CHAPTER FIVE

Mechanisms of Protein Kinase A Anchoring

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Contents

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International Review of Cell and Molecular Biology, Volume 283
ISSN 1937-6448, DOI: 10.1016/S1937-6448(10)83005-9

Abstract

The second messenger cyclic adenosine monophosphate (cAMP), which is produced by adenylyl cyclases following stimulation of G-protein-coupled receptors, exerts its effect mainly through the cAMP-dependent serine/threonine protein kinase A (PKA). Due to the ubiquitous nature of the cAMP/PKA system, PKA signaling pathways underlie strict spatial and temporal control to achieve specificity. A-kinase anchoring proteins (AKAPs) bind to the regulatory subunit dimer of the tetrameric PKA holoenzyme and thereby target PKA to defined cellular compartments in the vicinity of its substrates. AKAPs promote the termination of cAMP signals by recruiting phosphodiesterases and protein phosphatases, and the integration of signaling pathways by binding additional signaling proteins. AKAPs are a heterogeneous family of proteins that only display similarity within their PKA-binding domains, amphipathic helixes docking into a hydrophobic groove formed by the PKA regulatory subunit dimer. This review summarizes the current state of information on compartmentalized cAMP/PKA signaling with a major focus on structural aspects, evolution, diversity, and (patho)physiological functions of AKAPs and intends to outline newly emerging directions of the field, such as the elucidation of AKAP mutations and alterations of AKAP expression in human diseases, and the validation of AKAP-dependent protein–protein interactions as new drug targets. In addition, alternative PKA anchoring mechanisms employed by noncanonical AKAPs and PKA catalytic subunit-interacting proteins are illustrated.

Key Words: A-kinase anchoring protein (AKAP), Compartmentalization, Cyclic adenosine monophosphate (cAMP), Glycogen synthase kinase 3 β (GSK3β), GSK3β interaction protein (GSKIP), Protein kinase A (PKA), PKA-anchoring disruptor, RII-binding domain (RIIBD), Scaffolding protein.

1. Introduction

Extracellular stimuli as diverse as hormones, growth factors, cytokines, sensory inputs, or pathogens trigger intracellular signal transduction events to elicit specific responses. All signal transduction processes involving the second messenger cyclic adenosine monophosphate (cAMP) depend upon a similar core of molecular components. Cell-type-specific expression of different isoforms of these components together with a unique complement of scaffolding proteins that assemble spatially discrete signaling complexes facilitates specific regulation of cell functions. The molecular "toolbox" that allows for this comprises adenylyl cyclases (ACs), which generate cAMP, and phosphodiesterases (PDEs) degrading it. Together, ACs and PDEs not only determine the level of cAMP in cells but, through the defined spatial sequestration of specific isoforms of each of these enzymes, they also generate gradients of cAMP at specific cellular sites. These gradients of cAMP have to be interpreted locally and this role is undertaken by protein kinase A (PKA), exchange proteins

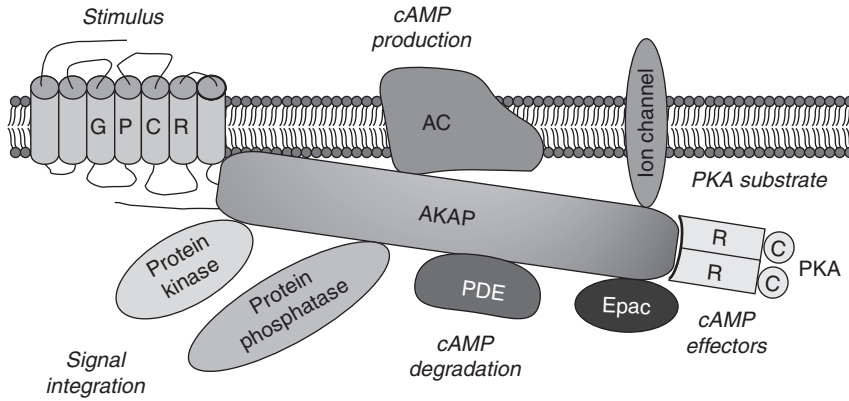

Figure 5.1 AKAPs bind key proteins of the cAMP and other signaling pathways and thereby integrate cellular signaling processes at distinct cellular sites.

activated by cAMP (Epacs) acting as GTP exchange factors and, in a few cell types, cyclic nucleotide gated ion channels (CNGs). The interpretation of signals at discrete cellular locations is achieved by sequestration of these cAMP effectors to particular signaling nodes, of which A-kinase anchoring proteins (AKAPs) play a major role. They direct PKA to specific cellular sites into close proximity of downstream substrates. Also, a specific subset of PDEs, which provide the sole means of degrading cAMP in cells, are sequestered by AKAPs. This enables these PDEs to gate the threshold for activation of tethered PKA by controlling cAMP concentrations locally. The more than 40 members of the diverse family of AKAPs are expressed in a cell- and organelle-specific fashion and not only tether PKA and PDEs but also interact with G-protein-coupled receptors (GPCRs), ACs, Epacs, and PKA substrates, thereby regulating cAMP signaling at all levels: cAMP generation, control of cAMP effectors, and cAMP signal termination (Fig. 5.1). In addition, AKAPs are platforms for the integration of cAMP and other signaling pathways as they can bind further protein kinases, protein phosphatases (PPs), ion channels, and small GTP-binding proteins (Fig. 5.1). Moreover, AKAPs may provide novel targets for therapeutic intervention as the dysregulation of compartmentalized cAMP signaling is associated with human disease.

2. Proteins Involved in Compartmentalized cAMP/PKA Signaling

2.1. Adenylyl cyclases

There are 10 human isoforms of ACs: 9 plasma membrane resident (AC1–AC9) and 1 soluble AC (sAC). AC1–AC9 are transmembrane proteins that are stimulated by $G\alpha_s$ subunits of heterotrimeric G proteins upon activation

of GPCRs. Additionally, ACs can be regulated by G$\beta\gamma$ and Gα_i subunits of G proteins, Ca^{2+}, and protein kinases (Cooper, 2005; Sunahara and Taussig, 2002; Willoughby and Cooper, 2007). sAC is abundantly expressed in sperm and activated by bicarbonate. sAC generates the cAMP necessary for sperm capacitation and is thus indispensable for sperm function (Kamenetsky et al., 2006). Recently, an association of several AC isoforms with plasma membrane targeted AKAPs (Yotiao, AKAP79 and muscle-selective AKAP, mAKAP) was discovered (see Table 5.3). Molecular details and functions of AC–AKAP interactions were recently reviewed elsewhere (Dessauer, 2009).

As a tool to study cAMP signaling, forskolin, a plant diterpene, has been widely used. It activates AC1–AC8 and to a lesser extent AC9 but not sAC and thereby elevates cellular cAMP levels. Forskolin is especially valuable when specific agonists of the GPCRs stimulating a cAMP signaling pathway under investigation are not available (Insel and Ostrom, 2003). The suppression of cAMP synthesis in experimental settings can be achieved with several modified nucleotides which inhibit ACs isoform selectively (Gille et al., 2004; Pierre et al., 2009; Suryanarayana et al., 2009; Ye et al., 2004).

2.2. Phosphodiesterases

Cyclic nucleotide PDEs hydrolyze the phosphodiester bond in cAMP and/or cyclic guanosine monophosphate (cGMP). The PDE superfamily is subdivided into 11 families, classified on the basis of their sequence similarities, substrate specificities, allosteric regulation, and pharmacological properties (Conti and Beavo, 2007; Houslay, 2010; Omori and Kotera, 2007). PDE4, 7, and 8 are cAMP selective, PDE5, 6, and 9 are cGMP selective, and PDE1, 2, 3, 10, and 11 can degrade both cAMP and cGMP. Development-specific and cell-type-specific expression of PDE isoforms, as well as organelle-specific localization, contribute crucially to the establishment of compartmentalized cAMP signaling. In the context of anchored PKA signaling, the PDE4 family is especially important (Houslay, 2010; Lynch et al., 2007; McCahill et al., 2008). There are four human genes encoding PDE4 isoforms PDE4A, 4B, 4C, and 4D, that give rise to more than 20 different human PDE4 proteins. They are the major PDEs responsible for the degradation of cAMP in cells (Conti et al., 2003; Houslay and Adams, 2010). PDE4 activity is regulated through phosphorylation by PKA and extracellular signal-regulated kinase (ERK) and often spatially limited by scaffold proteins controlling its localization (Li et al., 2010; McCahill et al., 2008). Several AKAPs (including AKAP18δ, mAKAP and Yotiao, see Table 5.3) have been shown to form signaling complexes containing PDE4 isoforms (Houslay, 2010). The discovery of PDE4 mutations has provided insight into the role of compartmentalized cAMP signaling in diseases such as schizophrenia, asthma, osteoporosis, stroke, and prostate cancer (Houslay, 2010; Houslay et al., 2007).

A commonly used research tool to elevate cAMP levels (often in combination with the AC activator forskolin, see above) is 3-isobutyl-1-methylxanthine (IBMX), a nonselective PDE inhibitor (Costa et al., 1975). To elucidate the involvement of particular PDE families, selective inhibitors have been developed (Houslay et al., 2005; Lugnier, 2006). For example, there are several PDE4 inhibitors, some of which are in preclinical development or in clinical trials (Houslay et al., 2005; Pages et al., 2009). The experimentally most widely used one is rolipram (Zhu et al., 2001).

2.3. Protein phosphatases

In addition to PDEs, PPs are the second class of proteins that terminate PKA signaling (Virshup and Shenolikar, 2009). PPs reverse the effect of kinases by hydrolytically cleaving phosphate off phosphorylated amino acids. Based on their substrates, PPs can be divided into protein serine/threonine phosphatases and protein tyrosine phosphatases (PTPs; Moorhead et al., 2009). Many AKAPs bind serine/threonine phosphatases (see Table 5.3), enabling them to remove phosphate from PKA substrates. This increases the temporal control of PKA phosphorylation. The AKAP-associated phosphatases can be regulated by different mechanisms. For example, calcineurin (CaN/PP2B) interacts with AKAP79 and is activated by Ca^{2+} (Oliveria et al., 2007), protein phosphatase 2A (PP2A) interacts with MAP2D and is activated by PKA phosphorylation (Flynn et al., 2008). AKAPs may also control phosphatases directly through binding as described for the inhibition of protein phosphatase 1 (PP1) by AKAP220 (Schillace et al., 2001).

2.4. Protein kinase A

cAMP-dependent protein kinase, formerly abbreviated cAPK, now named PKA is a member of the AGC kinase (cAMP-dependent protein kinase *A*, cGMP-dependent protein kinase *G*, PKG, and phospholipid-dependent protein kinase *C*, PKC) family (Pearce et al., 2010).

The PKA holoenzyme is a tetrameric complex consisting of a dimer of regulatory (R) subunits and two catalytic (C) subunits, each of which is bound and inhibited by one R subunit. PKA is activated by the binding of two cAMP molecules to each regulatory subunit. This decreases the affinity of the R subunits for binding of the C subunits, which are released and phosphorylate substrate proteins in close proximity. PKA preferentially phosphorylates substrates containing the consensus sequence R-R-X-*S*/*T* (Edelman et al., 1987; Shabb, 2001).

While many other AGC kinases possess canonical protein–protein or protein–lipid interaction modules regulating their targeting, these are absent in PKA (with the exception of the dimerization and docking (D/D)

domain, see Section 2.4.2). This explains and underlines the need for AKAPs to control the localization of PKA (Pearce et al., 2010).

2.4.1. PKA catalytic and regulatory subunit isoforms

Three genes encode the different catalytic subunit isoforms: Cα (Uhler et al., 1986b), Cβ (Showers and Maurer, 1986; Uhler et al., 1986a), and Cγ (Beebe et al., 1990). Additionally, an X-chromosomally encoded catalytic subunit named protein kinase, X-linked (PrkX) was identified (Zimmermann et al., 1999). In contrast to the other C subunits, PrkX forms holoenzymes exclusively with RI (Diskar et al., 2007). The human Y-chromosome encodes a protein named PrkY that shares 94% homology with PrkX. It remains unclear whether PrkY has catalytic activity and binds regulatory subunits (Schiebel et al., 1997).

In mammals, there are four isoforms of regulatory subunits encoded by four distinct genes: RIα, RIβ, RIIα, and RIIβ. Depending on the type of R subunit present (RI or RII), PKA holoenzymes are classified as type I or type II. Generally, R subunits homodimerize but RIα/RIβ heterodimers have also been reported (Carlson et al., 2003; Tasken et al., 1993). Type I PKA is mainly localized in the cytosol, but a minor amount is also anchored to specific cellular structures by AKAPs (Barradeau et al., 2002). RIα is expressed ubiquitously whereas RIβ is mainly expressed in the CNS (Cadd and McKnight, 1989). The majority of type II PKA is anchored to subcellular structures by AKAPs (Pidoux and Tasken, 2010; Scott, 1991; Welch et al., 2010; Wong and Scott, 2004). RIIα expression is ubiquitous, RIIβ is found predominantly in the brain as well as in neuroendocrine, adipose, and reproductive tissues (Skalhegg and Tasken, 2000).

Various splice variants of C and R subunits exist. Their expression is dependent on the tissue or developmental stage. In addition to the canonical Cα1, an alternative, sperm-specific splice variant Cα2/C(S) has been reported. Cα2 is essential for sperm function, male Cα2 knockout (KO) mice are infertile (Nolan et al., 2004). Six human splice variants of Cβ have been described: Cβ1, Cβ2, Cβ3, Cβ4, Cβ4ab, and Cβ4abc (Orstavik et al., 2001). Cβ2 was found to be specifically upregulated in prostate cancer cells, implying a connection of this splice variant to proliferation or tumor formation (Kvissel et al., 2007). No splice variants of the sperm-specific subunit Cγ are known.

The regulatory subunit RIα exists in two splice variants RIα1a and RIα1b. The expression of RIα1a is stimulated by cAMP (Solberg et al., 1997). Splice variants of RIβ, RIIα, and RIIβ are not known. Multiple different PKA holoenzymes can be formed from regulatory and catalytic subunit isoforms. Apparently, all C subunits can associate with any R subunit dimer (Skalhegg and Tasken, 2000). This diversity is enhanced by the combination of different splice variants. The function of novel PKA subunits or PKA-like proteins, their potential regulation by cAMP and

interaction with AKAPs are still largely unknown. Overall, the differences between the various PKA holoenzymes, for example, with respect to cAMP sensitivity, contribute to the specificity of PKA signaling.

An important model organism for studies of invertebrate cAMP signaling is *Drosophila melanogaster*. Its genome encodes three catalytic subunits, C1, C2, and C3, that are orthologs of human Cα, Cβ, and PrKX, respectively (Kalderon and Rubin, 1988; Melendez et al., 1995). These can form holoenzymes with the two *Drosophila* regulatory subunit isoforms, RI and RII, which show homologies to human RIα/RIβ and RIIα/RIIβ isoforms, respectively. Recently, the ER-resident transmembrane protein Swiss cheese has been described as a novel *Drosophila* regulatory subunit that interacts with PKA–C3 (Bettencourt da et al., 2008). The human ortholog of Swiss cheese, neuropathy target esterase (NTE), has so far not been shown to bind catalytic subunits. In contrast to the canonical R subunits, both human NTE and *Drosophila* NTE/Swiss cheese contain three cyclic nucleotide-binding (CNB) domains but they do not bind cAMP (Bettencourt da et al., 2008; Dremier et al., 2003).

2.4.2. Structural aspects of PKA

2.4.2.1. Regulatory subunits All PKA R subunits have the same general architecture, consisting of three domains: one N-terminal D/D domain and tandem CNB domains. An unstructured linker region is located between the D/D and the first CNB domain. This linker contains an inhibitor sequence that occupies the active site of a C subunit in the PKA holoenzyme. This sequence is a PKA pseudosubstrate in RI subunits and a PKA substrate in RII subunits. The D/D domains of two R subunit monomers form a four-helix bundle, thereby achieving the dimerization of R subunits and providing the docking site for AKAPs (see Section 3.2; Taylor et al., 2008).

2.4.2.2. Catalytic subunits The kinase core, which is conserved in all members of the protein kinase superfamily, is approximately 250 amino acids long and comprises a small, mostly β-strand N-terminal lobe, a short linker, and a large mostly helical C-terminal lobe (Taylor et al., 2008). While the N-terminal lobe harbors the ATP-binding site, the C-terminal lobe binds the substrate and contains most components of the catalytic machinery. In addition to the core, PKA C-subunits contain N- and C-terminal tails. Both fulfill important regulatory functions. The N-terminal tail can be modified by myristoylation, phosphorylation, and deamidation, which contributes to the control of C subunit localization (Breitenlechner et al., 2004; Gangal et al., 1999; Taylor et al., 2008; Tholey et al., 2001). The C-terminal tail, which is conserved in AGC kinases, is required for catalytic activity and serves as a docking site for modulators of PKA activity such as phosphoinositide-dependent kinase-1 (PDK-1; Kannan et al., 2008; Taylor et al., 2008).

2.4.3. R2D2 proteins: Similarity with R subunits of PKA

In mammals, there is a group of four proteins (ROPN1, ASP, CABYR and SP17) that contain an RII D/D domain (see above) and were therefore termed R2D2 proteins (Carr et al., 2001; Newell et al., 2008). Unlike PKA regulatory subunits, R2D2 proteins do not bind cAMP or catalytic subunits, but they can dimerize and bind AKAPs via their D/D domain. The AKAP–R2D2 interaction can be disrupted with PKA-anchoring disruptor peptides such as Ht31 (see Section 5.2). All four known R2D2 proteins were originally detected in sperm flagella but are also expressed in a variety of other tissues. The functions of R2D2 proteins are largely unknown but based on their expression pattern and cellular localization, they are likely to regulate the function of cilia and flagella (Chiriva-Internati et al., 2009; Newell et al., 2008).

2.4.4. Proteins interacting with C subunits of PKA

Most PKA interaction partners (e.g., AKAPs) bind R subunits, but several proteins have been shown to interact with C subunits. They are summarized in Table 5.1. In contrast to most AKAPs, C subunit-binding proteins often affect PKA activity directly. Several of these proteins are involved in the shuttling of C subunits between cytosol and nucleus.

A-kinase interacting protein (AKIP1) interacts with the helix A in the N-terminal tail of C subunits and anchors them in the nucleus (Sastri et al., 2005). AKIP1 is also involved in the control of the transcription factor nuclear factor κ B (NF-κB), an important regulator of immune function. NF-κB is a dimer consisting of the p50 and p65 subunits. In its inactive state, it is bound to the inhibitor of NF-κB (IκB) in the cytosol (Sun and Andersson, 2002). Stimulus-dependent IκB degradation releases NF-κB into the nucleus, where the now active form can induce transcription (Jacobs and Harrison, 1998; Sun and Andersson, 2002). AKIP1 interacts with NF-κB subunit p65 in the nucleus and mediates its PKA phosphorylation, thereby enhancing NF-κB-dependent transcription (Gao et al., 2008). IκB counteracts this. It masks the NF-κB DNA-binding sites and inhibits PKA C subunits by blocking the ATP-binding site, thereby preventing phosphorylation of p65 by PKA and thus activation of NF-κB-dependent transcription (Zhong et al., 1997).

