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MITOCHONDRIA: A kinase anchoring protein 1, a signaling platform for mitochondrial form and function

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Abstract

Mitochondria are best known for their role as cellular power plants, but they also serve as signaling hubs, regulating cellular proliferation, differentiation, and survival. A kinase anchoring protein 1 (AKAP1) is a scaffold protein that recruits protein kinase A (PKA) and other signaling proteins, as well as RNA, to the outer mitochondrial membrane. AKAP1 thereby integrates several second messenger cascades to modulate mitochondrial function and associated physiological and pathophysiological outcomes. Here, we review what is currently known about AKAP1's macromolecular interactions in health and disease states, including obesity. We also discuss dynamin-related protein 1 (Drp1), the enzyme that catalyzes mitochondrial fission, as one of the key substrates of the PKA/AKAP1 signaling complex in neurons. Recent evidence suggests that AKAP1 has critical roles in neuronal development and survival, which are mediated by inhibitory phosphorylation of Drp1 and maintenance of mitochondrial integrity.

1. Introduction

The second messenger cyclic AMP (cAMP) signals predominantly via cAMP-dependent activation of protein kinase A (PKA). In the absence of cAMP, PKA is a tetramer of two regulatory subunits (either type RI or RII) bound to two catalytic subunits. Upon binding of cAMP to the regulatory subunits, the catalytic subunits are released in an active state to phosphorylate serine/threonine residues. In addition to mediating the cAMP response, the regulatory subunits target the PKA catalytic subunits to various subcellular locations by binding to a group of proteins termed A kinase anchoring proteins (AKAPs). The AKAPs are an unrelated group of proteins that are defined by the presence of an amphipathic helix that binds the PKA regulatory subunit. The first AKAP to be identified, AKAP1 (a.k.a, D-AKAP1, AKAP121, AKAP149, S-AKAP84) localizes predominantly type II PKA holoenzymes to the outer mitochondrial membrane (OMM). In this review we will discuss the role of AKAP1, outer mitochondrial PKA, and other AKAP1 interactors in mitochondrial function under both normal and pathological states, focusing in particular on regulation of mitochondrial fission by AKAP1.

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2. Organelle function

2.1. AKAP1 isoforms

AKAP1 transcripts are broadly expressed in tissues including in heart, liver, kidney, skeletal muscle and brain, and they can be subject to alternative splicing (Huang et al., 1999). A common N-terminal exon (amino acids, aa 1–572 in human) encodes both the mitochondrial targeting sequence (aa 1–30) and the PKA binding helix (aa 347–360 in human). Full-length AKAP1 (AKAP121 in mouse; AKAP149 in human) is produced by splicing of this common exon to a series of highly conserved C-terminal exons that encode an RNA binding K homology (KH) domain and a Tudor domain. A short AKAP1 variant (S-AKAP84) is generated by alternative splicing of the first coding exon to a different C-terminal exon that encodes 22 residues, with low sequence conservation, followed by a stop codon. S-AKAP84 expression is largely restricted to testis (Lin et al., 1995). Additional AKAP1 splice variants have been described, but the majority are non-coding and their significance is unclear. The N1 variant was identified in the mouse and includes 33 additional N-terminal residues (Ma and Taylor, 2002). The N1 N-terminal exon was reported to target AKAP1 to the endoplasmic reticulum (Ma and Taylor, 2008). However, this exon is not represented in EST databases, is poorly conserved, and lacks a start codon in species other than mouse. The most abundant and best characterized product of the AKAP1 gene is full length AKAP1, which is the focus of this review.

2.2. AKAP1 interactions

The N-terminal mitochondrial targeting sequence for AKAP1 initiates import through the translocase of the outer membrane (TOM) complex, but it is then laterally released into the OMM to act as a transmembrane anchor, with the remainder of the protein facing the cytosol (Ma and Taylor, 2008).

In neuronal PC12 cells, overexpression of AKAP1 attenuated serum starvation-induced apoptosis and resulted in enhanced phosphorylation and inhibition of the proapoptotic BAD protein. Expression of an AKAP1 point mutant incapable of binding PKA (AKAP1 Δ PKA) increased the sensitivity of PC12 cells to apoptotic challenges (Affaitati et al., 2003). Treatment with a peptide derived from the AKAP1 N-terminus to delocalize endogenous AKAP1 reduced oxidative ATP synthesis and mitochondrial membrane potential ($\Delta\Psi_m$) and increased oxidative stress resulting in cardiomyocyte death, highlighting the critical role of mitochondrial-localized PKA in cell survival (Perrino et al., 2010). Recently, AKAP1 was shown to associate with the Na⁺/Ca²⁺ exchanger Ncx3 at the OMM to facilitate Ca²⁺ efflux from mitochondria and confer neuroprotection from hypoxia (Scorziello et al., 2013).

