Direct AKAP-Mediated Protein–Protein Interactions as Potential Drug Targets

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Abstract  A-kinase-anchoring proteins (AKAPs) are a diverse family of about 50 scaffolding proteins. They are defined by the presence of a structurally conserved protein kinase A (PKA)-binding domain. AKAPs tether PKA and other signalling proteins such as further protein kinases, protein phosphatases and phosphodiesterases by direct protein–protein interactions to cellular compartments. Thus, AKAPs form the basis of signalling modules that integrate cellular signalling processes and limit these to defined sites. Disruption of AKAP functions by gene targeting, knockdown approaches and, in particular, pharmacological disruption of defined AKAP-dependent protein–protein interactions has revealed key roles of AKAPs in numerous processes, including the regulation of cardiac myocyte contractility and vasopressin-mediated water reabsorption in the kidney. Dysregulation
of such processes causes diseases, including cardiovascular and renal disorders. In this review, we discuss AKAP functions elucidated by gene targeting and knockdown approaches, but mainly focus on studies utilizing peptides for disruption of direct AKAP-mediated protein–protein interactions. The latter studies point to direct AKAP-mediated protein–protein interactions as targets for novel drugs.

**Abbreviations** AKAP: A-kinase-anchoring protein; AVP: arginine-vasopressin; GEF: guanine nucleotide exchange factor; PKA: protein kinase A; SR: sarcoplasmic reticulum; PDE: phosphodiesterase; cAMP: cyclic adenosine monophosphate; PLN: phospholamban; RyR2: ryanodine receptors type 2; PP2B: protein phosphatase 2B/ calcineurin

1 A-Kinase-Anchoring Proteins Are Platforms for Cellular Signal Integration

The compartmentalization of cyclic adenosine monophosphate (cAMP)-dependent signalling is a prerequisite for numerous cellular processes, including cardiac myocyte contraction and exocytic processes, such as arginine-vasopressin (AVP)-mediated water reabsorption in renal collecting duct principal cells (Beavo and Brunton 2002; Houslay et al. 2005; Beene and Scott 2007; Szaszák et al. 2008).

Key players in compartmentalised cAMP signalling are A-kinase-anchoring proteins (AKAPs; see also Dodge-Kafka et al. this volume). They comprise a family of about 50 scaffolding proteins, which form the basis of cAMP-dependent signalling modules at defined cellular sites (Tasken and Aandahl 2004; Wong and Scott, 2004). AKAPs tether the main effector of cAMP, cAMP-dependent protein kinase (protein kinase A, PKA), to cellular compartments, and thereby limit its access to a subset of its substrates. Several AKAPs directly interact with PKA substrates. For example, AKAP18α, also termed AKAP15 or AKAP7α, directly interacts with L-type Ca\(^{2+}\) channels via a C-terminal leucine-zipper motif in cardiac myocytes and thereby facilitates β-adrenoceptor-dependent PKA phosphorylation of this channel. The phosphorylation increases channel open probability, enhances Ca\(^{2+}\) entry into the cytosol and thereby contributes to the β-adrenoceptor-mediated increase in cardiac myocyte contractility (Hulme et al. 2003).

The tethering of PKA through AKAPs by itself is not sufficient to compartmentalize and control a cAMP-dependent pathway since cAMP readily diffuses throughout the cell. Therefore, discrete cAMP signalling compartments are only conceivable if this diffusion is limited. Phosphodiesterases (PDE) establish gradients of cAMP by local hydrolysis of the second messenger and thereby terminate PKA activity locally (Lynch et al. 2006; Conti and Beavo 2007). Several AKAPs interact with PDEs and thus play a role at this level of control. For instance, AKAP450, mAKAP and AKAP18δ directly interact with PDE4D (Dodge et al. 2001; Tasken et al. 2001; Stefan et al. 2007). The AKAP18δ-PDE4D interaction, for example, appears to be