The α subunit of the heterotrimeric G protein G_o interacts directly with C subunits through an unknown binding site. $G\alpha_o$-bound C subunits retain full activity (Ghil et al., 2006). Overexpression of $G\alpha_o$ prevents nuclear translocation of C subunits. Since $G\alpha_o$ interacts with both PKA holoenzyme and free C subunits, it provides a mechanism for controlling the localization of activated PKA. Notably, AKAPs only tether C subunits as part of PKA holoenzymes which are inactive.

The endogenous PKA inhibitor (PKI) is a small protein that contains a PKA pseudosubstrate sequence (Scott et al., 1985). This pseudosubstrate binds to the substrate-binding site of free C subunits and thus prevents

Table 5.1 Proteins interacting with PKA C subunits

Protein	PKA-binding mode; function/properties (references)
AKIP1	Interacts with N-terminus of C subunit; anchors C subunit in nucleus; enhances NF-κB p65 phosphorylation by PKA (Gao et al., 2008; Sastri et al., 2005)
IκB	Binds to and bocks ATP-binding site; prevents NF-κB p65 phosphorylation by PKA (Zhong et al., 1997)
$G\alpha_o$	PKA binding mechanism unknown; prevents nuclear localization of C subunits (Ghil et al., 2006)
PKI	Contains PKA pseudosubstrate that binds to C subunit substrate-binding pocket; inhibits PKA activity; exports C subunits from nucleus; PKI peptide used as pharmacological PKA inhibitor (Dalton and Dewey, 2006; Olsen and Uhler, 1991; Scott et al., 1985; Wen et al., 1994)
PDE7A1	Binds to C-terminus of free catalytic subunits via an N-terminal PKA pseudosubstrate domain; inhibits PKA activity (Han et al., 2006)
Caveolin-1	Scaffolding domain and C-terminus of Caveolin-1 bind C subunits; Inhibits PKA activity; required for PKA phosphorylation of Perilipin (Cohen et al., 2004; Razani and Lisanti, 2001; Razani et al., 1999)
RSK1 (active) p90 ribosomal S6 kinase-1 (p90RSK-1)	Inactive RSK1 binds to RI and facilitates C subunit release, active RSK1 binds to C subunits and promotes PKA holoenzyme formation (Chaturvedi et al., 2006; Frodin and Gammeltoft, 1999; Gao and Patel, 2009; Gao et al., 2010)

phosphorylation of PKA substrates. PKI contains a nuclear export signal (NES) sequence through which it exports C subunits from the nucleus (Dalton and Dewey, 2006; Wen et al., 1994). PKI-derived peptides are frequently used to inhibit PKA activity in experimental settings (Dalton and Dewey, 2006). In contrast to most small molecule protein kinase inhibitors, they do not occupy the ATP-binding site but prevent substrate binding and are hence highly specific for PKA.

The N-terminus of PDE7A1 contains two PKA pseudosubstrate sequences that interact with C subunits (Han et al., 2006). Consequently, PDE7A1 inhibits PKA activity in two ways: inhibition by blocking the substrate-binding site and, like other PDEs, by degradation of cAMP in the vicinity of

C subunits, resulting in reassembly of PKA holoenzyme and thereby inhibition of PKA. The AKAP MTG16b also binds PDE7A1 directly (Asirvatham et al., 2004). The function of the MTG16b/PDE7A1/PKA complex is unclear but it most likely limits PKA activity spatially.

Caveolin-1 also binds C subunits directly and inhibits their activity (Razani and Lisanti, 2001; Razani et al., 1999). It does not contain a PKA substrate or pseudosubstrate sequence. Two regions of caveolin-1 contribute to C subunit binding and inhibition: the scaffolding domain and the C-terminus (Razani and Lisanti, 2001). This is in line with data from caveolin-1 KO mice, in which total PKA activity and consequently cAMP-response element-binding protein (CREB) phosphorylation are increased (Cohen et al., 2004). In addition, caveolin-1 KO mice have a drastically reduced lifespan partially caused by cardiac hypertrophy (Park et al., 2003), that presumably arises from hyperactivation of PKA and consequent hyperphosphorylation of PKA substrates in cardiac myocytes. Caveolin-1 is not exclusively located on caveolae but it is also present on lipid droplets in adipocytes (Le Lay et al., 2009). Perilipin is a protein that covers and protects lipid droplets. The phosphorylation of perilipin by PKA is a key step in catecholamine-induced lipolysis (Brasaemle, 2007). Caveolin-1 forms a complex with PKA and perilipin and is necessary for perilipin phosphorylation by PKA (Cohen et al., 2004). Thus, caveolin-1 is not only an inhibitor of PKA activity but also a scaffolding protein for C subunits that is required for phosphorylation of the PKA substrate perilipin.

There is an intricate interplay between p90 ribosomal S6 kinase-1 (RSK1) and PKA. RSK1 is bound to PKA RI or C subunits in a nuclear D-AKAP1 complex (Chaturvedi et al., 2006). Inactive RSK1 binds to RI subunits and decreases their affinity to C subunits, facilitating the release of C from R subunits and thereby PKA activation. In contrast, active RSK1 binds to C subunits and enhances their binding to R subunits, inhibiting PKA activity. The disruption of PKA anchoring with the peptide Ht31 decreases nuclear RSK1 (Chaturvedi et al., 2006). Taken together, there are only a few proteins known to interact with PKA C subunits, but they provide important insights into molecular mechanisms underlying the regulation of PKA. They can control PKA localization, activity, and substrate access.

3. AKAPs: Scaffolds for Local Signaling

PKA is recruited to intracellular domains by AKAPs, a family of scaffolding proteins with more than 40 members. AKAPs were first found as contaminants in purifications of RII subunits (Theurkauf and Vallee, 1982). More members of the AKAP family were identified by using radioactively labeled RII subunits as probes in far-western blotting assays

(RII overlays; Lohmann et al., 1984). The unifying feature of AKAPs is the presence of a PKA-binding domain, also termed RII-binding domain (RIIBD) because almost all AKAPs preferentially anchor RII subunits. The RIIBD consists of an amphipathic α-helix of 14–18 amino acids that binds to the four-helix bundle formed by the D/D domains of PKA R subunit dimers (Figs. 5.2 and 5.5). Additionally, AKAPs contain a targeting domain for anchoring to specific subcellular locations. AKAPs do not only serve as signaling nodes in the coordination of cAMP signaling by interacting with PKA, GPCRs (Appert-Collin et al., 2006), ACs (Dessauer, 2009), Epac (Nijholt et al., 2008), or PDEs (Houslay, 2010; Fig. 5.1). They also function as scaffolds to coordinate signaling events by forming multicomponent complexes with other signaling proteins (Fig. 5.1; Welch et al., 2010; Wong and Scott, 2004) like PPs (see Section 2.3) or protein kinases such as Akt/protein kinase B (PKB; Nijholt et al., 2008) PKC, protein kinase D (PKD), protein kinase N (PKN; Wong and Scott, 2004) ERK1/2 (Jivan et al., 2009), or glycogen synthase kinase 3 β (GSK3β; see Section 4.1; Flynn et al., 2008; Hundsrucker et al., 2010; Tanji et al., 2002). Thus, AKAPs facilitate the cross talk and integration of different signaling pathways. AKAPs can be subdivided into three classes depending on their specificity for the different R subunit isoforms of PKA: RI-specific, RII-specific, or dual-specific (Jarnaess et al., 2008).

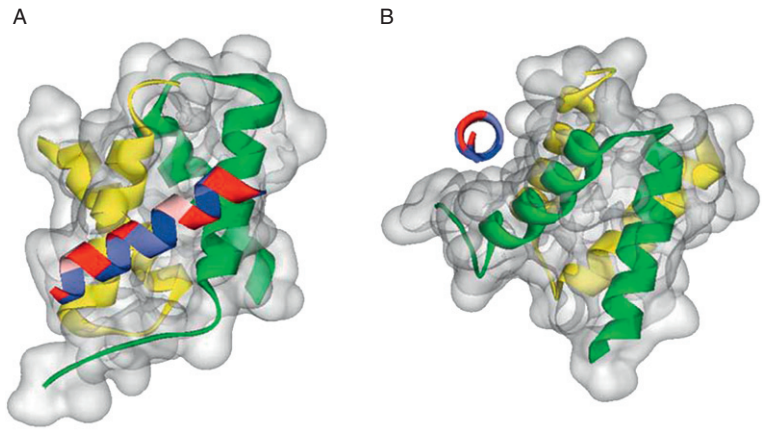

Figure 5.2 The crystal structure of the RIIα D/D domain dimer in complex with a D-AKAP2 peptide (PDB ID: 2HWN). The two RIIα protomers are shown in green and yellow, respectively. Coloring of the D-AKAP2 peptide represents amino acid polarity (blue: hydrophobic, red: polar). (A) View on top of the AKAP interaction site. (B) View from the side (visual axis = peptide helix axis) showing the interaction of the unpolar (Blue) side of the peptide with the hydrophobic groove of the AKAP interaction site on the top left side. Adopted from Kinderman et al. (2006).

3.1. AKAP nomenclature

Originally AKAPs were named after their apparent molecular weight determined by SDS gel electrophoresis. For example, AKAP79 migrates at 79 kDa in SDS-PAGE. The use of this nomenclature can be confusing since differently named AKAPs can be splice variants of the same gene (e.g., AKAP350 and AKAP450) or orthologs from different species (e.g., bovine AKAP75, human AKAP79, murine AKAP150).

The human genome organisation nomenclature committee (HGNC) renamed existing AKAPs with running numbers from AKAP1 to AKAP14. However, despite the recommendations of the HGNC, the molecular weight-derived names are more commonly used. Proteins which had been named before their AKAP function was revealed often retain their original name, such as MAP2 or GSK3β interaction protein (GSKIP).

3.2. Structural aspects of AKAP–PKA interactions

Structural studies of AKAPs have been mainly restricted to the elucidation of the molecular determinants of their interactions with PKA by analysis of the interacting domains. Recent studies yielded structural insights at the atomic level by NMR and X-ray crystallography studies.

Although the RIIBDs of different AKAPs share a low sequence identity ($<30\%$) it was proposed early on that there is a conserved secondary structural motif common to AKAPs (Carr et al., 1991). Indeed, RIIBDs display a pattern of pairs of hydrophobic and hydrophilic residues that have a high probability to form amphipathic α-helices. This motif is conserved throughout the AKAP family (Table 5.2).

This was initially revealed by helical wheel analysis which identified the RIIBD of AKAP-Lbc. Peptides derived from the predicted RIIBD of AKAP-Lbc (peptide Ht31) were shown to bind RIIα subunits of PKA (Carr et al., 1991). Since all R-binding peptides tested did not form secondary structures in CD measurements at physiological pH or amide H/D exchange experiments (Burns et al., 2003; Burns-Hamuro et al., 2005), the α-helical structure appears to be induced upon binding to the D/D domain. The importance of the helical structure for the interaction with the D/D domain was verified by amino acid substitution analysis showing reduction of R binding upon introduction of helix-distorting proline residues (Carr et al., 1991). The α-helical conformation of the RIIBD was initially confirmed in NMR structures comprising the D/D domain of recombinant RIIα (residues 1–44), and peptides encompassing the RIIBD of AKAP-Lbc (residues 493–515) and AKAP79 (residues 392–413; Newlon et al., 2001).

NMR analyses and crystal structures of the RIIα D/D domain show that the dimer forms an X-type four-helix bundle with the two protomers

Table 5.2 Alignment of RII-binding domains of the indicated AKAPs

AKAP	Sequence
AKAP1 (D-AKAP1)	GLDRNEEIKRAAFQIISQVISEATE
AKAP2 (AKAP-KL)	DDPLEYQAGLLVQNAIQQAIAEQVD
AKAP3 (AKAP110)	NLVIAMARKEINEKIDGSENKCVYQ
AKAP4 (AKAP82)	SIDDLSFYVNRLSSLVIQMAHKEIK
AKAP5 (AKAP79)	YETLLIETASSLVKNAIQLSIEQLV
AKAP6 (mAKAP)	KDAEDCSVHNFVKEIIDMASTALKS
AKAP7 (AKAP18)	PEDAELVRLSKRLVENAVLKAVQQY
AKAP8 (AKAP95)	KETPEEVAADVLAEVITAAVRAVDG
AKAP9 (1) (AKAP350)	YQEQLEEEVAKVIVSMSIAFAQQTE
AKAP9 (2) (Yotiao)	NLQKIVEEKVAAALVSQIQLEAVQE
AKAP10 (D-AKAP2)	GNTDEAQEELAWKIAKMIVSDVMQQ
AKAP11 (AKAP220)	VNLDKKAVLAEKIVAEAIEKAEREL
AKAP12 (Gravin)	GILELETKSSKLVQNIIQTAVDQFV
AKAP13 (AKAP-Lbc)	KGADLIEEAASRIVDAVIEQVKAAG
AKAP14 (AKAP-28)	TQDKNYEDELTQVALALVEDVINYA
GSKIP	TDMKDMRLEAEAVVNDVLFAVNNMF
MAP2	ETAEEVSARIVQVVTAEAVAVLKGE
Rab32	NINIEEAARFLVEKILVNHQSFPNE
AKAP-IS (peptide)	QIEYLAKQIVDNAIQQA
SuperAKAP-IS(peptide)	QIEYVAKQIVDYAIHQA
RIAD (peptide)	LEQYANQLADQIIKEATE

Note: The positions of conserved hydrophobic amino acid residues are highlighted.

adopting an antiparallel conformation (Fig. 5.2; Gold et al., 2006; Kinderman et al., 2006; Newlon et al., 1999, 2001). In all structures, the RII-binding peptides, such as Ht31, bind diagonally over one face of the D/D dimer creating a solvent-excluded interaction site. As predicted by helical wheel analysis, the interaction of R-binding peptides with the D/D domain is mediated by aliphatic residues located on one side of the peptides' α-helix, thereby forming a hydrophobic ridge (Fig. 5.2). The helix docks into a complementary hydrophobic groove preformed by side chains from the N-terminal helices from both protomers of the RIIα D/D (Fig. 5.2; Gold et al., 2006; Kinderman et al., 2006; Newlon et al., 1999, 2001).

There are X-ray structures available of the RIIα D/D domain bound to a peptide derived from the RIIBD of D-AKAP2 and one of the D/D domain bound to the peptide AKAP-*in silico* (AKAP-*IS*). When comparing the conformations of the RIIα D/D domain in the absence and the presence of the peptides, it appears that they are very similar regarding relative orientations of protomers within the dimer. This suggests that tertiary and quaternary structures, including the AKAP-binding site, are not changed by peptide binding with the exception of residues in the N-terminus (Gold et al., 2006). Hydrophobic amino acid side chains from the N-terminus of the R-binding peptide (for AKAP-*IS*: Ile5 and Ile8/D-AKAP2: Ile8, Ile12, Leu4 and Ala5) interact with residues of the dynamic N-terminus (Ile3 and

Ile5) of one of the D/D protomers. These results are in line with previous mutagenesis studies revealing that Ile3 and Ile5 are important for AKAP binding (Hausken et al., 1994). It appears that an additional binding site is induced upon formation of the PKA–AKAP complex since the residues of the N-terminal tail of the D/D domain in the absence of AKAP peptides are not detectable by X-ray crystallography.

This also means an induction of asymmetry into the symmetric D/D domain by the peptide, since only the N-terminal tail (Ile3, Gln4, Ile5) of one protomer is recruited for binding while the other N-terminal tail remains unstructured (Il3′, Gln4′, with Ile5′ being the first detectable/ordered residue in this protomer) and is probably not involved in binding. The induction of asymmetry is also implied by the observed higher B factor of Ile5′ compared to Ile5, respectively, indicating that Ile5′ is more dynamic than Ile5 (Gold et al., 2006; Kinderman et al., 2006). Moreover, these results are consistent with H/D exchange experiments. Free H/D exchange observed for Ile3 and Ile5 are due to the abovementioned asymmetry in the complex leaving one N-terminus solvent-exposed (Burns-Hamuro et al., 2005). The asymmetry induced by AKAP-derived peptides increases the probability for a productive interaction between the binding partners (Gold et al., 2006; Kinderman et al., 2006).

The helix backbones of different R-binding peptides adopt different orientations when bound to the D/D domain of RIIα, suggesting that side chains are involved in binding and that there is probably no significant contribution to binding or specificity from helix–helix interactions. This might serve as a way to accommodate the diverse array of R-binding sequences (Gold et al., 2006; Kinderman et al., 2006; Newlon et al., 2001). However, it cannot be excluded that the observed adoption of different orientations of the helices is due to different conditions used for solution structure analysis by NMR and structure analysis by X-ray crystallography.

As already mentioned, sequence alignment shows a similar number and distribution of hydrophobic amino acid residues within the RIIBDs of AKAPs. However, the binding affinities to RII differ from micromolar- (ERM family) to nanomolar-binding constants (AKAP18δ). Therefore, it is unlikely that hydrophobic interactions are the only factor contributing to high-affinity binding (Hundsrucker et al., 2006b). Although there is apparently no evidence for salt bridges or H-bonding between the R-binding peptides Ht31, AKAP79, or D-AKAP2 and RIIα from the respective structures, there are H-bonding interactions between AKAP-*IS* and RIIα as suggested from analysis of the crystal structure (Asp14/Thr10′; Gln19/Gln14; Asn15/Thr10′; Gold et al., 2006). In addition, there is evidence for helix-stabilizing H-bonding (Asn15/Gln19), stacking (Tyr7/Gln11), and N-terminal capping (Glu6) interactions within AKAP-*IS* (Gold et al., 2006; Kinderman et al., 2006; Newlon et al., 2001). In order to further elucidate

the contribution of nonhydrophobic interactions to AKAP–PKA binding, peptides derived from the high-affinity RIIBD of AKAP18δ were investigated by a combination of peptide SPOT and RII-overlay techniques (Hundsrucker et al., 2006b). The results revealed that amino acid residues from AKAP18δ and RIIα potentially form H bonds or salt bridges (Hundsrucker et al., 2006b; Fig. 5.3) which likely account for the high affinity of the binding. In addition, the results confirm the critical role of small, aliphatic residues for binding of R-binding peptides to RII subunits.

3.2.1. RIIBD consensus sequence

The RIIBDs of different AKAPs share a similar distribution of hydrophobic and polar amino acids and a high probability to form amphipathic α-helices (see above). While a certain pattern of hydrophobic amino acids may be applied to identify the RIIBD within an AKAP sequence (Vijayaraghavan et al., 1999), it is not suitable for a database search for novel AKAPs as it yields too many false positives. Therefore, an extended consensus sequence for RIIBDs was designed, resulting in the sequence [AVLISE]-X-X-[AVLIF]-[AVLI]-X-X-[AVLI]-[AVLIF]-X-X-[AVLISE] (X = any amino acid, Table 5.2; Hundsrucker et al., 2010). The number or position of H-bond- or salt bridge-forming amino acids within an RIIBD (Fig. 5.3) cannot be predicted. They do, however, influence the isoelectric point (pI) of the sequence. The pI of known RIIBDs ranges from 3.43 to 6.23. The consensus sequence complemented with a pI limitation (3.0–6.4) reduced the number of false positive hits in a database search and was shown to identify a previously unknown AKAP, GSKIP (Hundsrucker et al., 2010).