Besides PKA, AKAP1 recruits various other macromolecules to mitochondria, including a whole host of signaling proteins (summarized in Table 1, Fig. 1). For instance, AKAP1 has been shown to interact with a complex of protein tyrosine phosphatase D1 (PTPD1) (Cardone et al., 2004) and the non-receptor tyrosine kinase Src (Livigni et al., 2006). Overexpression of wild-type AKAP1 increased mitochondrial $\Delta\Psi_m$, while expression of either AKAP1 Δ PKA or an AKAP1 deletion mutant that cannot bind PTPD1/Src reduced $\Delta\Psi_m$ below control levels (Cardone, 2004, Livigni, 2006). An additional layer of complexity is added by the reported association of AKAP1 with type 4 phosphodiesterases (PDE4), which is predicted to limit the availability of cAMP for PKA activation (Asirvatham et al., 2004). In cardiomyocytes, AKAP1 recruits the calcium-responsive phosphatase calcineurin (CaN, aka PP2B) and prevents cardiac hypertrophy (Abrenica et al., 2009).

Interestingly, human AKAP1 (AKAP149) has also been localized to the nuclear envelope (NE), although this was not replicated by other laboratories. AKAP1 was proposed to target

protein phosphatase 1 (PP1) to facilitate reassembly of the NE at the end of mitosis (Steen et al., 2003). PP1 is known to interact with numerous regulatory proteins through an RVxF motif (Roy and Cyert, 2009), and the AKAP1 interaction site was initially postulated to be KGVLF (aa 155–159 in humans) (Steen et al., 2000). However, a subsequent report identified a C-terminal sequence (RYVSF, aa 637–641) as responsible for the PP1 interaction with AKAP1 (Rogne et al., 2009).

Through its C-terminal KH domain, AKAP1 was reported to bind to the 3'UTR of specific mRNAs. KH domains interact with 4 bases of single-stranded RNA or DNA via a binding cleft composed of two α -helices, a connecting GXXG loop, and a β -sheet (Valverde et al., 2008). AKAP1 associated mRNAs include those encoding the F0-f subunit of mitochondrial ATP synthase, manganese superoxide dismutase (MnSOD, SOD2), and steroidogenic acute regulator (STAR), a cholesterol-binding protein important for rapid steroid synthesis (Ginsberg et al., 2003, Grozdanov and Stocco, 2012). By localizing mRNAs close to the OMM, AKAP1 is believed to foster local translation of mitochondrial proteins; indeed, AKAP1 overexpression increased mitochondrial MnSOD levels (Ginsberg, 2003, Grozdanov and Stocco, 2012). In contrast, AKAP1 associates with the 3' UTR of the lipoprotein lipase (LPL) mRNA to inhibit LPL translation by a PKA-dependent mechanism (Ranganathan et al., 2002). Finally, AKAP1 can self-associate via its C-terminal KH and Tudor domains. RNA binding to the KH domain is required for AKAP1 self-association; however, the physiological role of AKAP1 self-association has yet to be determined (Rogne et al., 2006).

3. Cell Physiology

3.1 AKAP1 in fat metabolism and bone mineralization

AKAP1 is the most abundant AKAP in adipose tissue (Bridges et al., 2006), and recent evidence links AKAP1 to fat metabolism, cardiovascular function, and obesity. LPL hydrolyzes circulating triglycerides to promote fatty acid and monoacylglycerol uptake into adipose tissue, skeletal muscle, and heart tissue. LPL S447X is a common gain-of-function allele which provides modest cardiovascular protection (Rip et al., 2006). A recent report suggests that the S447X allele may enhance LPL mRNA translation because of reduced binding by the KH domain of AKAP1 (Ranganathan et al., 2012). Furthermore, AKAP1 transcription appears to be differentially regulated in lean and obese patients. Microarray and qPCR analyses of subcutaneous abdominal adipose tissue from an obese group of individuals showed a four-fold reduction in AKAP1 expression when compared to expression levels in a lean group, despite similar calorie and fat intake and exercise levels (Marrades et al., 2010). Perhaps reduced AKAP1 expression in obese individuals contributes to increased fat uptake into adipocytes by disinhibiting LPL translation. In another study, AKAP1 mRNA levels in bone tissue were positively correlated with bone mineral density in growing rats from several strains, indicating AKAP1 may promote bone growth and mineralization (Alam et al., 2010).

