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Review

Mitochondrial cAMP-PKA signaling: What do we really know?☆

Yasmine Ould Amer, Etienne Hebert-Chatelain*

Université de Moncton, Department of Biology, 18 Av Antonine Maillet, Moncton, NB E1A2Y5, Canada

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ABSTRACT

Mitochondria are key organelles for cellular homeostasis. They generate the most part of ATP that is used by cells through oxidative phosphorylation. They also produce reactive oxygen species, neurotransmitters and other signaling molecules. They are important for calcium homeostasis and apoptosis. Considering the role of this organelle, it is not surprising that most mitochondrial dysfunctions are linked to the development of pathologies. Various mechanisms adjust mitochondrial activity according to physiological needs. The cAMP-PKA signaling emerged in recent years as a direct and powerful mean to regulate mitochondrial functions. Multiple evidence demonstrates that such pathway can be triggered from cytosol or directly within mitochondria. Notably, specific anchor proteins target PKA to mitochondria whereas enzymes necessary for generation and degradation of cAMP are found directly in these organelles. Mitochondrial PKA targets proteins localized in different compartments of mitochondria, and related to various functions. Alterations of mitochondrial cAMP-PKA signaling affect the development of several physiopathological conditions, including neurodegenerative diseases. It is however difficult to discriminate between the effects of cAMP-PKA signaling triggered from cytosol or directly in mitochondria. The specific roles of PKA localized in different mitochondrial compartments are also not completely understood. The aim of this work is to review the role of cAMP-PKA signaling in mitochondrial (patho)physiology.

1. Introduction

Mitochondria are considered as the cellular bioenergetic powerhouses. They are the main converters of energy sources into ATP thanks to the oxidative phosphorylation process (OXPHOS) [1]. These organelles are however much more than simple ATP producers. They are important generators of reactive oxygen species (ROS) which can have signaling roles or pathological impacts depending on their levels [2,3]. Mitochondria contain pro-apoptotic proteins that trigger programmed cell death when released into cytoplasm [4]. Mitochondria buffer the variations in Ca^{2+} cytosolic levels and are involved in metabolism of several neurotransmitters, such as glutamate and aminobutyric acid [5]. Mitochondria form a dynamic network that spans throughout the cytoplasm, which can be modified by several processes, including biogenesis of mitochondrial proteins, specific and unspecific degradation of mitochondria, as well as fusion and fission events among the mitochondrial network [6]. Proper regulation of mitochondrial functions and dynamics is required since alterations of these organelles impair cellular homeostasis. The impact of chronic mitochondrial dysfunctions is well established in several pathologies including neurodegenerative diseases (such as Alzheimer's and Parkinson's disease), metabolic diseases (such as diabetes and obesity) and cancer [5]. Several cellular signaling pathways are implicated in the adjustment of mitochondrial functions according to physiological conditions. One of the best described signaling pathways regulating the mitochondrial metabolism involves the AMP-activated protein kinase (AMPK). During metabolic stress, AMPK is activated in response to ATP deficit and phosphorylates several targets, including acetyl-CoA carboxylase to increase oxidation of fatty acid [7], and the transcriptional coactivator peroxisome proliferator-activated receptor-gamma coactivator 1 (PGC-1), to boost mitochondrial biogenesis [8].

Kinases localized inside mitochondria emerged recently as powerful regulators of mitochondria. Several kinases such as Src kinases, Akt, extra-regulated kinases (Erk) 1/2, p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinases are translocated from the cytoplasm to the mitochondria where they modulate mitochondrial functions, including ATP production, calcium buffering and apoptosis, in response to specific stimuli [9–12]. Among these kinases, the protein kinase A (PKA) was one of the first to be described as an intra-mitochondrial kinase [13–16]. In the last 20 years, multiple studies described the role of intra-mitochondrial PKA (mtPKA) signaling in mitochondrial physiology. The aim of this work is to review the processes

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* Corresponding author.
E-mail address: etienne.hebert.chatelain@umoncton.ca (E. Hebert-Chatelain).

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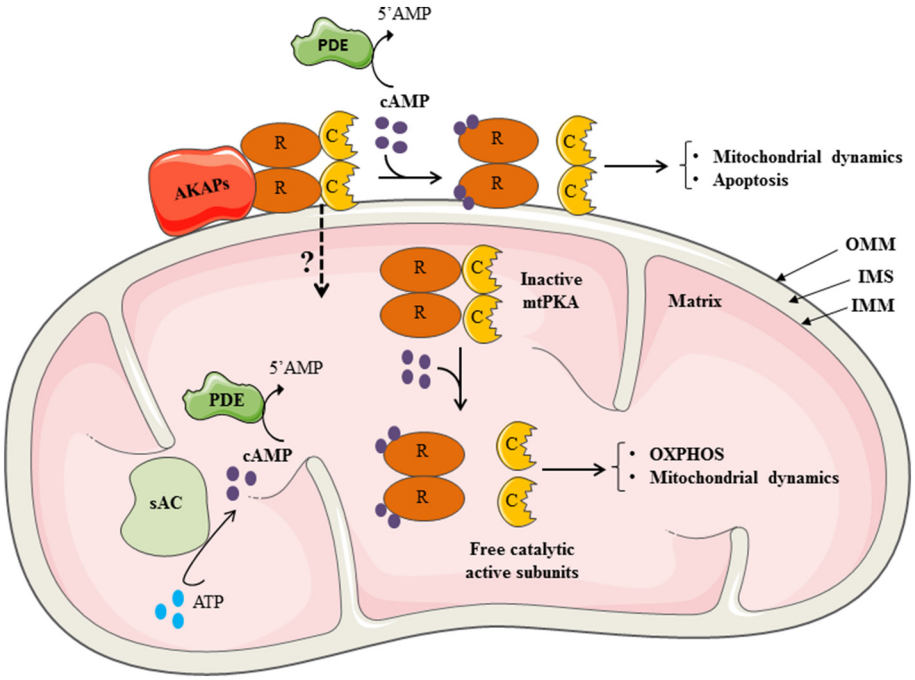