3.2.2. Insights from the full-length structure of GSKIP

AKAP–PKA interactions have been well characterized using AKAP-derived peptides and D/D domains of regulatory PKA subunits. Structural information on full-length AKAPs is, however, scarce. This is mainly due to fact that most AKAPs are high-molecular-weight proteins (e.g., AKAP450 and AKAP-Lbc, each >300 kDa) that consist of mainly unstructured parts

Figure 5.3 A schematic representation of potential H-bonding interactions (light gray) and salt bridges (dark gray) between the RIIBD of AKAP18δ and the D/D domain of RIIα. The residues of the two protomers of the D/D domain dimer are distinguishable by the presence and absence of apostrophes. The scheme is based on molecular modeling studies. Adopted from Hundsrucker et al. (2006b).

displaying no secondary or tertiary structures as predicted by *in silico* analyses (Malbon et al., 2004). This complicates the expression of AKAPs since large proteins cannot be expressed in common expression systems as full-length proteins. In addition, AKAPs often form insoluble aggregates. Moreover, AKAPs are often associated with cellular structures such as membranes, the cytoskeleton, or are part of multiprotein complexes. Any of these components may play an important role for the stabilization of AKAP structures and without them structural analysis of the protein may not be possible (Malbon et al., 2004). Consequently, full-length AKAPs are difficult to purify. Therefore, often only truncations can be used.

Partial structures are available for some AKAPs but none of the fragments resolved by NMR or X-ray crystallography contain their RIIBD. Although they lack information about the RIIBDs' environments and the PKA binding mechanism, these partial structures point to other AKAP functions. For instance, the structure of the AKAP18δ core domain (AKAP18δ^{CD}), comprising amino acids 76–292, contains a His-X-Thr motif which is a common feature of the 2H-phosphoesterase family (PDB ID: 2VFL; Gold et al., 2008). Cocrystallization with AMP and CMP revealed binding of these nucleotides to the His-X-Thr motif (Gold et al., 2008). However, the function of this motif and the nucleotide binding in AKAP18δ are not known. Further examples are an NMR structure of the Dbl homology/pleckstrin homology (DH/PH) domain of AKAP-Lbc (Sugawara et al., 2009) and crystal structures of the protein 4.1, ezrin, radixin, moesin (FERM) domains of Ezrin (PDB ID: 1NI2; Smith et al., 2003) and Moesin (PDB ID: 1SGH; Finnerty et al., 2004).

To date, the only full-length AKAP whose structure has been resolved is GSKIP (PDB ID: 1SGO, NMR analysis by the Northeast Structural Genomics Consortium). GSKIP was identified as an AKAP in an *in silico* screening of the Swissprot data bank using an extended model for a consensus sequence of RIIBDs (see above; Hundsrucker et al., 2010). GSKIP (15.6 kDa) is one of the smallest AKAPs. Its small size and excellent solubility permitted analysis of its structure by NMR. GSKIP can structurally be divided into four parts: a highly flexible unstructured N-terminus of unknown function (amino acids 1–32), an adjacent α-helix (amino acids 33–48), a central antiparallel β-sheet region (amino acids 49–115), and a second C-terminal α-helix (amino acids 116–139; Fig. 5.4A). The RIIBD of GSKIP is located between amino acid 28 and 52 and thus mostly α-helical with the conserved hydrophobic residues located in this helix in positions 37, 40, 41, 44, 45, and 48 (Fig. 5.4B). As expected for an amphipathic helix, the polar face is on the surface of the protein while the hydrophobic face is covered by the β-sheet region (Fig. 5.4).

Because solvent-exposed hydrophobic residues are energetically unfavorable, it is likely that the hydrophobic part of RIIBDs of other AKAPs are also buried in the absence of PKA. As a consequence, the interaction of

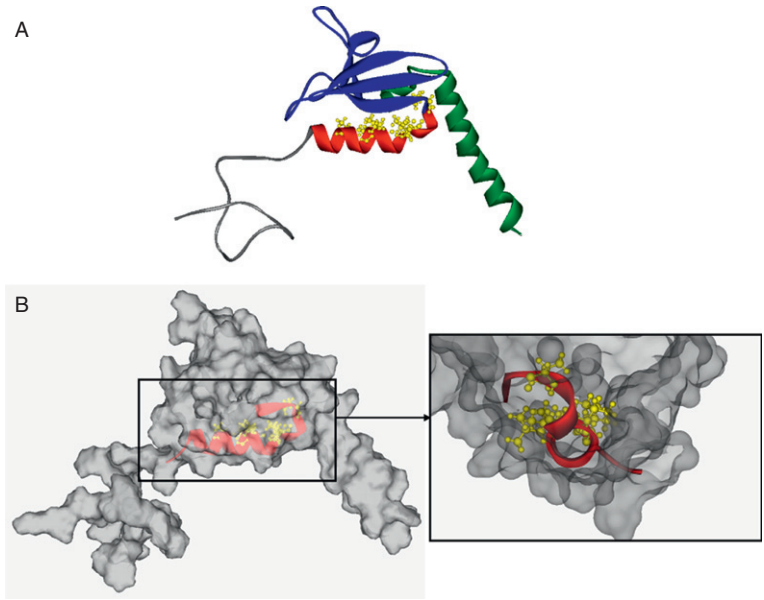

Figure 5.4 The NMR structure of GSKIP (PDB ID: 1SGO). (A) GSKIP consists of an unstructured N-terminus (gray, amino acids 1–32) followed by an α-helix (red, amino acids 33–48), a central β-sheet region (blue, amino acids 49–115) and a C-terminal α-helix (green, amino acids 116–139). Adopted from Hundsrucker et al. (2010). (B) The surface of the protein is illustrated in gray, the RIIBD is shown in red and conserved hydrophobic residues therein are labeled yellow.

AKAPs and the D/D domain of PKA regulatory subunits would have to be accompanied by conformational changes of the AKAP. Consistently, NMR experiments with GSKIP and the RIIα D/D domain show that the hydrophobic face of GSKIP's RIIBD is involved in the interaction with the D/D domain dimer. In addition, structural alterations in other regions of GSKIP, namely the β-sheet that functions as a lid for the hydrophobic face of the RIIBD in free GSKIP, and amino acids in the C-terminal helix adjacent to the RIIBD helix, were observed (Hundsrucker et al., 2010). These changes in the β-sheet structure are most likely conformational rearrangements necessary to compensate for the loss of hydrophobic interactions between the bottom of the β-sheet and the hydrophobic face of the RIIBD helix. Conformational changes induced by R subunit binding are likely to occur in other AKAPs such as AKAP18δ. Peptides comprising the RIIBD of AKAP18δ (amino acids 292–321) as well as an N-terminally truncated AKAP18δ (amino acids 124–353) bind with higher affinity to RIIα than the full-length protein (Henn et al., 2004; Hundsrucker et al., 2006b), suggesting that PKA binding causes a conformational change involving N-terminal domains of AKAP18δ. Such changes may make the

hydrophobic RIIBD accessible for binding. The understanding of conformational changes in AKAPs upon PKA binding will contribute to explain differences in binding affinities of various AKAPs to PKA that are independent from the residues in the RIIBD. PKA binding could also alter the conformation of other protein–protein interaction surfaces on AKAPs, thereby facilitating or inhibiting the binding of further proteins. On the other hand, proteins other than PKA interacting with AKAPs might modulate PKA binding.

3.2.3. PKA type I versus type II anchoring

There are differences in the specificity of AKAPs with regard to the binding of RI and RII isoforms: RII subunits generally bind with higher affinity to AKAPs and have a lower off-rate than RI subunits. For example, the dual-specific D-AKAP1 binds RIIα (K_D = 0.5 nM) with a higher affinity than RIα (K_D = 185 nM; Herberg et al., 2000). RI binds to fewer AKAPs and, in general, more mutations in R-binding peptides abolish RI binding (Burns-Hamuro et al., 2005). Several studies have revealed the molecular basis for this isoform specificity of RIIBDs: Comparison of the R isoforms shows differences in surface charge distribution. While RIIα has a mostly hydrophobic interaction surface, RIα contains additional acidic and basic residues at the proposed interaction site (Banky et al., 2003). NMR (amino acids 12–61), and more recently, crystallographic structure analyses (amino acids 1–61) of the RIα D/D domain show—similar to RIIα—an X-type four-helix bundle with antiparallel orientation of the protomers (Banky et al., 2003; Sarma et al., 2010). RIα contains an extended, yet ordered, N-terminus forming the additional helix N1 (Banky et al., 2000). H/D exchange experiments suggested that this N1 helix is involved in AKAP binding to RI subunits (Burns-Hamuro et al., 2005). A peptide derived from the RIIBD of D-AKAP2 binds diagonally onto the AKAP-binding site of RIα, similarly as to the D/D domain of RIIα (Sarma et al., 2010). This X-ray structure confirms the predicted participation of the N1 helices of RIα in AKAP binding and explains the role of the cysteine residues C16, C37, C16′, and C37′: RIα is oxidized in complex with the peptide and disulfide bridges are found between C16–C37′ and C16′–C37, respectively, thereby cross-linking the N1 helices of one protomer to the I helix of the other protomer (Fig. 5.5). Thus the cysteines apparently confer an ordered structure to the N-terminus of RIα. The cysteine residues are also a part of the binding pockets interacting with D-AKAP2 (see below; Sarma et al., 2010).

A comparison of the RIα with the RIIα structure in complex with the D-AKAP2 peptide discloses general molecular determinants for the R subunit specificity of AKAPs (Sarma et al., 2010). Four hydrophobic binding pockets were identified in RIα which interact with pairs of hydrophobic amino acids from four turns of the D-AKAP2 helix (Leu634, Ala635;

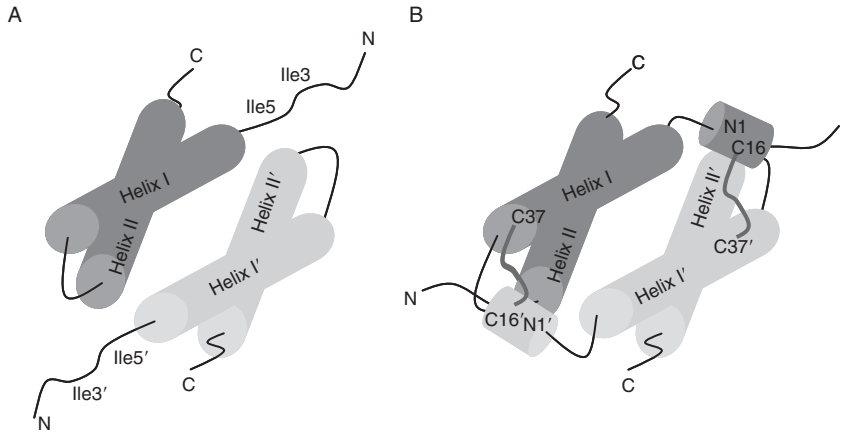

Figure 5.5 A schematic view on top of the AKAP-binding site of the D/D domain dimer of RIIα (A) and RIα (B). The two protomers depicted in light and dark gray are arranged in an antiparallel manner thereby forming the characteristic X-type four-helix bundle. The residues of the two protomers of the D/D domain dimer are distinguishable by the presence and absence of apostrophes. (A) Ile3, Ile3′, Ile5, and Il5′, located in the unordered N-terminal tails of the protomers, are involved in recognition and binding of RIIBD-derived peptides. (B) The N-terminal helices N1 and N1′ as well as the disulfide bridges between C16–C37′ and C16′–C37, respectively, are indicated. Adopted from Kinderman et al. (2006). See text for details.

Ile638, Ala639; Ile642, Val643; and Val646, Met647), while there are only two hydrophobic binding pockets in RIIα interacting with pairs of hydrophobic amino acids from two turns of the D-AKAP2 peptide (Ile638, Ala639 and Ile642, Val643). This observation corresponds to earlier results which predicted that a longer sequence within RIIBDs interacts with the RIα D/D domain compared to RIIα. This is probably one reason why RIα subunits interact with only a few AKAPs. An important factor limiting sequence recognition by RIα is the already mentioned presence of disulfide bridges. They reduce the flexibility of the dimer and restrict access to the AKAP-binding site in RIα compared to RIIα.

Based on the available structures of the D-AKAP2 peptide with the RI and RII D/D domains, Sarma et al. (2010) developed an approach to determine specificity for other AKAP sequences by using a combination of sequence alignment and projection of the sequence onto the available structures. This was, for example, used to analyze the determinants for isoform specificity of the peptides RI-anchoring disruptor (RIAD) (Carlson et al., 2006) and AKAP-*IS* (Gold et al., 2006). RIAD and AKAP-*IS* were developed as isoform-selective R-binding peptides (see Section 5.2). The apparent RI specificity of RIAD is based on amino acids that probably sterically interfere with RII binding while the core

binding region seems to fit to both RI and RII D/D domains. AKAP-*IS* on the other hand is RII-preferring due to one aliphatic residue that does not fit into the first core binding pocket of RIα (Sarma et al., 2010).

It was also recently shown that several dual-specific AKAPs have an additional PKA binding determinant termed RI specifier region (RISR) located outside the common amphipathic helix motif (Jarnaess et al., 2008). Within this region, basic residues are essential for RI binding. RISR-containing peptides bind specifically to RI subunits but not to RII subunits (Jarnaess et al., 2008).

3.3. Diversity within the AKAP family

According to the wide array of local PKA functions, AKAPs are present in virtually any tissue and cell type and they can occupy most organelles like the plasma membrane, the cytoskeleton, mitochondria, the Golgi apparatus, the nucleus, or vesicular structures (Wong and Scott, 2004). Table 5.3 summarizes the canonical AKAPs (i.e., proteins interacting with the D/D domain of PKA R subunits dimers via an amphipathic helix), their alternative names, expression patterns, localizations, protein–protein interactions, and selected functions.

Not all AKAPs bind to the D/D domain via an amphipathic helix. These "noncanonical AKAPs" include proteins such as pericentrin, whose PKA-binding domain is a longer (100 amino acids) nonhelical, leucine-rich region that interacts with RII (Diviani et al., 2000). Table 5.4 summarizes noncanonical AKAPs. Only a few noncanonical AKAPs are known, probably because they are often missed in screens for new AKAPs, in particular, when these are conducted with the D/D domain and not full-length R subunits as bait (Goehring et al., 2007). Or they may be classified as false positive hits when their binding to PKA is not diminished by PKA-anchoring disruptor peptides (Hundsrucker et al., 2010). Thus it is likely that a number of unidentified noncanonical AKAPs add to the regulation of PKA. Table 5.4 contains two proteins termed "putative AKAPs" as their mode of binding to R subunits has not yet been determined.

3.4. The evolution of AKAPs

The majority of identified AKAPs are from human or rodent origin (see Tables 5.3 and 5.4). Orthologs of several mammalian AKAPs were also found in lower vertebrates. In *Xenopus*, AKAP12 (X-gravin like; Isoldi et al., 2010; Klingbeil et al., 2001), Rab32 (Park et al., 2007), and Moesin (Semenova et al., 2009) have been described. *Danio rerio* homologs of D-AKAP2, MTG8, MyRIP (Goehring et al., 2007), and Myospryn (Reynolds et al., 2007) have been identified as PKA-binding proteins. Additional database entries indicate the existence of further lower vertebrate AKAPs

Table 5.3 AKAPs

Canonical AKAP (HGNC name)	Consensus RIIBD[a]/*R specificity*	Tissue expression pattern	Cellular localization	Interactions	Functions and properties (references)
D-AKAP1 AKAP140 AKAP149 AKAP121 AKAP84 S-AKAP84 (*AKAP1*)	Yes/*dual*	Ubiquitous, high expression in testis, thyroid, oocytes	Outer mitochondrial membrane, inner mitochondrial compartment, ER, nuclear envelope, sperm midpiece	AMY-1 AAT-1 PP1 CaN/PP2B PTPD1 Lamin B PDE4A HIV-1 RT RNA	Multiple splice variants; contains RNA-binding KH-Tudor domain; regulates nuclear envelope integrity via lamin phosphorylation status; binds HIV-1 reverse transcriptase and is involved in reverse transcription (Abrenica et al., 2009; Asirvatham et al., 2004; Chen et al., 1997; Furusawa et al., 2001, 2002; Ginsberg et al., 2003; Huang et al., 1997a, 1999; Lemay et al., 2008; Lin et al., 1995; Newhall et al., 2006; Rogne et al., 2009; Sardanelli et al., 2006; Steen and Collas, 2001; Steen et al., 2000, 2003; Trendelenburg et al., 1996; Yukitake et al., 2002)

(*continued*)

Table 5.3 (*continued*)

Canonical AKAP (HGNC name)	Consensus RIIBD[a]/*R specificity*	Tissue expression pattern	Cellular localization	Interactions	Functions and properties (references)
AKAP-KL (*AKAP2*)	Yes/*dual*	Kidney, lung, thymus, cerebellum, heart	Actin cytoskeleton/ apical membrane of epithelial cells		Multiple splice variants; disruption of the AKAP2 gene might play a role in Kallmann syndrome (Dong et al., 1998; Panza et al., 2007; Scholten et al., 2006)
AKAP110 Fibrousheathin-1 FSP95 (*AKAP3*)	No/*dual*	Testis	Acrosome, fibrous sheath of sperm tail	$G\alpha_{13}$ PDE4A AKAP4	Structural sperm protein (Bajpai et al., 2006; Mandal et al., 1999; Niu et al., 2001; Vijayaraghavan et al., 1999)
AKAP82 FSC1 (*AKAP4*)	No/*dual*	Testis	Fibrous sheath of sperm tail	AKAP3 FSIP1 FSIP2	Multiple splice variants; most abundant protein of fibrous sheath; marker for multiple myeloma (Brown et al., 2003a; Carrera et al., 1994; Chiriva-Internati et al., 2008; Miki and Eddy, 1998; Miki et al., 2002)
AKAP79 (human) AKAP75 (bovine) AKAP150 (murine) (*AKAP5*)	Yes/*RII*	Ubiquitous, high expression in brain	Plasma membrane, postsynaptic densities	CaN/PP2B Epac-1 IQGAP1 PKB/Akt	Targeted to plasma membrane via polybasic sequence; regulates multiple ion channels and receptors;

PKC	mediates feedback inhibition
AC5/AC6	of AC5/6 by PKA; required
AC8	for recycling of β_1-AR
NMDA receptor	(Bauman et al., 2006;
AMPA receptor	Brandon et al., 2003;
$mGluR_{1/5}$	Bregman et al., 1989; Carr
β_1-AR, β_2-AR	et al., 1992a; Chai et al.,
TRPV1/4 channel	2007; Coghlan et al., 1995; Colledge et al., 2000; Dart
TREK-1 channel	and Leyland, 2001;
KCNQ2 channel	Dell'Acqua et al., 1998,
L-type Ca^{2+} channel	2002; Fan et al., 2009; Fraser et al., 2000; Gao et al., 1997a;
ASIC1/2a	Gardner et al., 2006; Glantz
PSD-95	et al., 1992; Gomez et al.,
SAP97	2002; Hall et al., 2007; Higashida et al., 2005; Hirsch et al., 1992; Hoshi et al., 2003, 2010; Jeske et al., 2008; Kashishian et al., 1998; Klauck et al., 1996; Lu et al., 2008; Lynch et al., 2005; Nauert et al., 2003; Nijholt et al., 2008; Oliveria et al., 2007; Sandoz et al., 2006; Tunquist et al., 2008; Willoughby et al., 2010; Zhang et al., 2008)

(*continued*)