3.2 AKAP1 signaling in mitochondrial dynamics and neuronal development and survival

Mitochondria are highly dynamic organelles that undergo fission and fusion to change their morphology in a tightly regulated manner (Wilson et al., 2013). These changes in morphology have important consequences for mitochondrial functions ranging from ATP production and mitochondrial transport to apoptosis (Wilson, 2013). A key signaling event in the control of the mitochondrial morphology is the reversible phosphorylation of dynamin-related protein 1 (Drp1). Drp1 is a large GTPase that oligomerizes into spirals to physically constrict and sever mitochondria. While Drp1 is phosphorylated at several sites (Wilson, 2013), PKA only phosphorylates Ser637 (Ser656 in rat) resulting in Drp1

inhibition (Chang and Blackstone, 2007, Cribbs and Strack, 2007). AKAP1 promotes this phosphorylation, presumably by increasing the local concentration of PKA at the OMM (Merrill et al., 2011). The calcium-dependent phosphatase calcineurin dephosphorylates Ser637, thus relieving Drp1 inhibition (Cereghetti et al., 2008, Cribbs and Strack, 2007). It remains to be determined whether the reported association of calcineurin with AKAP1 (Abrenica, 2009) also plays a role in Drp1-dependent mitochondrial fission.

In hippocampal neurons, AKAP1 knockdown induces mitochondrial fragmentation and apoptosis. Conversely, overexpression of AKAP1 and Ser637-phosphorylation of Drp1 are neuroprotective, promoting mitochondrial elongation by unopposed fusion. Expression of AKAP1 Δ PKA is ineffective at promoting neuronal survival, indicating that PKA anchoring is critical for mitochondrial integrity and neuronal survival (Cribbs and Strack, 2007, Merrill, 2011). Another report suggested that AKAP1 inhibits Drp1 by direct protein-protein interaction, as well as by PKA-mediated phosphorylation of Drp1 (Kim et al., 2011). Additionally, in a cellular model of Parkinson's disease, AKAP1/PKA signaling protects from mitochondrial dysfunction resulting from the loss of PTEN-induced kinase 1 (Dagda et al., 2011).

Apart from regulating cell survival, AKAP1 is also implicated in neuronal development. In cultured hippocampal neurons, mitochondrial elongation induced by AKAP1 overexpression or Drp1 inhibition increased dendrite outgrowth at the expense of synapse formation. The effects of AKAP1 required PKA anchoring and appeared to be mediated by mitochondrial hyperpolarization and altered calcium homeostasis (Dickey and Strack, 2011).

4. Organelle Pathology

Mice lacking the first coding exon of AKAP1 are viable and grossly normal (Newhall et al., 2006). However, homozygous AKAP1 knockout females are infertile while heterozygous females and all genotypes of males have normal fertility. The infertility of the knockout females arises from a deficit in oocyte maturation. AKAP1 is required to sequester PKA at mitochondria during metaphase II to allow the irreversible maturation of the oocyte (Newhall, 2006). One possible explanation for why the global AKAP1 knockout has a relatively mild phenotype is that another mitochondria-targeted AKAP compensates for the absence of AKAP1 (Alto et al., 2002, Bui et al., 2010). Another explanation is that AKAP1 targets opposing kinases and phosphatases, whose combined delocalization could cancel out. A more detailed examination of AKAP1 knockout mice is clearly called for and may uncover additional phenotypes.

