrihan L, Rohlmann A, Fairless R, Andrae J, Doring M, Missler M *et al.* (2009). Neurobeachin, a protein implicated in membrane protein traffic and autism, is required for the formation and functioning of central synapses. *J Physiol* 587: 5095–5106.
- Miki H, Takenawa T (2003). Regulation of actin dynamics by WASP family proteins. *J Biochem* 134: 309–313.
- Miki K, Willis WD, Brown PR, Goulding EH, Fulcher KD, Eddy EM (2002). Targeted disruption of the Akap4 gene causes defects in sperm flagellum and motility. *Dev Biol* 248: 331–342.
- Miyazaki T, Fujiki H, Yamamura Y, Nakamura S, Mori T (2007). Tolvaptan, an orally active vasopressin V(2)-receptor antagonist – pharmacology and clinical trials. *Cardiovasc Drug Rev* 25: 1–13.
- Moretti E, Scapigliati G, Pascarelli NA, Baccetti B, Collodel G (2007). Localization of AKAP4 and tubulin proteins in sperm with reduced motility. *Asian J Androl* 9: 641–649.
- Mosenden R, Tasken K (2011). Cyclic AMP-mediated immune regulation – overview of mechanisms of action in T cells. *Cell Signal* 23: 1009–1016.
- Mosenden R, Singh P, Cornez I, Heglind M, Ruppelt A, Moutschen M *et al.* (2011). Mice with disrupted type I protein kinase a anchoring in T cells resist retrovirus-induced immunodeficiency. *J Immunol* 186: 5119–5130.
- Movsesian MA, Bristow MR (2005). Alterations in cAMP-mediated signaling and their role in the pathophysiology of dilated cardiomyopathy. *Curr Top Dev Biol* 68: 25–48.
- Nauert JB, Rigas JD, Lester LB (2003). Identification of an IQGAP1/AKAP79 complex in beta-cells. *J Cell Biochem* 90: 97–108.
- Navedo MF, Nieves-Cintrón M, Amberg GC, Yuan C, Votaw VS, Lederer WJ *et al.* (2008). AKAP150 is required for stuttering persistent Ca²⁺ sparklets and angiotensin II-induced hypertension. *Circ Res* 102: e1–e11.
- Nedvetsky PI, Tamma G, Beulshausen S, Valenti G, Rosenthal W, Klusmann E (2009). Regulation of aquaporin-2 trafficking. *Handb Exp Pharmacol* 190: 133–157.
- Negro A, Dodge-Kafka K, Kapiloff MS (2008). Signalosomes as therapeutic targets. *Prog Pediatr Cardiol* 25: 51–56.
- Neumann SA, Tingley WG, Conklin BR, Shrader CJ, Peet E, Muldoon MF *et al.* (2009). AKAP10 (I646V) functional polymorphism predicts heart rate and heart rate variability in apparently healthy, middle-aged European-Americans. *Psychophysiology* 46: 466–472.
- Newhall KJ, Criniti AR, Cheah CS, Smith KC, Kafer KE, Burkart AD *et al.* (2006). Dynamic anchoring of PKA is essential during oocyte maturation. *Curr Biol* 16: 321–327.
- Newlon MG, Roy M, Morikis D, Hausken ZE, Coghlan V, Scott JD *et al.* (1999). The molecular basis for protein kinase A anchoring revealed by solution NMR. *Nat Struct Biol* 6: 222–227.
- Newlon MG, Roy M, Morikis D, Carr DW, Westphal R, Scott JD *et al.* (2001). A novel mechanism of PKA anchoring revealed by solution structures of anchoring complexes. *EMBO J* 20: 1651–1662.
- Nichols CB, Rossow CF, Navedo MF, Westenbroek RE, Catterall WA, Santana LF *et al.* (2010). Sympathetic stimulation of adult cardiomyocytes requires association of AKAP5 with a subpopulation of L-type calcium channels. *Circ Res* 107: 747–756.
- Numata S, Iga J, Nakataki M, Tayoshi S, Tanahashi T, Itakura M *et al.* (2009). Positive association of the pericentrin (PCNT) gene with major depressive disorder in the Japanese population. *J Psychiatry Neurosci* 34: 195–198.
- Numata S, Nakataki M, Iga J, Tanahashi T, Nakadoi Y, Ohi K *et al.* (2010). Association study between the pericentrin (PCNT) gene and schizophrenia. *Neuromolecular Med* 12: 243–247.
- O'Connor CM, Miller AB, Blair JE, Konstam MA, Wedge P, Bahit MC *et al.* (2010). Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: results from Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) program. *Am Heart J* 159: 841–849 e841.
- Pare GC, Easlick JL, Mislow JM, McNally EM, Kapiloff MS (2005a). Nesprin-1alpha contributes to the targeting of mAKAP to the cardiac myocyte nuclear envelope. *Exp Cell Res* 303: 388–399.
- Pare GC, Bauman AL, McHenry M, Michel JJ, Dodge-Kafka KL, Kapiloff MS (2005b). The mAKAP complex participates in the induction of cardiac myocyte hypertrophy by adrenergic receptor signaling. *J Cell Sci* 118: 5637–5646.
- Patel HH, Hamuro LL, Chun BJ, Kawaraguchi Y, Quick A, Rebolledo B *et al.* (2010). Disruption of protein kinase A localization using a trans-activator of transcription (TAT)-conjugated A-kinase-anchoring peptide reduces cardiac function. *J Biol Chem* 285: 27632–27640.
- Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA *et al.* (2000). Molecular portraits of human breast tumours. *Nature* 406: 747–752.
- Pidoux G, Tasken K (2010). Specificity and spatial dynamics of protein kinase A signaling organized by A-kinase-anchoring proteins. *J Mol Endocrinol* 44: 271–284.
- Rauch A (2011). The shortest of the short: pericentrin mutations and beyond. *Best Pract Res Clin Endocrinol Metab* 25: 125–130.
- Rauch A, Thiel CT, Schindler D, Wick U, Crow YJ, Ekici AB *et al.* (2008). Mutations in the pericentrin (PCNT) gene cause primordial dwarfism. *Science* 319: 816–819.