Table 5.3 (*continued*)

Canonical AKAP (HGNC name)	Consensus RIIBD[a]/*R specificity*	Tissue expression pattern	Cellular localization	Interactions	Functions and properties (references)
mAKAP AKAP 100 (*AKAP6*)	Yes/*RII*	Heart, brain, skeletal muscle	Nuclear envelope, sarcoplasmic reticulum	RyR2 PDE4A PDE4D3 nesprin-1α Epac1 (via PDE4D3) ERK5 (via PDE4D3) PP2A PP3 AC2, AC5 NCX HIF-1α VHL PDK-1 Siah2	Spectrin repeat domains target mAKAP to nesprin in the nuclear envelope; potentiates PKA phosphorylation/ activation of RyR; mediates feedback inhibition of AC5 by PKA; conveys ERK5-induced cardiac hypertrophy (Carlisle Michel et al., 2005; Dodge et al., 2001; Dodge-Kafka et al., 2005; Kapiloff et al., 1999, 2001, 2009; Marx et al., 2000; McCartney et al., 1995; Pare et al., 2005a; Schulze et al., 2003; Wong et al., 2008; Zakhary et al., 2000) reviewed in Dodge-Kafka and Kapiloff (2006)

AKAP18/AKAP15 (*AKAP7*)					
Isoform α	Yes	Heart, brain, lung, pancreas, kidney	Plasma membrane	Brain sodium channel (α-subunit) ENaC PKCα L-type Ca^{2+} channel	Lipid anchored to plasma membrane; inhibits ENaC sodium channel by recruiting PKCα; interacts with L-type Ca^{2+} channel via leucine zipper and mediates its PKA phosphorylation; enhances glucose-stimulated insulin release (Bengrine et al., 2007; Fraser et al., 1998; Hulme et al., 2003; Josefsen et al., 2010; Tibbs et al., 1998; Trotter et al., 1999)
Isoform β	Yes	Kidney, brain	Plasma membrane		Lipid-anchored to plasma membrane; function unknown (Trotter et al., 1999)
Isoform γ	Yes/*dual*	Heart, brain, placenta, lung, pancreas	Cytosol, nucleus		Inhibits glucose-stimulated insulin release (Brown et al., 2003b; Josefsen et al., 2010; Trotter et al., 1999)
Isoform δ	Yes	Heart, kidney inner medulla	Cytosol, sarcoplasmic reticulum, Secretory vesicles	PDE4D3 Phospholamban	High-affinity AKAP; involved in AVP-induced AQP2 shuttle in the renal inner medulla; regulates cardiac Ca^{2+} uptake into SR by mediating PKA

(*continued*)

Table 5.3 (*continued*)

Canonical AKAP (HGNC name)	Consensus RIIBD[a]/*R specificity*	Tissue expression pattern	Cellular localization	Interactions	Functions and properties (references)
					phosphorylation of phospholamban; AKAP18δ peptides used to disrupt PKA anchoring (Henn et al., 2004; Hundsrucker et al., 2006a,b; Lygren et al., 2007; Stefan et al., 2007)
AKAP95 (*AKAP8*)	Yes/*RII*	Ubiquitous	Nuclear matrix	PDE4A hCAP-D2/Eg7 fidgetin DDX-5 AMY-1 MCM2 Cyclin D3 Caspase 3	Involved in chromatin condensation; (Akileswaran et al., 2001; Arsenijevic et al., 2004; Asirvatham et al., 2004; Coghlan et al., 1994; Collas et al., 1999; Eide et al., 1998, 2003; Furusawa et al., 2002; Kamada et al., 2005; Yang et al., 2006; Yun et al., 1998)
AKAP350 AKAP450 AKAP120 CG-NAP Hyperion (*AKAP9*)	Yes/*RII*	Ubiquitous	Centrosomes (most cell types), golgi (epithelial cells),	FBP17 CIP4 PKN PKCε PP1 PP2A CLIC GCP2/3	Regulates microtubule dynamics; targeted to centrosomes via PACT domain (Dransfield et al., 1997a; Eide et al., 1998; Gillingham and Munro, 2000; Kim et al., 2007; Larocca et al., 2004, 2006;

					Schmidt et al., 1999; Shanks et al., 2002; Sillibourne et al., 2002; Takahashi et al., 1999, 2000; Witczak et al., 1999)
Isoform Yotiao *(AKAP9)*	Yes	Brain, heart, placenta, skeletal muscle, pancreas, testis	Plasma membrane (postsynaptic density, neuromuscular junction)	NMDA receptor PP1 IP_3R1 AC1/2/3/9 PDE4D3 I_{KS} (subunit KCNQ1)	Interacts with membrane proteins via leucine-zipper motif; regulates cardiac I_{KS} K^+ channel currents; Yotiao mutation S1570L in KCNQ1-binding site causes long QT syndrome; Modulates NMDA receptor currents by recruiting PKA and PP1; facilitates bradykinin-induced PKA phosphorylation of IP_3R1; mediates phosphorylation of AC by PKA (Chen et al., 2005, 2007; Feliciello et al., 1999; Hur et al., 2005; Lin et al., 1998; Piggott et al., 2008; Terrenoire et al., 2009; Tu et al., 2004; Westphal et al., 1999)

(*continued*)

Table 5.3 (*continued*)

Canonical AKAP (HGNC name)	Consensus RIIBD[a]/*R specificity*	Tissue expression pattern	Cellular localization	Interactions	Functions and properties (references)
D-AKAP2 (*AKAP10*)	Yes/*dual*	Ubiquitous	Mitochondria, cytosol, endosomes	PDZK1 Rab4 Rab11	Contains two RGS domains and a PDZ-binding motif; I646V SNP increases RI-binding, causes arrhythmia and increases the risk of sudden cardiac death, colorectal cancer and familial breast cancer formation; regulates transferrrin receptor recycling; (Eggers et al., 2009; Gisler et al., 2003; Huang et al., 1997b; Kammerer et al., 2003; Neumann et al., 2009; Tingley et al., 2007; Wang et al., 2001, 2009; Wirtenberger et al., 2007)
AKAP220 (*AKAP11*)	Yes/*dual*	Testis, brain, kidney	Vesicles, peroxisomes, centrosome	PP1 GSK3β $GABA_c$ receptor AQP2	Mediates GABAc-dependent PKA activation; overexpressed in oral squamous cell carcinomas; colocalizes with AQP2,

					might be involved in PKA phosphorylation of AQP2; AKAP220 facilitates GSK3β phosphorylation by inhibiting PP1 and recruiting PKA (Garnis et al., 2005; Lester et al., 1996; Okutsu et al., 2008; Reinton et al., 2000; Schillace and Scott, 1999; Schillace et al., 2001; Tanji et al., 2002; Yang et al., 2008)
Gravin (human) AKAP250 SSeCKS (Src-suppressed C kinase substrate, rodent) (*AKAP12*)	Yes	Ubiquitous except for liver	Cytosol/Actin cytoskeleton	PKC β_2-AR Calmodulin CaN/PP2B cyclin D	Autoantigen in myasthenia gravis; involved in cell cycle regulation; regulates cytoskeletal architecture and migratory processes; tumor suppressor protein, expression reduced in many tumors (Akakura et al., 2008; Fan et al., 2001; Gelman et al., 1998, 2000; Gordon et al., 1992; Grove et al., 1994; Lin and Gelman, 2002; Lin et al., 1996; Liu et al., 2006b; Nauert et al., 1997; Streb et al., 2004) reviewed in (Gelman 2002)

(*continued*)

Table 5.3 (*continued*)

Canonical AKAP (HGNC name)	Consensus RIIBD[a]/*R specificity*	Tissue expression pattern	Cellular localization	Interactions	Functions and properties (references)
AKAP-Lbc Ht31 Rt31 Brx-1 (*AKAP13*)	Yes	Ubiquitous	Cytosol/Actin cytoskeleton	RhoA PKD PKCη Gα_{12} 14-3-3 Estrogen receptor alpha LC3 a-catulin	Ht31 peptide derived from RIIBD used to disrupt PKA anchoring; mediates catecholamine-induced cardiac hypertrophy; Rho-GEF activated by Gα_{12}; C-terminal truncation increases Rho-GEF activity in oncogenic Lbc; induces stress fiber formation in a Rho-dependent manner (Appert-Collin et al., 2007; Baisamy et al., 2005, 2009; Carnegie et al., 2004, 2008 Carr et al., 1992b; Diviani et al., 2001; Diviani et al., 2004; Klussmann et al., 2001; Rubino et al., 1998; Sterpetti et al., 1999) reviewed in Diviani et al. (2006)
AKAP28 (human) TAKAP80 (rat) (*AKAP14*)	Yes	Lung (AKAP28), testis (TAKAP80)	Cilia of airway epithelia (AKAP28), fibrous sheath of sperm tail (TAKAP80)		Probably involved in the regulation of ciliar/flagellar beat (Kultgen et al., 2002; Mei et al., 1997)

GSKIP C14ORF129 HSPC210	Yes/*RIIα/β*	Ubiquitous	Cytosol	GSK3*β*	NMR structure solved (PDB: 1SGO), mediates inhibitory phosphorylation of GSK3*β* Ser-9 by PKA (Chou et al., 2006; Hundsrucker et al., 2010)
MyRIP SlaC2-c	Yes	Ubiquitous	Secretory vesicles, actin cytoskeleton, retinal melanosomes	Rab27a actin myosin Va myosinVIIa	Involved in retinal melanosome and insulin secretion; required for exocytosis of pathogenic *E. coli* (El-Amraoui et al., 2002; Fukuda and Kuroda, 2002; Goehring et al., 2007; Lopes et al., 2007; Song et al., 2009)
Rab32	Yes	Ubiquitous	Mitochondria, melanosomes	Varp	Involved in mitochondrial fission (Alto et al., 2002; Bao et al., 2002; Park et al., 2007; Tamura et al., 2009; Wasmeier et al., 2006)
SKIP SPHKAP	Yes	Heart, brain, ovary, spleen	Cytosol	SPHK-1	Antiproliferative due to inhibition of sphingosine kinase-1 (SPHK-1) activity (Lacana et al., 2002; Scholten et al., 2006)

(*continued*)

Table 5.3 (*continued*)

Canonical AKAP (HGNC name)	Consensus RIIBD[a]/*R specificity*	Tissue expression pattern	Cellular localization	Interactions	Functions and properties (references)
BIG2 (brefeldin A-inhibited guanine nucleotide-exchange protein 2) ARFGEF2 ARFGEP2	Yes/*dual*, *3 PKA-binding sites*	Placenta, lung, heart, brain, kidney, pancreas	Golgi, cytosol	FKBP13 $GABA_A$ receptor PDE3A PP1γ	GEF for ADP-ribosylation factors; involved in $GABA_A$ receptor trafficking (Charych et al., 2004; Kuroda et al., 2007; Li et al., 2003; Puxeddu et al., 2009)
Ezrin AKAP78 Villin-2	No/*dual*	Blood cells, placenta, secretory epithelia, brain	Actin cytoskeleton	EBP50/NHERF NHERF2 CD43 CD44 ICAM-1 ICAM-2 Actin FAK Merlin S100P	Interacts with CFTR via NHERF2, complex enhances PKA activation of CFTR; mediates inhibition of T cell immune functions by PKA (Bonilha et al., 2006; Dransfield et al., 1997b; Gronholm et al., 1999; Heiska et al., 1998; Koltzscher et al., 2003; Poullet et al., 2001; Reczek and Bretscher, 1998; Ruppelt et al., 2007; Saotome et al., 2004; Stokka et al., 2010; Sun et al., 2000a,b; Takahashi et al., 1997; Tamura et al., 2005; Yao et al., 1996; Yonemura et al., 1998; Yun et al., 1998)

WAVE-1 Scar	No	Brain, platelets, liver	Actin cytoskeleton, mitochondria	Actin WRP Arp2/3 Rac Abl Abi-1/2 Bad Glucokinase PP1 Bcl-2	Regulates actin cytoskeleton dynamics; regulates apoptosis and glycolysis (Danial et al., 2003; Eden et al., 2002; Kang et al., 2010; Machesky and Insall, 1998; Miki et al., 1998; Oda et al., 2005; Rawe et al., 2004a,b; Soderling et al., 2002, 2003, 2007; Westphal et al., 2000)
MAP2 Isoforms a, b, c, d	No	Brain, ovaries	Microtubules	Tubulin Actin Grb-2 Src Fyn Myosin VIIa (MAP2b) NEFL GSK3β (MAP2D) PP2A L-type Ca^{2+} channel	Involved in neuritogenesis, synapse formation and dendrite remodeling; PKA phosphorylation of MAP2 decreases tubulin and increases actin binding; MAP2D mediates phosphorylation of GSK3β by PKA (Davare et al., 1999; Flynn et al., 2008; Frappier et al., 1991; Hall et al., 2007; Harada et al., 2002; Khuchua et al., 2003; Kim et al., 1979; Lim and Halpain, 2000; Obar et al., 1989; Ozer and Halpain, 2000; Roger et al., 2004; Salvador et al., 2004; Teng et al., 2001; Todorov

(*continued*)

Table 5.3 (*continued*)

Canonical AKAP (HGNC name)	Consensus RIIBD[a]/*R specificity*	Tissue expression pattern	Cellular localization	Interactions	Functions and properties (references)
					et al., 2001; Zamora-Leon et al., 2001)
Neurobeachin	No/*RIIα*, *RIIβ*	Ubiquitous, high in brain	Golgi, postsynaptic plasma membrane		Contains WD40 and BEACH domains; essential for evoked transmission at neuromuscular junctions; gene disruption can cause autism (Castermans et al., 2003; Medrihan et al., 2009; Su et al., 2004; Wang et al., 2000)
MTG8 RUNX1T1	No	Brain, lymphocytes	Golgi		A reciprocal chromosomal translocation t(8;21)(q22; q22), resulting in an MTG8/AML-1 fusion gene causes acute myeloid leukemia (AML-M2; Fukuyama et al., 2001; Miyoshi et al., 1993)
Myosin VIIA	No/*RIα*	Ubiquitous	Actin cytoskeleton	Actin MyRIP Calmodulin MAP2b	(Kussel-Andermann et al., 2000; Todorov et al., 2001)

MTG16b CBFA2T3 ZMYND4	No/*dual*	Ubiquitous	Golgi	PDE4A PDE7A Plexin	Chromosomal translocation t (16;21)(q24;q22) results in an MTG16b/AML-1 fusion gene, causing acute myeloid leukemia (AML-M1 or -M2; Asirvatham et al., 2004; Fiedler et al., 2010; Gamou et al., 1998; Schillace et al., 2002)
Synemin desmuslin	No	Muscle (skeletal, heart, smooth)	Intermediate filaments, Z-discs	α-dystrobrevin Desmin vimentin	Overexpressed in failing hearts; possibly involved in cytoskeletal remodeling during cardiac hypertrophy and failure (Granger and Lazarides, 1980; Mizuno et al., 2001; Russell et al., 2006)
PAP7	No/*dual*	Ubiquitous	Mitochondria	PBR	Involved in regulation of cholesterol transport and steroid synthesis (Li et al., 2001a; Liu et al., 2003, 2006a)
Myospryn	No/*3 PKA-binding sites* *RIIα*	Muscle (skeletal, heart)	Z-discs	α-actinin Dysbindin Desmin Dystrophin	Member of tripartite motif (TRIM) superfamily; dysregulated PKA signaling due to reduced myospryn expression contributes to the pathogenesis of Duchenne

(*continued*)

Table 5.3 (*continued*)

Canonical AKAP (HGNC name)	Consensus RIIBD[a]/R *specificity*	Tissue expression pattern	Cellular localization	Interactions	Functions and properties (references)
					muscular dystrophy; K2906N polymorphism associated with cardiac left ventricular hypertrophy (Durham et al., 2006; Kouloumenta et al., 2007; Nakagami et al., 2007; Reynolds et al., 2007, 2008) reviewed in Sarparanta (2008)
SFRS17A XE7	No/*dual*	Ubiquitous	Nucleus (splicing factor compartments)	ASF/SF2 ZNF265	Involved in pre-mRNA splicing (Jarnaess et al., 2009; Mangs et al., 2006)
Merlin schwannomin Neurofibromin 2	No/*RI*	CNS	Actin cytoskeleton, adherens junctions	Spectrin β chain, brain1 Ezrin	Tumor suppressor, mutation causes neurofibromatosis type 2 (Golovnina et al., 2005; Gronholm et al., 1999, 2003)
Moesin	No	Blood, epithelia, *Xenopus* melanophores	Cytoplasm, plasma membrane-cytoskeleton interface, Pigment granules	ICAM1 ICAM3 CD43 VCAM-1	Facilitates actin-dependent transport of pigment granules; marker protein for basal carcinomas (Charafe-Jauffret et al., 2007; Dransfield et al., 1997b; Semenova et al., 2009; Serrador et al., 1997; Shcherbina et al., 1999)

AKAP85	Not cloned	Lymphocytes	Golgi		Rios et al. (1992)
Radial spoke protein 3 homolog (RSPH3)	No/*RII*	Epithelial cells	Motile cilia	ERK1/2	Interacts with ERK1/2, ERK phosphorylation of RSPH3 reduces RII binding (Jivan et al., 2009)
Drosophila melanogaster AKAP550 DAKAP550 rugose neurobeachin	Yes/ *2 canonical RIIBDs*	Ubiquitous	Plasma membrane/ cytosol		Required for retinal pattern formation; contains WD40 and BEACH domains (Han et al., 1997; Shamloula et al., 2002)
D. melanogaster AKAP200 DAKAP200	No	Oocytes, olfactory neurons	Plasma membrane	F-actin Ca^{2+}/ calmodulin	MARCKS-like protein; PKC substrate; regulates actin structures during oogenesis; targeted to the plasma membrane by myristoylation; involved in olfactory map formation (Jackson and Berg, 2002; Li et al., 1999; Rossi et al., 1999; Zhang et al., 2006)
D. melanogaster AKAP Yu	No	Mushroom bodies in brain			Required for olfactory long-term memory formation; homolog of AKAP1; molecular determinants of PKA binding not characterized (Lu et al., 2007a)

(*continued*)

Table 5.3 (*continued*)

Canonical AKAP (HGNC name)	Consensus RIIBD[a]/*R specificity*	Tissue expression pattern	Cellular localization	Interactions	Functions and properties (references)
D. melanogaster Nervy	No	Neurons		Plexin A	Involved in axon guidance, required for PKA regulation of Semaphorin-1a-mediated axon repulsion; homolog of MTG8/16 (Terman and Kolodkin, 2004)
Caenorhabditis elegans $AKAP_{CE}$	No/*RI*				Contains an FYVE-finger and a TGFβ receptor-binding domain (Angelo and Rubin, 1998, 2000; Herrgard et al., 2000)
Chlamydomonas reinhardtii Radial spoke protein 3 (RSP3) AKAP97	No	Unicellular organism	Flagellar axonemes		Located at the base of the radial spoke stalk, important for flagellar movement (Gaillard et al., 2001, 2006)

[a] Consensus RII-binding domain sequence [AVLISE]-X-X-[AVLIF]-[AVLI]-X-X-[AVLI]-[AVLIF]-X-X-[AVLISE] (X = any amino acid) according to Hundsrucker et al. (2010).