In some human pathologies, AKAP1 mRNA expression is correlated with cellular metabolism. As mentioned above, obesity is associated with AKAP1 downregulation in adipose tissue (Marrades, 2010, Rodriguez-Cuenca et al., 2012). Additionally, expression of the AKAP1 gene is regulated through response elements for the transcriptional coactivator peroxisome proliferator-activated receptor γ (PPAR γ). Knock-in mice expressing PPAR γ P465L, a dominant-negative allele associated with severe dyslipidemia in humans, show reduced AKAP1 expression, whereas obese humans treated with the PPAR γ agonist rosiglitazone show increased AKAP1 mRNA levels (Rodriguez-Cuenca, 2012). In breast cancer tissue, a group of fifteen markers were identified as elevated in the epithelial layer of the tumor, when compared to the inner stromal cells (Sotgia et al., 2012). The epithelial layer is characterized by predominantly oxidative energy production and high rates of mitochondrial biogenesis, which correlated with a greater than three-fold increase in AKAP1 levels (Sotgia, 2012).

In addition to the regulation of AKAP1 transcript levels, the protein is subject to posttranslational regulation. Induction of apoptosis targets AKAP1 for caspase cleavage at a

single site, DSVD (aa 579–582 in human). This cleavage results in an N-terminal fragment that includes the mitochondria-targeting sequence and the PKA binding site and a C-terminal fragment with the KH and Tudor domains (Fig. 1) (Yoo et al., 2008). Whether caspase cleavage of AKAP1 is functionally involved in the apoptotic program is not known. Furthermore, ischemic insults were shown to promote ubiquitination and degradation of AKAP1. This occurs through the activation of the transcription factor hypoxia induced factor 1a (HIF-1a), which induces the E3 ubiquitin-protein ligase seven in absentia homolog 2 (SIAH2) to ubiquitinate AKAP1 (Carlucci et al., 2008, Kim, 2011). Ubiquitination occurs at a degron immediately C-terminal of the PKA binding site, hastening degradation of AKAP1 and promoting apoptosis (Kim, 2011). Thus, AKAP1 expression is tightly regulated at both mRNA and proteins levels, reflecting the critical role of the signaling scaffold in mitochondrial physiology and pathophysiology.

5. Future Outlook

AKAP1 has emerged as an important regulator of mitochondrial function. In neurons, PKA recruitment by AKAP1 opposes mitochondrial fragmentation and dysfunction, providing neuroprotection. Reduced cAMP levels are associated with many forms of neuronal injury and neurodegenerative diseases, including Alzheimers disease (Chen et al., 2012, Pozueta et al., 2013, Wang and Zhang, 2012). Future studies should reveal whether the AKAP1→PKA→Drp1 signaling axis is compromised in and contributes to these neuropathologies. If so, activating PKA or inhibiting phosphatases in the AKAP1 complex could be a viable therapeutic strategy, acting to prevent the mitochondrial damage seen in brain injury and disease.

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Abbreviations

AKAP	A kinase anchoring protein
BAD	Bcl-2-associated death promoter
cAMP	cyclic AMP
CaN	calcineurin
Casp	caspase
Drp1	dynammin-related protein 1
Fo-f	ATP synthase Fo complex
HIF-1a	hypoxia induced factor 1a
KH	K homology
LPL	lipoprotein lipase
Mff	mitochondrial fission factor
MnSOD	manganese superoxide dismutase
OMM	outer mitochondrial membrane
PDE4a	phosphodiesterase type 4a
PKA	protein kinase A

PP1	protein phosphatase 1
PTEN	phosphatase and tensin homolog
PPARγ	coactivator peroxisome proliferator-activated receptor γ
PTPD1	protein tyrosine phosphatase D1
Siah2	seven in absentia homolog
StAR	steroidogenic acute regulatory
TOM	transporter outer membrane
Ub	ubiquitin
$\Delta\Psi_m$	mitochondrial membrane potential.

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Organelle facts

- Mitochondria carry out many essential processes including ATP production.
- Mitochondria are shaped by fission and fusion reactions, which influence function.
- The scaffold protein AKAP1 assembles a “signalosome” at the mitochondrial surface, including kinases, phosphatases, and mRNA.
- AKAP1 maintains mitochondrial and cellular health.
- AKAP1 is highly expressed in adipocytes and may play a role in obesity.
- PKA in the AKAP1 complex inhibits mitochondrial fission and apoptosis, but promotes dendrite development by phosphorylating the mitochondrial fission enzyme Drp1.

Fig. 1.