- Rawe VY, Payne C, Navara C, Schatten G (2004a). WAVE1 intranuclear trafficking is essential for genomic and cytoskeletal dynamics during fertilization: cell-cycle-dependent shuttling between M-phase and interphase nuclei. *Dev Biol* 276: 253–267.
- Rawe VY, Ramalho-Santos J, Payne C, Chemes HE, Schatten G (2004b). WAVE1, an A-kinase anchoring protein, during mammalian spermatogenesis. *Hum Reprod* 19: 2594–2604.
- Rosenmund C, Carr DW, Bergeson SE, Nilaver G, Scott JD, Westbrook GL (1994). Anchoring of protein kinase A is required for modulation of AMPA/kainate receptors on hippocampal neurons. *Nature* 368: 853–856.
- Ruppelt A, Mosenden R, Gronholm M, Aandahl EM, Tobin D, Carlson CR *et al.* (2007). Inhibition of T cell activation by cyclic adenosine 5'-monophosphate requires lipid raft targeting of protein kinase A type I by the A-kinase anchoring protein ezrin. *J Immunol* 179: 5159–5168.
- Scanlan MJ, Simpson AJ, Old LJ (2004). The cancer/testis genes: review, standardization, and commentary. *Cancer Immun* 4: 1.
- Schillace RV, Miller CL, Pisenti N, Grotzke JE, Swarbrick GM, Lewinsohn DM *et al.* (2009). A-kinase anchoring in dendritic cells is required for antigen presentation. *PLoS ONE* 4: e4807.
- Schillace RV, Miller CL, Carr DW (2011). AKAPs in lipid rafts are required for optimal antigen presentation by dendritic cells. *Immunol Cell Biol* 89: 650–658.
- Schrier RW, Cadnapaphornchai MA (2003). Renal aquaporin water channels: from molecules to human disease. *Prog Biophys Mol Biol* 81: 117–131.
- Schulze DH, Muqhal M, Lederer WJ, Ruknudin AM (2003). Sodium/calcium exchanger (NCX1) macromolecular complex. *J Biol Chem* 278: 28849–28855.
- Scott JD, Santana LF (2010). A-kinase anchoring proteins: getting to the heart of the matter. *Circulation* 121: 1264–1271.
- Sit ST, Manser E (2011). Rho GTPases and their role in organizing the actin cytoskeleton. *J Cell Sci* 124: 679–683.
- Skalhegg BS, Tasken K, Hansson V, Huitfeldt HS, Jahnsen T, Lea T (1994). Location of cAMP-dependent protein kinase type I with the TCR-CD3 complex. *Science* 263: 84–87.
- Skroblin P, Grossmann S, Schafer G, Rosenthal W, Klusmann E (2010). Mechanisms of protein kinase A anchoring. *Int Rev Cell Mol Biol* 283: 235–330.
- Smith M, Woodroffe A, Smith R, Holguin S, Martinez J, Filipek PA *et al.* (2002). Molecular genetic delineation of a deletion of chromosome 13q12→q13 in a patient with autism and auditory processing deficits. *Cytogenet Genome Res* 98: 233–239.
- Smith FD, Langeberg LK, Cellurale C, Pawson T, Morrison DK, Davis RJ *et al.* (2010). AKAP-Lbc enhances cyclic AMP control of the ERK1/2 cascade. *Nat Cell Biol* 12: 1242–1249.
- Soderling TR, Derkach VA (2000). Postsynaptic protein phosphorylation and LTP. *Trends Neurosci* 23: 75–80.
- Soderling SH, Langeberg LK, Soderling JA, Davee SM, Simerly R, Raber J *et al.* (2003). Loss of WAVE-1 causes sensorimotor retardation and reduced learning and memory in mice. *Proc Natl Acad Sci U S A* 100: 1723–1728.
- Su B, Bu Y, Engelberg D, Gelman IH (2010). SSeCKS/Gravin/AKAP12 inhibits cancer cell invasiveness and chemotaxis by suppressing a protein kinase C- Raf/MEK/ERK pathway. *J Biol Chem* 285: 4578–4586.