Table 5.4 Noncanonical AKAPs that do not interact with R subunits via an amphipathic helix and putative AKAPs with uncharacterized PKA binding mechanism

Noncanonical AKAP	Putative AKAP	*R specificity*	Tissue expression pattern	Localization	Interactions	Functions and properties (references)
Pericentrin kendrin			Ubiquitous, high in skeletal muscle	Centrosomes	γ-tubulin PKCβII dynein PCM1 AKAP350	Unique RII-binding site, a 100-amino acid leucine-rich region interacts with RII; targeted to centrosomes via PACT domain; regulates centrosome function, cell cycle checkpoints, spindle formation, cytokinesis, pericentrin mutations cause primordial dwarfism (Chen et al., 2004; Delaval and Doxsey, 2010; Diviani et al., 2000; Doxsey et al., 1994; Eide et al., 1998; Gillingham and Munro, 2000; Li et al., 2001b; Rauch et al., 2008; Takahashi et al., 2002) reviewed in Delaval and Doxsey (2010)
RSK1 (inactive) p90 ribosomal S6 kinase-1 (p90RSK-1) MAPKAP1A		*RI*	Ubiquitous	Cytosol Nucleus		Inactive RSK1 binds RI and facilitates C subunit release, active RSK1 binds C subunits and promotes PKA holoenzyme formation; RSK1/RI interaction insensitive to AKAP–PKA disruptor Ht31 (Chaturvedi et al., 2006; Frodin and Gammeltoft, 1999; Gao and Patel, 2009; Gao et al., 2010)
	α/β-tubulin	*RI*	Ubiquitous	Cytosol		Molecular determinants of PKA binding not characterized; SDS-stable tubulin/RI complex (Kurosu et al., 2009)
	Actin		Ubiquitous	Actin cytoskeleton	Myosin	Putative noncanonical AKAP; disruption of canonical AKAP–PKA interactions does not abolish actin/RII-colocalization; direct interaction with PKA not shown (Rivard et al., 2009)

whose PKA binding has not yet been experimentally validated. In this context it is noteworthy that all vertebrate orthologs of the human AKAP GSKIP bind RII, suggesting a conservation of its AKAP function within vertebrates. Apparently, none of the invertebrate or fungal GSKIP orthologs bind RII, indicating that the ability of GSKIP to anchor PKA was gained with vertebrate evolution (Hundsrucker et al., 2010).

Invertebrate AKAPs were identified in the nematode *Caenorhabditis elegans* and the fruit fly *D. melanogaster*. The only known AKAP in *C. elegans* is $AKAP_{CE}$ (Angelo and Rubin, 1998, 2000). $AKAP_{CE}$ binds human RI but not RII subunits and is thus prototypical for RI-specific AKAPs (Angelo and Rubin, 2000). *C. elegans* only expresses one regulatory isoform of PKA, R_{CE}, which is homologous to human RIα (Angelo and Rubin, 1998). The known *Drosophila* AKAPs are AKAP550, AKAP200, AKAP Yu, and Nervy (Table 5.3). AKAP550, a protein with two consensus RIIBDs both able to bind *Drosophila* and human RII subunits (Han et al., 1997; Hundsrucker et al., 2010), is a homolog of the human AKAP neurobeachin (Han et al., 1997; Wang et al., 2000). Surprisingly, the respective RIIBDs are not located in homologous regions of the proteins and are possibly of different evolutionary origin. *Drosophila* Nervy is homologous to the human AKAPs MTG8 and MTG16b (Terman and Kolodkin, 2004). The Nervy mutation Val423Pro disrupts RII binding, as does the corresponding mutation Val408Pro in human MTG16b, indicating that Nervy and MTGs bind PKA with the same motif (Schillace et al., 2002; Terman and Kolodkin, 2004). In addition, both Nervy and MTG16b interact with and control Plexin, a protein involved in axon guidance and immunological synapse formation (Fiedler et al., 2010; Terman and Kolodkin, 2004). Another neuronal process in *Drosophila* involves AKAP Yu. It is required for olfactory long-term memory formation (Lu et al., 2007a). Apparently other AKAPs fulfill similar functions in other organisms: A yet unidentified AKAP is necessary for synaptic plasticity in the sea hare (*Aplysia californica*; Liu et al., 2004a) and many mammalian AKAPs are involved in synaptic function, most importantly AKAP79/150 (Bauman et al., 2004).

In *Chlamydomonas reinhardtii*, a unicellular green alga with two motile flagella, radial spoke protein 3 (RSP3) is the only established nonanimal AKAP (Gaillard et al., 2001). PKA anchoring to flagella by RSP3 is required for normal flagellar motility (Gaillard et al., 2006). The human ortholog of RSP3, RSPH3 was also shown to bind RII and, in addition, ERK1/2 (Jivan et al., 2009). Its function is not clear but its presence in motile cilia of epithelial cells also implies a regulatory role in ciliar motility.

In summary, the knowledge of invertebrate AKAPs is still scarce. It is likely that vertebrates express a higher number of AKAPs than invertebrates, contributing to the coordination of the signaling processes which are essential for their specialized cell functions and complex communication systems between cells in a multicellular organism. The examples given here

illustrate that the mechanism of PKA anchoring is similar in AKAPs from evolutionarily early species to vertebrates and that there are common processes in which AKAPs seem to be indispensible. These are, for example, flagellar/ciliar movement or synaptic processes.

4. Cellular Functions Regulated by AKAP-Anchored PKA

AKAPs regulate important functions in every human cell. Prime examples are synaptic plasticity (Dell'Acqua et al., 2006), sperm motility (Carr and Newell, 2007), T-cell immune responses (Torgersen et al., 2008) and several exocytic processes (Szaszak et al., 2008). As an example for the ability of AKAPs to integrate cellular signaling, we will outline the link between PKA and GSK3β established by several AKAPs and other scaffolding proteins in the following section. In following sections, we will focus on the role of various AKAPs in the control of cardiac myocyte contractility (Section 4.2) and renal vasopressin-mediated reabsorption (Section 4.3).

4.1. AKAPs, PKA, and GSK3β

Glycogen synthase kinase 3 (GSK3) is a serine/threonine protein kinase involved in many cellular processes including glycogen metabolism, proliferation, and differentiation. Evolutionary highly conserved orthologs of GSK3 with sequence identities $>50\%$ are found in all eukaryotes. In mammals, there are two ubiquitously expressed isoforms of GSK3 encoded by distinct genes: GSK3α (51 kDa) and GSK3β (47 kDa), which share 83% sequence identity. Their functions are partially redundant but GSK3β has been much better characterized (Ali et al., 2001; Doble and Woodgett, 2003; Forde and Dale, 2007). Two features determine a close functional connection of GSK3β to other protein kinases: (1) GSK3β is constitutively active and the main mechanism of its regulation is an inhibitory phosphorylation of its N-terminus by other kinases. (2) Many GSK3β substrates need to be primed, that is, prephosphorylated by another kinase. Here, we outline on the involvement of PKA and AKAPs in GSK3β function, first in the context of phosphorylation of the GSK3β N-terminus, then with regard to primed GSK3β substrates.

4.1.1. AKAPs control the inhibition of GSK3β

Several kinases catalyze the inhibitory phosphorylation of GSK3β at Ser9: PKA, PKB, p70 ribosomal S6 kinase (p70RSK), RSK1, PKG (Zhao et al., 2005), Serum/glucocorticoid-regulated kinase 1 (SGK1; Sakoda et al., 2003), integrin-linked kinase (ILK; Persad et al., 2001), and different PKC isoforms (Fang et al., 2002). The fact that all of the abovementioned

kinases phosphorylate the same residue, the lack of specific kinase inhibitors and the cross talk between the different kinases complicate the unequivocal identification of GSK3β-phosphorylating kinases in a specific cellular context. Various physiological agonists have been described to mediate a PKA-dependent phosphorylation of GSK3β, such as adrenaline (Jensen et al., 2007), prostaglandin E_2 (PGE_2; Fujino et al., 2002), endothelin 1 (Taurin et al., 2007), Wnt5a (Torii et al., 2008), parathyroid hormone (Suzuki et al., 2008), glucagon-like peptide-1 (Juhaszova et al., 2004) and -2 (Yusta et al., 2002), human chorionic gonadotropin (hCG; Flynn et al., 2008), corticotropin-releasing hormone (Bayatti et al., 2003), and basic fibroblast growth factor (O'Driscoll et al., 2007). The PKA-dependent GSK3β phosphorylation triggered by these agents is in several instances facilitated by AKAPs. The involvement of an unidentified AKAP has been demonstrated for PGE_2-induced and PKA-dependent GSK3β phosphorylation. It is abolished by the AKAP–PKA-anchoring disruptor peptide Ht31 (Kleiveland et al., 2008). For hCG-induced GSK3β phosphorylation, the relevant AKAP has been identified as MAP2D. In resting preovulatory granulosa cells, MAP2D interacts with type II PKA, GSK3β, and PP2A. In this complex, the constitutively active GSK3β phosphorylates MAP2D on Thr256 and Thr259 (Flynn et al., 2008). Stimulation of the luteinizing hormone receptor by hCG activates the $G\alpha_s$/AC system and cAMP levels rise. cAMP activates PKA, which catalyzes an inhibitory phosphorylation of GSK3β on Ser9 and an activating phosphorylation of PP2A in the MAP2D complex (Fig. 5.6). This simultaneous inactivation of GSK3β and activation of PP2A leads to a dephosphorylation of MAP2D on Thr256 and Thr259 which increases microtubule binding of MAP2D and may affect microtubule dynamics (Flynn et al., 2008).

In addition to MAP2D, two further AKAPs interact with GSK3β and promote its PKA-dependent phosphorylation: AKAP220 and GSKIP (Hundsrucker et al., 2010; Tanji et al., 2002). AKAP220 interacts with RIIα subunits of PKA, GSK3β, and PP1 in rat PC12 cells, which has a dual effect on GSK3β (Fig. 5.6). AKAP220 facilitates PKA phosphorylation of GSK3β Ser9 and suppresses dephosphorylation of the same residue by inhibiting PP1 (Tanji et al., 2002). The inhibition of PP1 is enhanced by the presence of RII in the complex (Schillace et al., 2001).

GSKIP has originally been described as an interaction partner of GSK3β (Chou et al., 2006). Recently, it was revealed that GSKIP is an AKAP and that PKA anchoring by GSKIP facilitates PKA phosphorylation of GSK3β at Ser9 (Fig. 5.6; Hundsrucker et al., 2010). In addition, the direct binding of GSKIP inhibits GSK3β (Chou et al., 2006). GSKIP enhances PKA phosphorylation of GSK3β on Ser9 independently of the AKAP function, probably by altering the conformation of GSK3β (Hundsrucker et al., 2010). The classical view is that AKAPs merely provide docking sites for proteins and thereby control their localization. The induction of

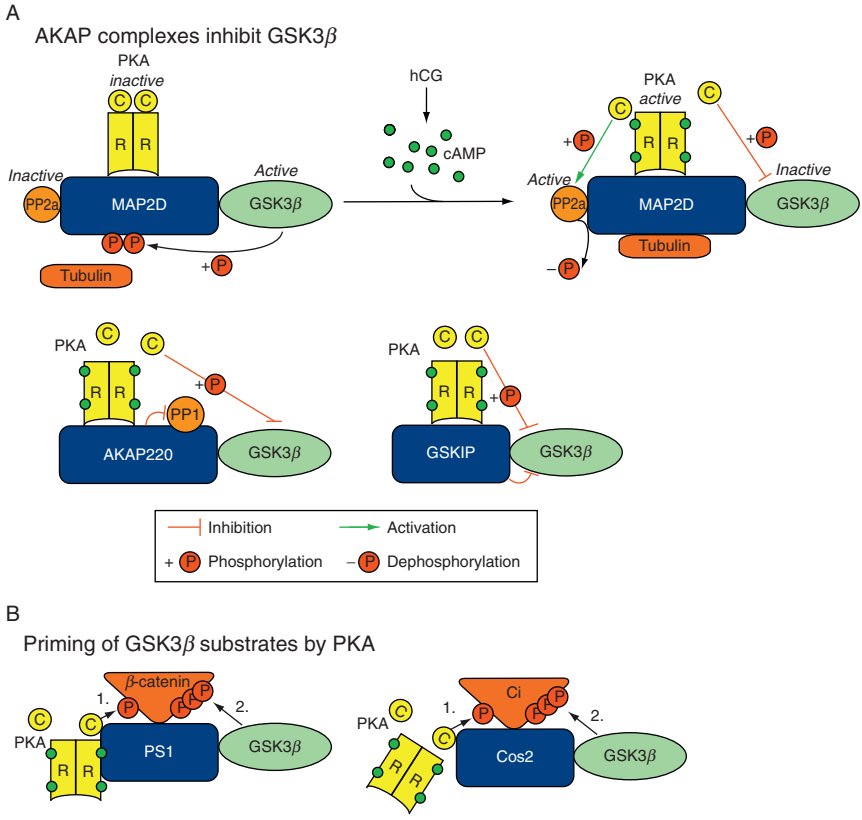

Figure 5.6 PKA–GSK3β complexes formed by AKAPs (A) and other scaffold proteins (B). (A) AKAPs facilitate inhibition of GSK3β. (B) Other scaffolding proteins mediate the priming of GSK3β substrates by PKA (see text for details).

conformational changes by binding of proteins to AKAPs (or scaffolding proteins in general) is poorly understood. AKAP binding could change the properties of interacting proteins. AKAP220, for example, inhibits PP1 (see above) and it was recently demonstrated that the interaction with AKAP79 protects PKC from inhibition by certain ATP-competitive inhibitors (Hoshi et al., 2010). Thus modulation of proteins through interaction with AKAPs or other scaffolding proteins could contribute to the regulation of signal transduction processes.

4.1.2. PKA as a priming kinase for GSK3β

GSK3β can phosphorylate serine or threonine residues in two types of substrates. Primed substrates need to be phosphorylated 4 amino acids C-terminal of the residue phosphorylated by GSK3β within the consensus

site S/T-X-X-X-S^P/T^P (Fiol et al., 1987). In unprimed substrates, negative residues mimic a phosphorylation of the priming site. PKA can function as a priming kinase for GSK3β, as was demonstrated for the substrate proteins β-catenin (Kang et al., 2002), Gli/*cubitus interruptus* (Ci; Jia et al., 2002), tau (Liu et al., 2004b), and CREB (Fiol et al., 1994).

In the canonical Wnt signaling pathway, casein kinase I (CK1) acts as the priming kinase for GSK3β by phosphorylating Ser45 on β-catenin. This enables GSK3β to phosphorylate Thr41 and subsequently Ser37/33 of β-catenin. These consecutive phosphorylations induce proteasomal degradation of β-catenin (Liu et al., 2002). An analogous pathway for β-catenin degradation, which is not regulated by Wnt signaling, involves presenilin 1 (PS1). PS1 forms a complex containing PKA, GSK3β, and β-catenin, in which PS1 facilitates PKA priming, GSK3β phosphorylation, and proteasomal targeting of β-catenin (Fig. 5.6; Kang et al., 2002). PS1 interacts directly with β-catenin (Murayama et al., 1998) and GSK3β (Gantier et al., 2000) but it is unclear whether PS1 interacts with PKA directly. PS1 contains a canonical AKAP consensus sequence (DTETVGQRA**L**HS**IL**NA**AI**MI**S**VIVV) but the cognate peptide does not bind PKA RII subunits (Hundsrucker et al., 2010). Thus it is conceivable that PS1 is either a noncanonical AKAP or that complex formation with PKA is mediated by another protein.

The transcription factor Ci is a central mediator of the hedgehog signaling pathway in *Drosophila*. In the absence of a hedgehog signal, Ci is phosphorylated by the protein kinases CK1, PKA, and GSK3β, which induces its proteolytic conversion into a transcriptional repressor (Smelkinson et al., 2007). GSK3β phosphorylation of Ci requires priming by PKA (Jia et al., 2002). The scaffolding protein costal-2 (Cos2) binds Ci and its upstream kinases directly, that is, CK1, PKA catalytic subunits and GSK3β (Fig. 5.6; Zhang et al., 2005). Ci phosphorylation depends on the presence of Cos2, demonstrating the importance of this scaffold for the association of substrate and kinases (Aikin et al., 2008).

One of the best described PKA substrates is CREB. CREB is phosphorylated by PKA but also by other kinases on S133. This phosphorylation enhances the interaction of CREB with the transcriptional coactivator CREB-binding protein (CBP; Sands and Palmer, 2008). CREB phosphorylated on S133 is also a primed substrate for GSK3β, which then phosphorylates S129 (Fiol et al., 1994). This phosphorylation decreases binding of CREB to CBP (Martin et al., 2005). Thus, GSK3β negatively regulates PKA-induced CREB-dependent transcription (Tullai et al., 2007). In a similar scenario PKA phosphorylates and activates the transcription factor heterogeneous nuclear ribonucleoprotein D (hnRNP D) at Ser87, thereby allowing phosphorylation of Ser83 by GSK3β, which inhibits transcriptional activity (Tolnay et al., 2002). Thus CREB and hnRNP D integrate PKA and GSK3β signaling. Phosphorylation of CREB and hnRNP D only leads to transcriptional activation if phosphorylation by GSK3β is prevented.

4.2. AKAP-dependent protein–protein interactions in the control of cardiac myocyte contractility

Stimulation of β-adrenoceptors enhances the chronotropic (heart rate), inotropic (contraction), and lusitropic (relaxation) response of the heart by triggering cAMP production and activation of PKA subpopulations which regulate Ca^{2+}-cycling via the L-type Ca^{2+} channel, the ryanodine receptor 2 (RyR_2) and the sarco/endoplasmic reticulum Ca^{2+}-ATPase 2 (SERCA2; Diviani, 2008; Jurevicius and Fischmeister, 1996; Zaccolo and Pozzan, 2002). For this AKAP–PKA interactions are required (Mauban et al., 2009; Figs. 5.7 and 5.8): AKAP18α anchors PKA to L-type Ca^{2+} channels ($Ca_v1.2$) in the sarcolemma and mAKAP anchors PKA to RyR_2 in the membrane of the sarcoplasmic reticulum (SR), facilitating β-adrenoceptor-triggered, PKA-catalyzed phosphorylation of the respective channels (Dodge-Kafka et al., 2006; Hulme et al., 2006). Such phosphorylation events increase the channel open probability, resulting in cytosolic Ca^{2+} increases. AKAP18δ binds directly to phospholamban (PLN) at the SR and

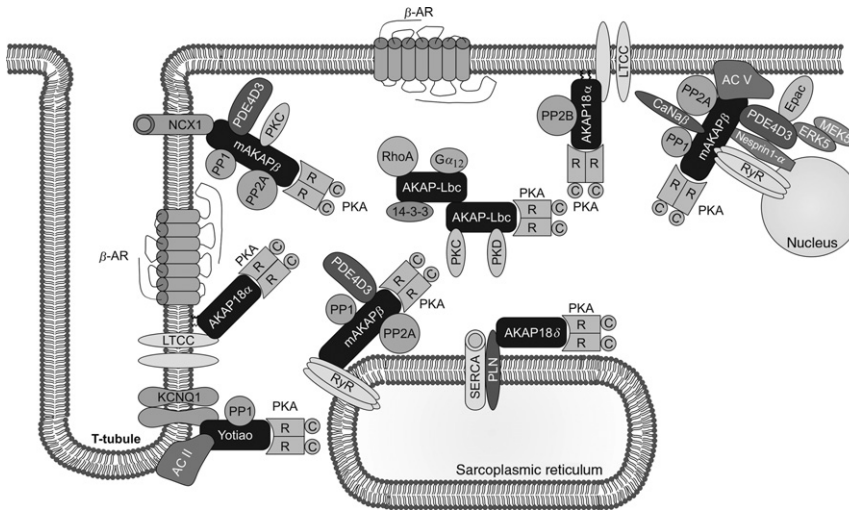

Figure 5.7 AKAP complexes in cardiomyocytes. See text for details. ACII, adenylyl cyclase II; ACV, adenylyl cyclase V; β-AR, β-adrenoceptor; C, catalytic subunit; CaNaβ, calcineurin Aβ; Epac, exchange protein activated by cAMP; ERK5, extracellular signal-regulated kinase 5; KCNQ1, I_{KS} K^+ channel; LTCC, L-type Ca^{2+} channel; MEK5, mitogen signal-regulated kinase kinase 5; NCX1, Na^+–Ca^{2+} exchanger 1; PDE4D3, phosphodiesterase 4D3; PKA, protein kinase A; PKC, protein kinase C; PKD, protein kinase D; PLN, phospholamban; PP1, protein phosphatase 1; PP2A, protein phosphatase 2A; PP2B, protein phosphatase 2B; R, regulatory subunit; RhoA, Ras homolog gene family member A; RyR, ryanodine receptor; SERCA, sarco/endoplasmic reticulum Ca^{2+}-ATPase.