AKAP1 recruits diverse signaling proteins and mRNA to the outer mitochondrial membrane. AKAP1 is depicted in green and has an N-terminal OMM targeting sequence and C-terminal KH and Tudor domains. AKAP1 targets PKA and opposing phosphatases (CaN and PP1), and also many other signaling proteins. Additionally, AKAP1 is modified by Siah ubiquitin ligases and caspases, leading to AKAP1 degradation. Through the KH domain, AKAP1 regulates the translation of mRNAs by binding to and either enhancing (StAR, MnSOD and Fo-f) or inhibiting (LPL) translation. Abbreviations – CaN, calcineurin; Casp, caspase; Drp1, dynamin related protein 1; Fo-f, ATP synthase Fo complex; KH, K homology; LPL, lipoprotein lipase; Mff, mitochondrial fission factor; MnSOD, manganese superoxide dismutase; PDE4a, phosphodiesterase type 4a; PP1, protein phosphatase 1; PTPD1, protein tyrosine phosphatase D1; Siah2, seven in absentia homolog; StAR, steroidogenic acute regulatory; TOM, transporter outer membrane; Ub, ubiquitin.

Table 1

AKAP1 interactors

	tissue/cell type	Dmain/region aa	reference
Protein			
AAT-1	In vitro, 293T	aa 31–252	Yukitake et al., 2002
AMY-1	In vitro, 293T	N.D.	Furusawa et al., 2002
AMY-1	Yeast two-hybrid, 293T, AM416	aa 253–530	Furusawa et al., 2001
Ago2	In vitro, H295R adreno. carcin.	KH	Grozdanov and Stocco, 2012
Calcineurin	Cardiomyocytes	N.D.	Abrenica et al., 2009
Drp1	MEFs, HEK293T	aa 351–857	Kim et al., 2011
HIV RT p66	HEK293T	aa 331–817	Lemay et al., 2008
Lfc	NIH3T3 fibroblast	N.D.	Meiri et al., 2009
NCX3	BHK fibroblasts	N.D.	Scorziello et al., 2013
PDE4a	In vitro and Jurkat	N.D.	Asirvatham et al., 2004
PP1 α , PP1 γ , PP1 δ	Hela, 293T	aa 627–631	Rogne et al., 2009
PP1 α , PP1 γ 1	Rat epididymal adipose	N.D.	Bridges et al., 2006
PP1, PKC	Hela	N.D.	Küntziger et al., 2006
PP1	Hela, 293T, HUVEC, Jurkat, Bjab	N.D.	Steen et al., 2003
PTPD1, Src	HEK293	N.D.	Livigni et al., 2006
PTPD1	In vitro, rat testis	aa 1–117	Cardone et al., 2004
RSK1, PP2A	B82L	N.D.	Chaturvedi et al., 2009
RI-RSK1 complex	B82L	regulatory binding	Chaturvedi et al., 2006
self-dimerization	Hela, 293T	KH-Tudor	Rogne et al., 2006
Siah2	In vitro, yeast two-hybrid, 293T	aa 329–573	Carlucci et al., 2008
VEGFR-2	HEK293T	N.D.	Meyer et al., 2011
mRNA			
Fo-f (ATP synthase), MnSOD	Hela cells	KH	Ginsberg et al., 2003
LPL	3T3-F442A	KH	Ranganathan et al., 2012
LPL	F442A adipocyte	N.D.	Unal et al., 2008
LPL	3T3-F442A	N.D.	Ranganathan et al., 2002
Non-specified RNA	Hela, 293T	KH-Tudor	Rogne et al., 2009
Non-specified RNA	Hela, 293T	KH-Tudor	Rogne et al., 2006
StAR, MnSOD, ATP5J2, GAPDH, MLN64	In vitro, H295R adreno. carcin.	KH	Grozdanov and Stocco, 2012

Abbreviations - AAT-1, AMY-1-binding protein; Ago2, argonaute 2; AMY-1, associate of Myc-1; ATP5J2, ATP synthase Fo complex; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; LPL, lipoprotein lipase; MLN64, metastatic lymph node 64 protein; MnSOD, manganese superoxide dismutase; NCX3, sodium/calcium exchanger 3; N.D., not determined; PDE4a, phosphodiesterase type 4a; PKC, protein kinase C; PP1, protein phosphatase 1; PP2A, protein phosphatase 2A; PTPD1, protein tyrosine phosphatase D1; RSK1, ribosomal s6 kinase 1; Siah2, seven in absentia homolog; StAR, steroidogenic acute regulatory; VEGFR-2, vascular endothelial growth factor receptor 2