- Suri A (2005). Contraceptive vaccines targeting sperm. *Expert Opin Biol Ther* 5: 381–392.
- Szaszak M, Christian F, Rosenthal W, Klusmann E (2008). Compartmentalized cAMP signalling in regulated exocytic processes in non-neuronal cells. *Cell Signal* 20: 590–601.
- Tao J, Shumay E, McLaughlin S, Wang HY, Malbon CC (2006). Regulation of AKAP-membrane interactions by calcium. *J Biol Chem* 281: 23932–23944.
- Tasken K, Aandahl EM (2004). Localized effects of cAMP mediated by distinct routes of protein kinase A. *Physiol Rev* 84: 137–167.
- Tingley WG, Pawlikowska L, Zaroff JG, Kim T, Nguyen T, Young SG *et al.* (2007). Gene-trapped mouse embryonic stem cell-derived cardiac myocytes and human genetics implicate AKAP10 in heart rhythm regulation. *Proc Natl Acad Sci USA* 104: 8461–8466.
- Torheim EA, Jarnaess E, Lygren B, Tasken K (2009). Design of proteolytically stable RI-anchoring disruptor peptidomimetics for *in vivo* studies of anchored type I protein kinase A-mediated signalling. *Biochem J* 424: 69–78.
- Trotter KW, Fraser ID, Scott GK, Stutts MJ, Scott JD, Milgram SL (1999). Alternative splicing regulates the subcellular localization of A-kinase anchoring protein 18 isoforms. *J Cell Biol* 147: 1481–1492.
- Tunquist BJ, Hoshi N, Guire ES, Zhang F, Mullendorff K, Langeberg LK *et al.* (2008). Loss of AKAP150 perturbs distinct neuronal processes in mice. *Proc Natl Acad Sci USA* 105: 12557–12562.
- Turner RM, Foster JA, Gerton GL, Moss SB, Patrizio P (2001). Molecular evaluation of two major human sperm fibrous sheath proteins, pro-hAKAP82 and hAKAP82, in stump tail sperm. *Fertil Steril* 76: 267–274.
- Vang T, Torgersen KM, Sundvold V, Saxena M, Levy FO, Skalhegg BS *et al.* (2001). Activation of the COOH-terminal Src kinase (Csk) by cAMP-dependent protein kinase inhibits signaling through the T cell receptor. *J Exp Med* 193: 497–507.
- Vijayaraghavan S, Goueli SA, Davey MP, Carr DW (1997). Protein kinase A-anchoring inhibitor peptides arrest mammalian sperm motility. *J Biol Chem* 272: 4747–4752.
- Vijayaraghavan S, Liberty GA, Mohan J, Winfrey VP, Olson GE, Carr DW (1999). Isolation and molecular characterization of AKAP110, a novel, sperm-specific protein kinase A-anchoring protein. *Mol Endocrinol* 13: 705–717.
- Wan M, Sun T, Vyas R, Zheng J, Granada E, Dubeau L (1999). Suppression of tumorigenicity in human ovarian cancer cell lines is controlled by a 2 cm fragment in chromosomal region 6q24-q25. *Oncogene* 18: 1545–1551.
- Webb RJ, Tinworth L, Thomas GM, Zaccolo M, Carroll J (2008). Developmentally acquired PKA localisation in mouse oocytes and embryos. *Dev Biol* 317: 36–45.
- Weisenhaus M, Allen ML, Yang L, Lu Y, Nichols CB, Su T *et al.* (2010). Mutations in AKAP5 disrupt dendritic signaling complexes and lead to electrophysiological and behavioral phenotypes in mice. *PLoS ONE* 5: e10325.
- Welch EJ, Jones BW, Scott JD (2010). Networking with AKAPs: context-dependent regulation of anchored enzymes. *Mol Interv* 10: 86–97.
- Wells JA, McClendon CL (2007). Reaching for high-hanging fruit in drug discovery at protein-protein interfaces. *Nature* 450: 1001–1009.