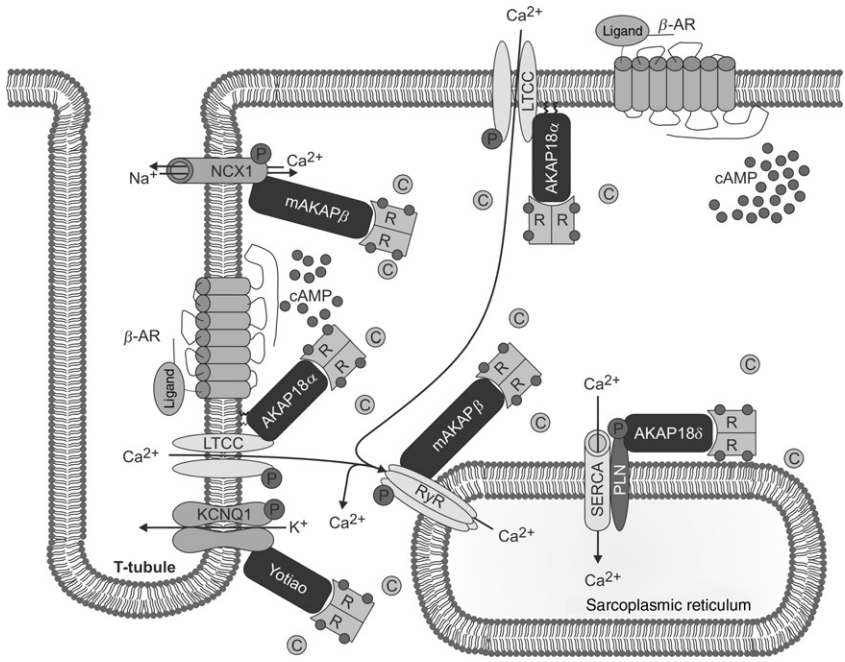

Figure 5.8 Calcium signaling in cardiac myocytes. See text for details. β-AR, β-adrenoceptor; C, catalytic subunit; KCNQ1, I_{KS} K^+ channel; LTCC, L-type Ca^{2+} channel; NCX1, Na^+–Ca^{2+} exchanger 1; PLN, phospholamban; R, regulatory subunit; RyR, ryanodine receptor; SERCA, sarco/endoplasmic reticulum Ca^{2+}-ATPase.

facilitates its β-adrenoceptor-induced PKA phosphorylation. Phospho-PLN dissociates from SERCA2, which is thereby activated. The result is an increased Ca^{2+} reuptake into the SR (Lygren et al., 2007). The AKAP Yotiao anchors PKA to sarcolemmal K^+-channels (I_{Ks}) and facilitates their β-adrenoceptor/PKA-dependent phosphorylation. Phosphorylation of these channels enhances repolarization of the myocytes (Chen et al., 2005). In addition, PKA phosphorylates several proteins of the contractile apparatus upon β-adrenoceptor activation (e.g., cardiac troponin I (cTnI) and myosin-binding protein C (MyBP-C); Colson et al., 2008; Dong et al., 2007). Collectively, these phosphorylations contribute to an increase of cardiac myocyte contractility upon β-adrenoceptor stimulation (Figs. 5.7 and 5.8). In the failing heart, β-adrenergic signaling is altered and phosphorylation of PKA substrates such as PLN, MyBP-C, and cTnI is reduced (Bodor et al., 1997; El-Armouche et al., 2006; Hasenfuss, 1998; Sipido and Eisner, 2005; Waggoner and Kranias, 2005; Zakhary et al., 2000). Interfering with AKAP–PKA interactions in cardiac myocytes or in hearts *in vivo* using PKA-anchoring disruptor peptides such as Ht31, abolished the

phosphorylation of cTnI, RyR_2, and MyBP-C and still increased the rate and amplitude of cell shortening and relaxation compared to control cells upon stimulation of β-adrenoceptors (Fink et al., 2001; McConnell et al., 2009). This shows that it is anchored PKA that specifically regulates phosphorylation events and underlines the relevance of compartmentalized PKA signaling in the heart.

Here, we point out the roles of AKAP18α and δ, AKAP-Lbc, mAKAPβ, and Yotiao in cardiac myocyte control (Fig. 5.7; Diviani et al., 2001; Fraser et al., 1998; Gray et al., 1997; Kurokawa et al., 2004; Lygren et al., 2007; Potet et al., 2001; Reynolds et al., 2007; Ruehr et al., 2004). Several further AKAPs were identified in the heart (Table 5.3) but their functions are not clear. For further reading we recommend recent reviews (Diviani, 2008; Dodge-Kafka et al., 2006; Mauban et al., 2009; Ruehr et al., 2004; Scott and Santana, 2010).

4.2.1. AKAP18α

The AKAP18 family consists of four isoforms (α, β, γ and δ) with apparent molecular weights ranging from 15 to 53 kDa (Fraser et al., 1998; Gray et al., 1997, 1998; Henn et al., 2004; McSorley et al., 2006; Trotter et al., 1999). Except for AKAP18β, all isoforms are expressed in cardiac tissue (Henn et al., 2004; Lygren et al., 2007; Trotter et al., 1999) with AKAP18 α and δ being of importance in the regulation of cardiac contractility (Fig. 5.8).

AKAP18α, the shortest AKAP18 isoform, contains 81 amino acids and is located at the plasma membrane due to palmitoylation and myristoylation of its N-terminus (Fraser et al., 1998; Gray et al., 1997). There it forms a complex with the L-type Ca^{2+} channel, the major voltage-gated Ca^{2+} channel in the heart (Burton et al., 1997; Fraser et al., 1998; Gray et al., 1997, 1998; Fig. 5.7). The binding between the two proteins occurs directly via a leucine-zipper motif between amino acids 1774 and 1841 in the C-terminus of the α_1 subunit of the Ca^{2+} channel and amino acids 25–54 of AKAP18α (Hulme et al., 2002). It appears that AKAP18α facilitates the PKA-dependent phosphorylation of the L-type Ca^{2+} channel since expression of an AKAP18α mutant with defective plasma membrane targeting in HEK293 cells transiently expressing the Ca^{2+} channel abolishes the increase in Ca^{2+} currents upon PKA activation (De Jongh et al., 1996; Fraser et al., 1998; Gao et al., 1997a; Gray et al., 1997, 1998; Hulme et al., 2006; Kamp and Hell, 2000). In addition, disruption of the interaction between AKAP18α and the L-type Ca^{2+} channel using synthetic peptides derived from AKAP18α, or an AKAP18α mutant that cannot bind the L-type Ca^{2+} channel inhibits the voltage-dependent potentiation in MM14 skeletal myotubes and blocks β-adrenergic regulation of the channel in ventricular myocytes (Fraser et al., 1998; Gao et al., 1997b; Hulme et al., 2002, 2003). β-adrenergic stimulation also fails to induce L-type Ca^{2+} currents in the

presence of AKAP18δ-derived peptides that displace PKA from the complex (Hulme et al., 2003; Hundsrucker et al., 2006b). Therefore, anchoring of PKA to the L-type Ca^{2+} channel via AKAP18α allows for a rapid and specific response to changes in cAMP levels upon β-adrenoceptor stimulation (Dodge-Kafka et al., 2006).

The exact phosphorylation site responsible for the increased Ca^{2+} flux through the channel is under controversy. While one study describes serine 1928 of the α_{1C} subunit as the critical phosphorylation site for channel modulation (Gao et al., 1997a), another study revealed that a substitution of this site by an alanine does not abolish the β-adrenergic response (Ganesan et al., 2006).

AKAP18α may also interact with PP2B (Sacchetto et al., 2001) and could tether PP2B to L-type Ca^{2+} channels. PP2B was suggested to play a role in the regulation of the associated L-type Ca^{2+} channel currents (Sacchetto et al., 2001). Additionally, a direct interaction of AKAP18α with the β_2-adrenoceptor and the L-type Ca^{2+} channel has been identified in the brain (Davare et al., 2001). This complex may also exist in cardiac myocytes and thereby safeguard a tight regulation of β-adrenergic responses.

4.2.2. AKAP18δ

AKAP18δ is the longest isoform of the AKAP18 family (353 amino acids, apparent molecular weight 53 kDa) and plays a major role in the β-adrenoceptor-induced Ca^{2+} reuptake into the SR of cardiac myocytes (Henn et al., 2004; Lygren et al., 2007; Figs. 5.7 and 5.8). AKAP18δ, PKA, SERCA2, and PLN form a complex at the SR in cardiac myocytes (Fig. 5.7). AKAP18δ promotes the PKA-dependent phosphorylation of PLN on serine 16 in its cytoplasmic N-terminus, which in turn induces the dissociation of PLN from SERCA2 and SERCA2 activation. The interaction between AKAP18δ and PLN is direct and can be disrupted using synthetic peptides derived from PLN's AKAP18δ-binding site. This disruption results in a decreased phosphorylation of PLN, reduced Ca^{2+} reuptake into the SR and thus reduced lusitropic effects upon β-adrenergic stimulation. Silencing of AKAP18δ in cardiac myocytes has a similar effect (Lygren et al., 2007). Based on these data, AKAP18δ has been suggested as a potential drug target for the treatment of heart failure (Diviani, 2008; Lygren and Taskén, 2008).

4.2.3. AKAP-Lbc

AKAP-Lbc, 320 kDa large, not only associates with PKA but also with the small GTP-binding protein RhoA, PKC, and PKD in cardiac myocytes (Fig. 5.7; Appert-Collin et al., 2007; Baisamy et al., 2005, 2009; Carnegie et al., 2004, 2008; Diviani et al., 2001, 2006; Klussmann et al., 2001). AKAP-Lbc functions as a guanine nucleotide exchange factor (GEF) for

RhoA but not Rac or Cdc42 (Diviani et al., 2001). Activation of RhoA is mediated by tandem DH and PH domains present in the C-terminus of AKAP-Lbc that induce the exchange of GDP for GTP (Diviani et al., 2001, 2006; Klussmann et al., 2001). The Rho-GEF activity of AKAP-Lbc is activated upon α_1-adrenoceptor stimulation via the G protein $G\alpha_{12}$ (Appert-Collin et al., 2007; Diviani et al., 2001). Inhibition of the GEF activity is mediated by β-adrenoceptor-induced PKA-dependent phosphorylation of Ser1565 of AKAP-Lbc which facilitates the binding of an adaptor protein of the 14-3-3 family (Diviani et al., 2004). This inhibitory effect only occurs when AKAP-Lbc has homooligomerized (Baisamy et al., 2005). This homooligomerization is mediated by two leucine-zipper motifs in the C-terminal region of AKAP-Lbc (amino acids 2616–2679; Baisamy et al., 2005).

AKAP-Lbc mediates hypertrophic responses of the heart. Stimulation of α_1-adrenoceptors with phenylephrine (chronic infusion) increased the cardiac weight index (ventricular weight/body weight) of mice and the levels of AKAP-Lbc mRNA expression in ventricular myocytes. This effect as well as the activation of RhoA was inhibited in rat neonatal cardiac myocytes by silencing AKAP-Lbc expression (Appert-Collin et al., 2007; Diviani et al., 2001). The Rho effectors Rho kinase, PKN, and stress-activated protein kinase (SAPK) have been suggested to mediate the hypertrophic effects of AKAP-Lbc as they control the transcription of prohypertrophic genes downstream of Rho (Maruyama et al., 2002; Morissette et al., 2000; Yanazume et al., 2002). AKAP-Lbc-bound PKD also seems to mediate a hypertrophic response upon α_1-adrenergic stimulation by activating the fetal gene expression program as overexpression of AKAP-Lbc in neonatal cardiac myocytes increases PKD activity and activates the PKD/HDAC5 (histone deacetylase 5)/MEF2 (myocyte enhancer factor-2) pathway (Carnegie et al., 2004, 2008). Taken together, the interactions of AKAP-Lbc–RhoA as well as AKAP-Lbc–PKD play key roles in the development of cardiac hypertrophy and thus could be novel drug targets for the treatment of cardiac diseases such as hypertrophy and consequent heart failure.

4.2.4. Muscle-selective AKAP

4.2.4.1. mAKAP complexes Two alternatively spliced variants of mAKAP have been identified: mAKAPα and mAKAPβ. mAKAPα is mainly expressed in the brain whereas the shorter mAKAPβ (lacking the N-terminal 224 amino acids compared to mAKAPα) is preferentially expressed in cardiac myocytes (Carlisle Michel et al., 2005) but it is also present in skeletal muscle (Ruehr et al., 2003). In the perinuclear region and SR of cardiac myocytes, the 250 kDa mAKAPβ forms complexes with PKA, PDE4D3, RyR_2, PP1 and PP2A, nesprin-1α, calcineurin Aβ (CaNaβ), Epac, 3-PDK-1, ERK5, and the cardiac Na^+–Ca^{2+} exchanger (NCX1; Bers, 2002; Blaustein and Lederer, 1999; Carlisle Michel et al., 2005; Dodge

et al., 2001; Dodge-Kafka et al., 2005; Kapiloff et al., 1999, 2001; Marx et al., 2000; Mauban et al., 2009; McCartney et al., 1995; Pare et al., 2005a; Ruehr et al., 2003; Schulze et al., 2003; Yang et al., 1998; Fig. 5.7). Thus, mAKAPβ integrates cAMP signaling with that of Ca^{2+} and MAP kinases.

The interaction between mAKAPβ, PKA, and RyR_2 is important for RyR_2-dependent Ca^{2+} entry into the cytosol (Fig. 5.8). mAKAPβ associates with RyR_2 via a leucine-zipper motif (Marx et al., 2000, 2001). β-adrenoeptor-induced and PKA-dependent phosphorylation of cardiac RyR_2 at serine 2809 increases the channel open probability thereby increasing cytosolic Ca^{2+} and consequently the contraction of cardiac myocytes (Bers, 2002; Kapiloff et al., 1999; Marx et al., 2000, 2001; Ruehr et al., 2003). Studies in which an RII phosphomimetic (RIIS96D) was overexpressed resulted in an increased PKA phosphorylation of the RyR_2 (serine 2809) in neonatal rat cardiac myocytes (Manni et al., 2008). The impact of RyR_2 phosphorylation is still controversially discussed: it has been proposed that the effects of phosphorylation are only minor and mainly lead to increased Ca^{2+} release and Ca^{2+} cycling (Benkusky et al., 2007; Ginsburg and Bers, 2004; MacDonnell et al., 2008) whereas others report that PKA-mediated hyperphosphorylation of RyR_2 results in channel leakage and plays a role in the development of heart failure (Doi et al., 2002; Marx et al., 2000; Reiken et al., 2003).

mAKAPβ is targeted to the nuclear envelope by three spectrin-repeat domains within amino acids 772–1187 of mAKAPβ of which the third (mAKAP TF) interacts with the membrane-spanning nesprin-1α. Nesprin-1α itself is inserted into the nuclear envelope by a C-terminal Klarsicht-related transmembrane domain (Kapiloff et al., 1999; Pare et al., 2005a; Zhang et al., 2001). Displacement of mAKAPβ from the nuclear envelope can be achieved by overexpressing mAKAP TF or a truncated form of nesprin-1α that lacks the transmembrane domain (nesprinΔTM; Kapiloff et al., 1999; Pare et al., 2005a; Zhang et al., 2001). Nuclear mAKAPβ also interacts with the plasma membrane-resident AC5 in cardiac myocytes thus constituting a link between the nuclear envelope and the plasma membrane. The region binding AC5 is located within amino acids 245–340 in mAKAPβ and does not overlap with binding sites for other known mAKAPβ interaction partners (Dessauer, 2009; Kapiloff et al., 2009). Another binding partner of the mAKAPβ complex is PDE4D3 (Dodge et al., 2001), which is regulated by PKA and the phosphatase PP2A (Dodge-Kafka et al., 2010). PDE4D3 contains two PKA phosphorylation sites: Ser54 and Ser13 (Sette and Conti, 1996). Phosphorylation at Ser54 increases the catalytic activity of PDE4D3 two- to threefold and the subsequent decrease in cAMP inhibits PKA activity (Dodge-Kafka and Kapiloff, 2006; Sette and Conti, 1996). Activation of PP2A by phosphorylation of its B56δ subunit by PKA (Ahn et al., 2007) leads to increased dephosphorylation of mAKAPβ-bound PDE4D3 at Ser54 (Dodge-Kafka et al., 2010).

Phosphorylation of Ser13 does not affect cAMP hydrolysis but increases the binding affinity of PDE4D3 for mAKAPβ (Carlisle Michel et al., 2004). This tight local regulation of PKA, in turn, allows for close control of PKA-dependent RyR_2 phosphorylation. PDE4D3 bound to mAKAPβ also serves as an adaptor for ERK5 and Epac at the mAKAPβ complex (Dodge-Kafka et al., 2005). ERK phosphorylation of PDE4D3 on Ser579 decreases its activity resulting in increased cAMP levels and subsequent PKA and Epac activation (Hoffmann et al., 1999; Li et al., 2010; Pidoux and Tasken, 2010). Epac, in turn, can activate the small GTP-binding protein Rap1, which inhibits the ERK5 upstream activator MEKK and thereby results in an inhibition of ERK5 and PDE4D3 (Dodge-Kafka et al., 2005). This suggests the association of a number of parallel negative and positive feedback loops in the mAKAPβ complex regulating myocyte cAMP signaling (Dodge-Kafka et al., 2010). Defects in this cAMP signaling can lead to various cardiac diseases including hypertrophy (Dodge-Kafka et al., 2008).

At the plasma membrane of cardiac myocytes, mAKAPβ interacts with NCX1 (Bers, 2002; Blaustein and Lederer, 1999; Mauban et al., 2009; Schulze et al., 2003) thereby regulating the extrusion of Ca^{2+} from cardiac myocytes. Na^+ entering the cell is extruded by a Na^+/K^+ pump (NKA), which is regulated by phospholemman (PLM), a small sarcolemmal protein (72 amino acids). PLM interacts with NKA in a similar manner as PLN interacts with SERCA2. Phosphorylation of PLM by PKA is associated with a decrease in the interaction and induces activation of NKA (Bers and Despa, 2009). This limits the rise in intracellular Na^+ and, as a consequence, the Ca^{2+} transient amplitude during β-adrenergic stimulation (Bers and Despa, 2009). Recent evidence suggests that NCX1 is also controlled by PLM as β-adrenoceptor-induced phosphorylation of PLM by PKA inhibits NCX1 activity (Cheung et al., 2007). This appears to contribute to a rise in intracellular Ca^{2+} and an increase in contractility upon β-adrenoceptor stimulation (Cheung et al., 2007). An association of PKA RI subunits with the mAKAPβ–NCX1 complex has been suggested (Schulze et al., 2003). However, in surface plasmon resonance (SPR) studies the canonical RIIBD of mAKAPβ did not bind RI (Zakhary et al., 2000).

4.2.4.2. mAKAP and cardiac hypertrophy Knockdown (RNA interference) of mAKAPβ inhibits isoproterenol-, phenylephrine-, and leukemia inhibitory factor (LIF)-induced cardiac hypertrophy (Dodge-Kafka et al., 2005; Pare et al., 2005b). In addition, β-adrenoceptor-mediated phosphorylation of the mAKAPβ-bound RyR_2 results in an increase in perinuclear Ca^{2+} that activates CaNaβ. CaNaβ then dephosphorylates and thereby activates the prohypertrophic transcription factor nuclear factor of activated T cells (NFATc). Active NFATc translocates into the nucleus and promotes cell growth and differentiation (Dodge-Kafka and Kapiloff, 2006; Kapiloff et al., 2001; Pare et al., 2005b). A similar mechanism has been found to be

controlled by the mitochondrial AKAP121, which, like mAKAPβ, is a negative regulator of cardiac myocyte hypertrophy via CaNa and NFATc (Abrenica et al., 2009).

The interaction of ERK5 with mAKAPβ was also suggested to play a role in the development of cardiac hypertrophy (Dodge-Kafka et al., 2006). ERK5 is an activator of the prohypertrophic transcription factor MEF2c downstream of α_1-adrenoceptors and glycoprotein 130/LIF receptors (Nicol et al., 2001; Zhao et al., 2009). The hypertrophic effect of LIF which requires mAKAP expression (see above) is blocked by active Epac. Epac appears to be the cAMP effector responsible for cAMP-mediated inhibition of mAKAP-bound ERK5 (Dodge-Kafka et al., 2005). Therefore, it was suggested that ERK5 contributes to the regulation of hypertrophic genes and that disruption of the mAKAPβ/ERK5 interaction provides a novel concept for the treatment of cardiac hypertrophy (Diviani, 2008; Nicol et al., 2001).

A dysregulation in cAMP production (AC5) and degradation (PDE4D3) at the nuclear mAKAP complex apparently causes various diseases. For example, deletion of the PDE4D3 gene can lead to cardiomyopathy, heart failure, and arrhythmia in mice (Lehnart et al., 2005). Overexpression of the AC5-binding domain of mAKAPβ results in increases in basal and isoproterenol-stimulated cAMP levels and consequently to cardiac hypertrophy (Dessauer, 2009; Piggott et al., 2008). In contrast, the deletion of AC5 protects from cardiac stress and hypertrophy (Dessauer, 2009; Okumura et al., 2003; Yan et al., 2007).

4.2.5. Yotiao

Yotiao is the smallest splice variant of AKAP9 (210 kDa). In cardiac myocytes, it directly interacts with the α subunit of the I_{KS} K^+ channel (KCNQ1) and thereby tethers other interactions partners, PKA, PDE4D3, PP1, and AC to this K^+ channel (Fig. 5.7; Dessauer, 2009; Marx et al., 2002; Piggott et al., 2008; Terrenoire et al., 2009). Upon β-adrenoceptor stimulation, Yotiao-bound PKA phosphorylates KCNQ1 at Ser27 and thereby enhances the current and thus cardiac myocyte relaxation (Fig. 5.8; Chen and Kass, 2006; Chen et al., 2007; Marx et al., 2002; Potet et al., 2001). Substitution of this serine by an asparte or glutamate and coexpression with Yotiao increases channel currents and decreases channel deactivation in CHO cells (Kurokawa et al., 2003, 2004).

The direct interaction of Yotiao and KCNQ1 is mediated by two domains of Yotiao: an N-terminal 17 amino acid long binding site and a C-terminal leucine-zipper motif. This leucine zipper interacts with a leucine-zipper motif of KCNQ1 (Chen et al., 2007; Marx et al., 2002). Interfering with this interaction by disruption with a leucine-zipper peptide derived from KCNQ1 (KCNQ1-LZ_m) or by amino acid substitutions G589D and S1570L in KCNQ1 decreases PKA-dependent

phosphorylation of KCNQ1 (Chen et al., 2005, 2007; Marx et al., 2002; Westphal et al., 1999). The amino acid substitutions G589D and S1570L have also been identified in patients suffering from long QT syndrome (LQTS), a disease characterized by a prolonged repolarization of the cardiac action potential. LQTS is associated with cardiac arrhythmias and may lead to sudden cardiac death (Chen and Kass, 2006; Chen et al., 2007; Marx et al., 2002; Saucerman et al., 2004; Westphal et al., 1999).

In addition to PKA, Yotiao also recruits PDE4D3 to the I_{KS} channel where PDE4D3 regulates channel activity locally through cAMP hydrolysis (Terrenoire et al., 2009). Moreover, Yotiao targets PKA to AC. In cardiac myocytes and in the brain Yotiao seems to interact with the AC isoforms 2 and 9 (Dessauer, 2009; Piggott et al., 2008). However, only for AC2 a direct binding has been demonstrated. AC9 seems to be associated with Yotiao through other proteins (Dessauer, 2009; Piggott et al., 2008; Terrenoire et al., 2009). Upon activation of AC and the generation of cAMP, Yotiao-bound PKA is activated and phosphorylates AC. This, in turn, inhibits the cyclase and thus terminates cAMP signaling.

4.3. AKAP–PKA interactions and water reabsorption in the kidney

The arginine vasopressin (AVP)-induced water reabsorption is another process that depends on compartmentalized cAMP signaling (Fig. 5.9). In renal collecting duct principal cells, vasopressin V_2 receptors (V_2R) are activated on the basolateral surface by AVP resulting in AC activation and cAMP elevation. cAMP activates PKA which phosphorylates aquaporin-2 (AQP2) at Ser256 in its C-terminal cytoplasmic domain (Christensen et al., 2000). This PKA-dependent phosphorylation leads to a redistribution of AQP2 from intracellular vesicles into the apical plasma membrane thereby increasing the osmotic water permeability of the cells facilitating water reabsorption from the collecting duct. It is the translocation of AQP2 into the plasma membrane that constitutes the molecular basis of AVP-regulated water reabsorption. When water homeostasis is restored, AQP2 is being internalized and the principal cells are watertight again (Boone and Deen, 2009; King et al., 2004; Klussmann et al., 2000; Nedvetsky et al., 2009; Takata et al., 2008; Valenti et al., 2005). In contrast to many other exocytic events such as neurotransmitter release, the translocation of AQP2 is a rather slow process taking about 20 s for the vesicles to fuse with the plasma membrane (Lorenz et al., 2003).

The redistribution of AQP2 into the plasma membrane is prevented when AKAP–PKA interactions are disrupted with peptides mimicking the RIIBD of AKAP-Lbc and AKAP18δ (Hundsrucker and Klussmann, 2008; Klussmann et al., 1999; Nedvetsky et al., 2009; Szaszak et al., 2008). Therefore, the interactions of AKAPs with PKA are essential for

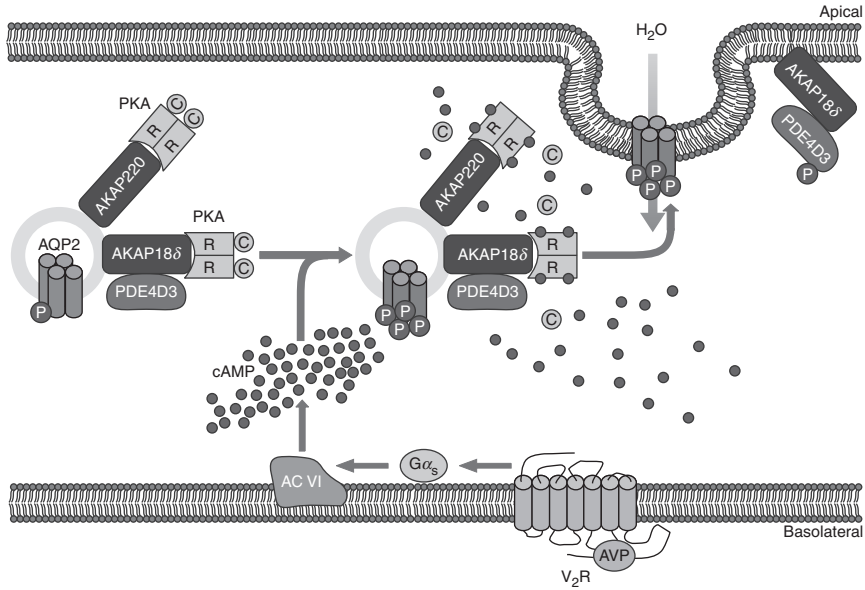

Figure 5.9 AVP-induced water reabsorption. See text for details. ACVI, adenylyl cyclase VI; AQP2, aquaporin 2; AVP, arginine vasopressin; C, catalytic subunit; PDE4D3, phosphodiesterase 4D3; PKA, protein kinase A; R, regulatory subunit; V_2R, vasopressin V_2 receptor.

AVP-induced water reabsorption. In the AVP-activated signaling cascade, AKAP18δ and AKAP220, which colocalize with AQP2, appear to play a role as they sequester PKA in close proximity of the water channel (Henn et al., 2004, 2005; Klussmann and Rosenthal, 2001; Klussmann et al., 1999; Okutsu et al., 2008). AKAP220 was suggested to form a complex with AQP2 and to facilitate the AVP-induced phosphorylation of the water channel by PKA (Okutsu et al., 2008). AKAP18δ not only binds PKA but also PDE4D (Stefan et al., 2007). PDE4D controls local cAMPs levels and thus PKA activity and thereby presumably PKA phosphorylation of AQP2 and its localization (Hundsrucker and Klussmann, 2008; Stefan et al., 2007).

Defects in the AVP-induced AQP2 redistribution cause nephrogenic diabetes insipidus (NDI), a disease characterized by a massive loss of hypotonic urine (polyuria) and polydipsia (King et al., 2004; Klussmann et al., 2000; Nedvetsky et al., 2009; Robben et al., 2006; Valenti et al., 2005). On the other hand, heart failure is associated with elevated AVP levels and a consequent upregulation of AQP2 expression and predominant localization of AQP2 in the plasma membrane of renal principal cells (Chen and Schrier, 2006; King et al., 2004; Kwon et al., 2009; Schrier and Cadnapaphornchai, 2003).

This is prevented by V_{1a}/V_2 receptor antagonists (vaptans) which improve clinical symptoms of chronic heart failure and result, for example, in increased urine output and reduced body weight without affecting blood pressure or heart rate (Gheorghiade et al., 2003; Lemmens-Gruber and Kamyar, 2006; Udelson et al., 2001). An alternative strategy may be the interference with AKAP–PKA interactions which also prevents the AVP-induced AQP2 redistribution (see above; Klussmann et al., 1999; Stefan et al., 2007).

In conclusion, the AVP-mediated redistribution of AQP2 from intracellular vesicles into the plasma membrane of renal collecting duct principal cells depends on compartmentalized cAMP signaling maintaining close local control of PKA activity in the vicinity of AQP2.

5. AKAP Dysfunction in Human Disease

5.1. Lessons from AKAP KO mouse models

KO and mutant mouse models are invaluable tools to study *in vivo* protein function in a mammalian system. Several genes encoding AKAPs were disrupted or mutated, resulting in diverse phenotypes. These are summarized in Table 5.5.

Other reviews analyzed the KO models for AKAP149/AKAP1, AKAP4, AKAP150/AKAP5, mAKAPα/AKAP6, WAVE-1, MAP2, and Ezrin (Carnegie et al., 2009; Hundsrucker and Klussmann, 2008; Kirschner et al., 2009; Mauban et al., 2009; Welch et al., 2010). Here, we focus on recently developed AKAP KO and mutant mouse models.

5.1.1. SSeCKS/AKAP12

SSeCKS (Src-suppressed C kinase substrate)/AKAP12, the rodent ortholog of gravin, is a tumor suppressor protein involved in the regulation of cell cycle and cell migration (Gelman, 2002). SSeCKS KO causes prostate hyperplasia, hyperactivation of Akt/PKB and the loss of basal epithelial cells and E-cadherin cell–cell contacts, which are hallmark features of a hyperplasia/early neoplasia transition (Akakura et al., 2008). This is in line with the observation that SSeCKs/gravin expression is reduced in prostate cancer and the chromosomal location of the gravin gene 6q24–25.2 is a deletion hotspot in advanced prostate, breast, and ovarian cancers (Wan et al., 1999; Xia et al., 2001). A recent study also revealed that AKAP12 expression is lost in radiation-induced osteosarcomas (Daino et al., 2009).

Table 5.5 Mouse models to study AKAP functions

AKAP	Genotype	Lethality	Phenotype (references)
AKAP140 AKAP149 (*AKAP1*)	Knockout	No	Female KO mice subfertile due to defects in oocyte maturation; mitochondrial localization of RIIα during oocyte maturation is lost (Newhall et al., 2006)
AKAP4	Knockout	No	Male KO mice infertile due to impaired sperm motility; defects in sperm fibrous sheath formation; shortened sperm flagella; redistribution of RIIα from particulate to soluble fraction in sperm (Huang et al., 2005; Miki et al., 2002)
AKAP150 (*AKAP5*)	Knockout	No	Loss of β-AR mediated L-type Ca^{2+} channel phosphorylation by PKA; various neuronal processes abnormal: deficits in spatial memory, reduced anxiety, defective motor coordination, resistant to pilocarpine-induced seizures; hypotension and protection from angiotensin II-induced hypertension (Hall et al., 2007; Navedo et al., 2008; Tunquist et al., 2008)
	Truncation mutant; C-terminal 36 aa of AKAP150 deleted (loss of PKA anchoring)	No	RIIα and RIIβ protein levels reduced in postsynaptic densities; hippocampal long-term potentiation impaired in 8- but not in 4-week-old KO mice; PGE_2-mediated modulation of TRPV1 channels by PKA impaired, leading to diminished PGE_2-induced thermal hyperalgesia (Lu et al., 2007b, 2008; Schnizler et al., 2008)
mAKAPα (*AKAP6*)	Knockout	Yes (reduced number of KO mice compared to wiltype and heterozygous littermates)	Reduced body weight and size (Carlisle Michel et al., 2005)

AKAP95 (*AKAP8*)	Knockout	No	Without phenotype; AKAP95/Fidgetin double KO mice die postnatally due to cleft palate (Yang et al., 2006)
D-AKAP2 (*AKAP10*)	Truncation mutant; C-terminal 51 aa of D-AKAP2 deleted (loss of PKA anchoring)	Yes (50% of homozygous mutant mice die within first year of life)	Increased cardiac cholinergic response; arrhythmia (Tingley et al., 2007)
SSeCKS (*AKAP12*)	Knockout	No	Prostate hyperplasia, hyperactivation of Akt/PKB and the loss of basal epithelial cells and E-cadherin cell–cell contacts (Akakura et al., 2008)
AKAP-Lbc (*AKAP13*)	Knockout	Yes (embryonic day 11)	Defective cardiac development; thinned myocardium; KO mice die from cardiac arrest; decreased cardiac MEF2c and SRF-dependent transcription (Mayers et al., 2010)
WAVE-1	Knockout	Yes (1/3 of KO mice die 24–48 h after birth)	Reduced body weight and size; sensorimotor retardation; reduced anxiety; deficits in hippocampal learning and memory; reduced spine density and altered synaptic plasticity of hippocampal neurons (Soderling et al., 2003, 2007)
MAP2	Knockout	No	Reduced body weight and size; decreased microtubule density and levels of PKA RII and C subunits in dendrites; reduced dendrite length; MAP2/MAP1b double KO mice die postnatally due to defects in microtubule bundling and neurite elongation (Harada et al., 2002; Teng et al., 2001)
	Truncation mutant; N-terminal 158 aa of MAP2 deleted (loss of PKA anchoring)	No	Decreased MAP2 phosphorylation by PKA; aberrant hippocampal CA1 neuron architecture; altered contextual memory (Khuchua et al., 2003)

(*continued*)

Table 5.5 (*continued*)

AKAP	Genotype	Lethality	Phenotype (references)
Ezrin	Knockout	Yes (die within 25 days after birth)	Abnormal intestinal villus morphology; retardation in photoreceptor development; reduction of apical microvilli in retinal pigment epithelium and Müller cells (Bonilha et al., 2006; Saotome et al., 2004)
	Knockdown (insertion of neomycin cassette between exons 2 and 3 of the ezrin gene)	Yes (93% die within 25 days after birth)	Achlorhydria due to defects in the formation/expansion of apical canaliculi in gastric parietal cells (Tamura et al., 2005)
Pericentrin	Knockout	No	Primordial dwarfism with microcephaly; loss of astral microtubules; misoriented mitotic spindles (Delaval and Doxsey, 2010)
	Transgenic expression of Pericentrin	No	Aneuploidy; increased number of centrosomes; multipolar spindles; mice develop a syndrome resmbling human myelodysplasia, carcinoma, and sarcoma (Delaval and Doxsey, 2010)
Neurobeachin	Knockout	Yes (immediately after birth)	Absence of evoked neuromuscular transmission; mice die from inability to breathe; abnormalities in fetal synapse formation and function (Medrihan et al., 2009; Su et al., 2004)
Ht31 (300 aa fragment of AKAP-Lbc, contains RIIBD, PKA-anchoring disruptor)	Transgenic expression of Ht31, forebrain-specific	No	Defects in hippocampal long-term potentiation and spatial memory (Nie et al., 2007)

5.1.2. Pericentrin

The noncanonical AKAP pericentrin (Table 5.4; Diviani et al., 2000) is localized at the centrosomes where it regulates centrosome function, cell cycle checkpoints, spindle formation, and cytokinesis. Mutations in the pericentrin gene cause primordial dwarfism with microcephaly. These symptoms are most likely due to defective chromosomal segregation during mitosis (Rauch et al., 2008). Similarly, pericentrin KO mice show primordial dwarfism, loss of astral microtubules, and misoriented mitotic spindles, that is, they are not perpendicular to the longitudinal dimension of the cells (Delaval and Doxsey, 2010). Pericentrin is upregulated in solid tumors where it leads to the formation of multiple mitotic spindle poles and consequently chromosomal aberrations and aneuploidy in daughter cells. This was also observed in a mutant mouse model with increased pericentrin levels. These mice have a syndrome similar to human myelodysplasia, carcinoma, and sarcoma (Delaval and Doxsey, 2010). In summary, patient data and KO/mutant mouse experiments underline the importance of balanced pericentrin expression and its oncogenic potential. The exact role of PKA anchoring for processes involving pericentrin remains unclear. In addition to binding PKA directly, pericentrin interacts with AKAP350/AKAP9 in centrosomes, which could add to recruiting PKA to pericentrin complexes. PKA is known to phosphorylate dynein and could thus contribute to centrosomal microtubule dynamics (Inaba et al., 1998). This might be dependent on anchoring by pericentrin and/or AKAP350.