Welsh JB, Zarrinkar PP, Sapinoso LM, Kern SG, Behling CA, Monk BJ *et al.* (2001). Analysis of gene expression profiles in normal and neoplastic ovarian tissue samples identifies candidate molecular markers of epithelial ovarian cancer. *Proc Natl Acad Sci USA* 98: 1176–1181.

Willems M, Genevieve D, Borck G, Baumann C, Baujat G, Bieth E *et al.* (2010). Molecular analysis of pericentrin gene (PCNT) in a series of 24 Seckel/microcephalic osteodysplastic primordial dwarfism type II (MOPD II) families. *J Med Genet* 47: 797–802.

Wirtenberger M, Tchatchou S, Hemminki K, Klaes R, Schmutzler RK, Bermejo JL *et al.* (2005). Association of genetic variants in the Rho guanine nucleotide exchange factor AKAP13 with familial breast cancer. *Carcinogenesis* 27: 593–598.

Wirtenberger M, Schmutzhard J, Hemminki K, Meindl A, Sutter C, Schmutzler RK *et al.* (2007). The functional genetic variant

Ile646Val located in the kinase binding domain of the A-kinase anchoring protein 10 is associated with familial breast cancer. *Carcinogenesis* 28: 423–426.

Wong W, Scott JD (2004). AKAP signalling complexes: focal points in space and time. *Nat Rev Mol Cell Biol* 5: 959–970.

Wu W, Zhang J, Yang H, Shao Y, Yu B (2011). Examination of AKAP12 promoter methylation in skin cancer using methylation-sensitive high-resolution melting analysis. *Clin Exp Dermatol* 36: 381–385.

Xia W, Unger P, Miller L, Nelson J, Gelman IH (2001). The Src-suppressed C kinase substrate, SSeCKS, is a potential metastasis inhibitor in prostate cancer. *Cancer Res* 61: 5644–5651.

Yan X, Walkiewicz M, Carlson J, Leiphon L, Grove B (2009). Gravin dynamics regulates the subcellular distribution of PKA. *Exp Cell Res* 315: 1247–1259.