5.1.3. Neurobeachin

Neurobeachin is a WD40- and beige and Chediak–Higashi syndrome (BEACH)-domain containing protein which appears to be involved in membrane trafficking (Wang et al., 2002). Both mammalian neurobeachin and its *Drosophila* ortholog AKAP550/rugose are AKAPs (Han et al., 1997; Wang et al., 2000). The neurobeachin gene lies within a candidate region for autism on chromosome 13 identified by linkage analysis (Barrett et al., 1999). A disruption of the neurobeachin gene by a chromosomal translocation (5;13)(q12.1;q13.2) has been found in a patient with idiopathic autism (Castermans et al., 2003). Moreover, a deletion of the region on chromosome 13 containing the neurobeachin gene was identified in another autism patient (Smith et al., 2002). Su et al. (2004) described the absence of evoked neuromuscular transmission due to a failure in neurotransmitter release in neurobeachin KO mice. Newborn neurobeachin KO mice lacked spontaneous movement, or reflexive movement in response to tail pinch and died immediately after birth from the inability to breathe. A recent study from Medrihan et al. (2009) confirmed the previous observations. Because of the perinatal lethality of the neurobeachin KO mice, further experiments were

performed at embryonic day 18. These studies identified several additional abnormalities in the formation and function of central synapses: altered postsynaptic currents, probably due to reduced transmitter release, a reduced number of asymmetric contacts in the fetal brainstem, and reduced expression levels of several synaptic marker proteins. Taken together, the disruption of neurobeachin causes defects in neurotransmitter release and thereby an excitatory–inhibitory imbalance. The involvement of PKA anchoring in neurobeachin-mediated membrane trafficking processes is unknown. PKA has, however, been shown to increase neurotransmitter release and regulate synapse formation (Abel and Nguyen, 2008; Byrne and Kandel, 1996). Thus it is conceivable that impaired PKA anchoring by neurobeachin contributes to synaptic abnormalities and is involved in the development of autism in patients with inactivation of one neurobeachin allele.

5.1.4. AKAP-Lbc

AKAP-Lbc (see Section 4.2.3) KO mice were recently generated (Mayers et al., 2010). The homozygous ablation of AKAP-Lbc expression is lethal, embryos show a cardiac arrest at embryonic day 9 and die around embryonic day 11. The myocardium of AKAP-Lbc KO embryos is thinned due to reduced proliferation of myocytes. Apparently, embryonic expression of AKAP-Lbc is required for cardiac development. AKAP-Lbc induces serum response factor expression via RhoA activation (Mayers et al., 2010) and MEF2c expression via PKC/PKD/HDAC5 (Carnegie et al., 2008). An activation of this pathway in adult hearts, for example, through α_1-adrenoceptors (Appert-Collin et al., 2007), increases MEF2c, causing a ''fetal gene response'' that leads to hypertrophy (Carnegie et al., 2008).

5.1.5. Transgenic expression of PKA-anchoring disruptors

The existing KO mouse models underline the relevance of AKAPs for the control of various neuronal, cardiac, and reproductive functions. In several cases the observed phenotypes reflect the situation in human patients in whom genetic alterations affect the respective ortholog. However, while complete ablation of an AKAP by KO yields information about its overall functions, it remains unclear to what extent a particular protein–protein interaction such as the one with PKA is important.

Transgenic expression of PKA-anchoring disruptors could answer this question. The only established mouse model based on this approach features a forebrain-specific expression of Ht31, a 300-amino acid fragment of AKAP-Lbc (see Section 5.2), containing the high-affinity RIIBD (Nie et al., 2007) but not other functional domains identified in AKAP-Lbc (Diviani et al., 2006). This forebrain-specific disruption of PKA anchoring causes an impairment of hippocampal long-term potentiation, emphasizing

the relevance of AKAPs for synaptic function (Nie et al., 2007). Additional studies based on this approach may elucidate the role of PKA anchoring in organs other than the brain, and the use of transgenic mice expressing RI- or RII-specific PKA-anchoring disruptors such as RIAD (Carlson et al., 2006) or SuperAKAP-*IS* (Gold et al., 2006) would further narrow down the roles of anchored PKA type I and II, respectively.

5.1.6. Targeted deletion of RIIBDs

Alternatively, to clarify the role of PKA anchoring by distinct AKAPs, additional mutant mouse models expressing AKAPs that lack PKA-binding ability but retain their other functions need to be generated. One example for this approach is a mouse model with a homozygous mutation in the D-AKAP2/AKAP10 gene. In the mutant protein, the 51 C-terminal amino acid residues containing the PKA-binding region are deleted. Mutant mice display an increased cardiac cholinergic response and arrhythmia. Fifty percent of the homozygous mutant mice die within their first year of life (Tingley et al., 2007). The cause of death is unknown but likely to be related to the observed cardiac abnormalities. The human SNP I646V, which is located in the PKA-binding region of the D-AKAP2/AKAP10 gene, leads to an increased anchoring of RI subunits of PKA by D-AKAP2/AKAP10 and is also associated with a cardiac phenotype (Kammerer et al., 2003). Moreover, the I646V SNP increases the risk of colorectal cancer (Wang et al., 2009) and familial breast cancer formation (Wirtenberger et al., 2007). Taken together, data from D-AKAP2/AKAP10 mutant mice and human genetic analyses demonstrate the requirement of balanced PKA anchoring by D-AKAP2/AKAP10 for proper cardiac function and tumor suppression, thus providing starting points for a detailed analysis of the cellular and molecular function of AKAP10.

Another example for a PKA-binding defective system is a mouse model for a truncated version of AKAP150 (Lu et al., 2007b, 2008). These mice express a variant of AKAP150 lacking the 36 C-terminal amino acids which contain the RIIBD. RIIα and RIIβ protein levels are decreased in postsynaptic densities of the animals and hippocampal long-term potentiation is impaired in 8- but not in 4-week-old mice (Lu et al., 2007b, 2008). Another study showed that PGE_2-mediated modulation of TRPV1 channels by PKA, which normally causes enhanced thermal sensitivity, is impaired in these mice (Schnizler et al., 2008).

Deletion of the 158 N-terminal amino acids of the neuronal AKAP MAP2, which harbor the RIIBD, resulted in decreased MAP2 phosphorylation by PKA, aberrant hippocampal CA1 neuron architecture and altered contextual memory formation in mice (Khuchua et al., 2003). This demonstrates that PKA anchoring is necessary for MAP2 phosphorylation by PKA and correct hippocampal neuron architecture and function. In summary,

the disruption of PKA binding was achieved by truncating the C-termini of D-AKAP2/AKAP10 and AKAP150 and the N-terminus of MAP2, revealing the importance of anchored PKA for the control of cardiac contraction and various neuronal functions.

5.2. Understanding AKAP functions through pharmacological interference with their protein interactions: Implications for novel therapeutic concepts

The depletion of AKAPs by knockdown (reviewed in Hundsrucker and Klussmann, 2008), or KO experiments (see above) leads to a specific phenotype and yields evidence for the relevance of the respective AKAP in certain signaling pathways and defined physiological processes. AKAP functions are mainly defined by their protein–protein interactions. Therefore, the pharmacological disruption of each of these interactions may be used for the elucidation of their function. This could also lead to new therapeutic strategies because many AKAPs are involved in pathological processes (see above).

5.2.1. Peptides targeting AKAP-dependent protein–protein interactions

To address the question whether PKA anchoring by AKAPs is involved in a process, AKAP–PKA interactions can be disrupted with peptides. As described in Section 3, AKAPs are a structurally diverse family of proteins that only display similarity within the RIIBDs. Peptides comprising the RIIBD of AKAPs can bind to R subunit dimers and effectively disrupt their interaction with AKAPs (for a more detailed overview see Hundsrucker and Klussmann, 2008). This was first demonstrated for the peptide Ht31 which represents the RIIBD of AKAP-Lbc/AKAP13 (Carr et al., 1992b). Ht31 can disrupt both RI– and RII–AKAP complexes (Herberg et al., 2000) in cells and in animal experiments (McConnell et al., 2009). Ht31 peptides bind RIIα with low nanomolar affinity ($K_D = 2.2 \pm 0.03$ nM; Newlon et al., 2001). Further peptides with higher affinities were established: AKAP18δ is a high-affinity AKAP and, accordingly, a peptide encompassing its RIIBD (or modified versions thereof such as AKAP18δ-L314E) bind RII subunits with high affinity ($K_D = 0.4 \pm 0.3$ nM; Hundsrucker et al., 2006a,b). The R subunit selectivity of the AKAP18δ peptides is not defined, but they are presumably nonselective. AKAP-*IS* was derived from an alignment of RIIBDs of 10 AKAPs and optimized for RII binding. It binds RII subunits with ~500-fold higher affinity than RI (RII: $K_D = 0.45 \pm 0.07$ nM, RI: $K_D = 227 \pm 55$ nM; Alto et al., 2003). Based on the AKAP-*IS* sequence, R subunit selectivity was refined, resulting in the RI-preferring peptide RIAD (RI: $K_D = 1.0 \pm 0.2$

nM, RII: $K_D = 1760 \pm 290$ nM; Carlson et al., 2006) and the RII-preferring SuperAKAP-*IS* (Gold et al., 2006). An alternative approach resulted in RI- and RII-preferring peptides derived from the dual-specific D-AKAP2, named AKB (A-Kinase Binding)-RI (RI: $K_D = 5.2 \pm 0.5$ nM, RII: $K_D = 456 \pm 33$ nM) and AKB-RII (RI: $K_D = 2493 \pm 409$ nM, RII: $K_D = 2.7 \pm 0.1$ nM; Burns-Hamuro et al., 2003).

In addition to PKA anchoring, other protein–protein interactions of AKAPs can be targeted with peptides. AKAP18α/AKAP15 interacts with the L-type Ca^{2+}-channel via a leucine-zipper motif (see Table 5.3 and Section 4.2.1). The peptide $AKAP15_{LZ}$, comprising this motif, prevents PKA phosphorylation of the channel at serine 1928 by disrupting its interaction with the AKAP–PKA complex (Hulme et al., 2002). The splice variant AKAP18δ interacts with PLN in the SR of cardiac myocytes (see Table 5.3, Section 4.2.1 and Fig. 5.7). A peptide containing 8 amino acids of the PLN cytosolic domain can bind to AKAP18δ and disrupts the PLN/AKAP18δ interaction, thus preventing PKA phosphorylation of PLN and reducing β-adrenoceptor induced reuptake of Ca^{2+} into the SR (Lygren et al., 2007). These protein–protein interaction disruptor peptides can be modified for immobilization, visualization, or cell permeation by conjugation with affinity tags, fluorescent dyes, or cell penetrating tags (e.g., stearate, poly-arginine, penetratin, MAP- or Tat-peptide; Faruque et al., 2009; Hundsrucker and Klussmann, 2008; Smith et al., 2007; Vives, 2005; Zorko and Langel, 2005). However, the application of PKA-anchoring disruptor peptides in cells or *in vivo* has limitations: (1) The global disruption of AKAP–PKA complexes elevates free PKA in the cytosol (Wojtal et al., 2006). This leads to an ablation of compartmentalized PKA signaling and an aberrant phosphorylation of PKA substrates; (2) Depending on the modification, peptides could be enriched in certain compartments and thus not be distributed evenly within cells; (3) Peptide stability in cell culture or *in vivo* experiments is limited. The oral applicability is also limited due to enzymatic degradation in the digestive tract; (4) Chemical peptide synthesis is expensive and may technically be highly demanding. In cell or animal models, some of these drawbacks can be overcome by encoding peptides genetically or by utilizing peptidomimetics or small molecules (Hundsrucker and Klussmann, 2008; Klussmann and Rosenthal, 2008). For example, adenoviral expression of Ht31 in the rat heart has been achieved. It leads to global disruption of AKAP–PKA interactions, has been shown to increase contractility (McConnell et al., 2009). Peptidomimetics comprise peptides containing unnatural amino acids or molecules mimicking a peptide structure (Jochim and Arora, 2009). In general, peptidomimetics are more stable than peptides and more resistant to enzymatic degradation. Recently, peptidomimetics were derived from the RIAD peptide (Torheim et al., 2009). These peptidomimetics retain the

ability to selectively bind to RI but not to RII subunits. Their *in vitro* stability in human serum is drastically increased compared to the peptide RIAD which suggests usability in *in vivo* studies.

5.2.2. AKAPs as potential drug targets

The major current drug targets are GPCRs, nuclear receptors, ion channels and pumps, and enzymes (Overington et al., 2006). Targeting protein–protein interactions mediated by scaffold proteins has several advantages compared to interfering with the conventional drug targets (Yin and Hamilton, 2005). Influencing protein–protein interactions, such as AKAP-dependent ones, would specifically alter a defined cellular event (like substrate phosphorylations), thus increasing drug specificity and lowering side effects (Klussmann and Rosenthal, 2008). The plethora of intracellular protein–protein interactions presumably accommodates numerous drug targets which would increase drug diversity and open up new therapeutic options.

Most oral drugs are small molecules that comply with Lipinski's rule-of-five, which predicts water solubility and cell permeability (Lipinski et al., 2001). They usually bind to ligand-binding pockets of receptors or substrate-binding pockets of enzymes which have a rather small surface. In addition, the knowledge of the natural ligands simplifies the identification of potential synthetic ligands. In contrast, protein–protein interactions are often achieved by multiple molecular interactions distributed over large surfaces. Nevertheless, it is possible for small molecules to inhibit protein–protein interactions as they may target specific regions on the interaction surfaces, so called hotspots, which contribute most of the binding energy (Wells and McClendon, 2007). Because of the similarity between different AKAP–PKA interactions, small molecules binding to the interaction surface would most likely disrupt all AKAP–PKA interactions or in the best case display RI/RII specificity. AKAP-specific disruption of PKA anchoring could be achieved by small molecules binding allosterically to AKAPs. Allosteric small molecules targeting intracellular protein–protein interactions have only recently been developed (Arkin and Wells, 2004; Arkin and Whitty, 2009; Gorczynski et al., 2007; McMillan et al., 2000). Allosteric AKAP-binders would allow for selective modification of compartmentalized cAMP signaling events. Such molecules could be identified by screening approaches or rational drug design (Erlanson, 2006; Villoutreix et al., 2009). The latter approach is limited by the lack of structural information on AKAPs and their interactions. AKAP-dependent protein–protein interactions are considered potential drug targets in cancer, cardiac, and neurological disorders (see above). In the following, AKAPs as potential targets in human immunodeficiency virus (HIV) infection and contraception are briefly highlighted.

5.2.3. AKAP149 (AKAP1) in HIV infection

AKAP149 interacts with the reverse transcriptase (RT) of the HIV type 1 and is necessary for viral replication in HeLa cells (Lemay et al., 2008). AKAP149 expression is upregulated by the HIV transactivator of transcription (Tat) protein (Liang et al., 2005), which might promote efficient virus replication. Although PKA has been shown to be involved in HIV infection (Skalhegg et al., 2005), it is not known whether its anchoring to AKAP149 is required. In any case, AKAP149 could be a drug target in HIV therapy because blocking the AKAP149–RT interaction could inhibit early viral replication.

5.2.4. AKAPs and novel contraceptives

AKAPs may be suitable targets in the development of novel contraceptive agents. AKAPs are highly abundant in sperm and are essential for sperm function (Carr and Newell, 2007). The disruption of PKA anchoring with the Ht31 peptide (see above) is known to inhibit sperm motility (Vijayaraghavan et al., 1997). A recent study has shown that quinones can alkylate AKAP3 and AKAP4 in human spermatozoa, thereby abolishing PKA anchoring (Hughes et al., 2009). As a consequence, sperm motility and PKA-dependent activation of Src kinase are inhibited (Hughes et al., 2009). These spermostatic compounds are far less cytotoxic than the approved and clinically used spermicide nonoxynol-9 (N9), which damages the vaginal epithelium (Hughes et al., 2007). In addition, a microbicidal effect has been observed for the spermatostatic quinones. They alkylate the major outer membrane protein of *Chlamydia*, the most common bacterial pathogen causing sexually transmitted disease (STD), thereby reducing infectivity (Hughes et al., 2009). Hence, quinones targeting AKAPs could lead to better topical contraceptives that also decrease the risk of infection with STD.

6. Concluding Remarks

Apart from their similarities in PKA binding, AKAPs are a highly diverse family of proteins, anchoring PKA to most organelles. By binding components of the cAMP signaling machinery such as GPCRs, ACs, and PDEs, AKAPs are crucial for the spatial and temporal control of cAMP/PKA signaling. This facilitates specific responses to multiple cAMP-elevating stimuli. While the vast majority of PKA-interacting proteins are canonical AKAPs that bind to the PKA regulatory subunit dimer via an amphipathic helix, an increasing number of noncanonical AKAPs and proteins that bind catalytic subunits of PKA are emerging. AKAPs achieve the integration of

cAMP and other signaling pathways by interacting with further signaling proteins including protein kinases, PPs, small GTP-binding proteins, ion channels, and cytoskeletal proteins.

AKAPs have been found in all metazoans and the green alga *Chlamydomonas*. The PKA binding mechanism is conserved and essentially the same in all AKAPs. The number and functional diversity of AKAPs has increased throughout evolution, thus contributing to compartmentalization and cross talk of signaling pathways. AKAPs may regulate ubiquitously required processes such as ciliar/flagellar motility from *Chlamydomonas* to mammals, and have apparently acquired novel functions with the development of specialized cell types, for example, in the regulation of synaptic processes (invertebrates and vertebrates) or the control of cardiac development and contractility (vertebrates).

Most structural information on AKAP–PKA interactions has been obtained with AKAP-derived peptides bound to D/D domain dimers of R subunits. This has, in combination with amino acid substitution analyses, revealed the amino acids important for R subunit binding and for discrimination between RI and RII. The NMR structure of GSKIP, to date the only available full-length structure of an AKAP, revealed that the hydrophobic residues essential for binding PKA are buried in the core of the protein in the absence of PKA. This implies that PKA binding requires structural rearrangements, which may have consequences on other protein–protein interactions an AKAP is engaged in. It will be a major challenge to solve three-dimensional structures of protein complexes composed of full-length AKAPs and their interaction partners to gain a more dynamic view of AKAPs.

Our understanding of the physiological and pathophysiological functions of AKAPs has greatly increased through the development of KO and mutant mouse models. These results are often in line with clinical data, revealing the involvement of AKAPs in human diseases such as cancer, heart failure, or arrhythmia. AKAP-mediated protein–protein interactions are intriguing targets for the development of novel drugs, for example, for the treatment of cardiovascular diseases or as contraceptive agents. In summary, new findings from structural studies, animal models, and clinical data will help to shape a more refined understanding of AKAP functions, opening new opportunities for a therapeutic exploitation of this class of scaffolding proteins.

ACKNOWLEDGMENTS

This work was supported by grants from the Deutsche Forschungsgemeinschaft (Kl1415/3-2 and 4-2) and the GoBio program of the Bundesministerium für Bildung und Forschung (FKZ 0315516).

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