Fig. 1. Mitochondrial cAMP-PKA signaling. A-kinase anchoring proteins (AKAPs) bind to the regulatory subunits of PKA (R) and tether PKA to the outer mitochondrial membrane (OMM). Although the mechanisms allowing PKA to be moved across the mitochondrial membranes are unknown, PKA is also observed in the mitochondrial matrix. In the mitochondrial matrix, the soluble adenylyl cyclase (sAC) generates cAMP, whereas phosphodiesterase (PDE) degrades cAMP. Activation of PKA occurs when cAMP binds to the R subunits and induces the release of catalytic subunits (C). The functional impact of cAMP-PKA signaling depends on the sub-mitochondrial localization of PKA. See text for more details. IMS: inter membrane space; IMM: inner mitochondrial membrane.

involved in mtPKA signaling, from generation and degradation of cyclic adenosine monophosphate (cAMP), translocation of PKA inside mitochondria, to mtPKA-dependent phosphorylation of mitochondrial proteins and its role in regulation of mitochondrial and cellular homeostasis.

2. Regulation and activation of PKA

2.1. Structure of PKA

PKA, also known as cAMP-dependent protein kinase, consists of two regulatory subunits bound to two catalytic subunits (Fig. 1) [17]. Although distinct catalytic subunits have been isolated and characterized, biochemical and functional features of PKA appear largely determined by the structure and properties of the regulatory subunits [17,18]. There are four different isoforms of regulatory subunits divided in two classes, i.e., RI- and RII-α or -β [19–21]. The cAMP is considered the major activator of PKA. Binding of cAMP to PKA regulatory subunits induces dissociation of the holoenzyme, release of catalytic subunits and subsequent phosphorylation of PKA substrates (Fig. 1, for more details, please see [22,23]). Phosphorylation of PKA substrates is critical for various cell functions, including metabolism, differentiation, synaptic transmission, ion channel activity, growth and development [22–24].

2.2. Generation and degradation of cAMP

Intracellular levels of cAMP are regulated by the balance between the activities of two types of enzymes: adenylyl cyclases (ACs) which produce cAMP and phosphodiesterases (PDEs) which degrade cAMP (Fig. 1) [25]. Pioneer studies using Forster resonance energy transfer (FRET) based assays revealed that cAMP is not a freely diffusible second messenger and that cAMP signaling is compartmentalized within cells [26–28]. In fact, subcellular microdomains of cAMP appear mostly dictated by the subcellular localization of ACs and PDEs.

In mammalian cells, ACs are divided into two superfamilies: plasma membrane-bound adenylyl cyclases (tmACs) and soluble (intracellular) adenylyl cyclases (sACs) [29,30]. There are nine genes encoding tmACs and a single gene encoding the isoforms of sAC [31]. TmACs are ubiquitous and are important for cellular responses to extracellular stimuli [32]. Notably, tmACs are modulated by different types of heterotrimeric G proteins that are released from G protein-coupled receptors [33]. They are also sensitive to the pharmacological activator forskolin [34]. Although their activation by forskolin or by isoproterenol-dependent stimulation of β-adrenoceptors can impact on mitochondrial activity [35–37], no tmACs have been observed within mitochondria. The intracellular sACs are distributed to discrete locations throughout the cell, including nuclei and mitochondria, centrioles and the mitotic spindle as well as midbody [38]. They are sensitive to ATP, bicarbonate and Ca^{2+} [39].

PDEs selectively remove the phosphate from cAMP or cGMP [40,41]. Their subcellular localization is also a major regulator of the local concentrations of cAMP or cGMP within the cell [40,41]. There are 11 known PDE families with some specific for cAMP, some specific to cGMP and others able to degrade both [40,41]. To date only few PDEs have been observed in mitochondria. The phosphodiesterase A2 (PDEA2) isoform is present in the matrix of mouse liver and brain mitochondria [42]. In *Drosophila*, the mitochondrial PDE Prune degrades cAMP in the matrix and promotes replication of mitochondrial DNA trough stabilization of the transcription factor A (TFAM) [43].

There are two distinct cAMP microdomains among mitochondrial compartments e.g., matrix and outer mitochondrial membrane (OMM) (Fig. 1). Inside mitochondrial matrix, cAMP is generated by sAC in a CO_2/bicarbonate-dependent manner (Fig. 1) [44,45]. At the OMM, cAMP levels increase in response to the tmACs activator forskolin [44,45]. These two different intra-mitochondrial cAMP domains have different outcomes. Indirect evidence showed that sAC-dependent increases of cAMP in mitochondrial matrix increases OXPHOS [44] whereas higher cAMP levels at the OMM induces mitochondrial elongation, increases mitochondrial membrane potential and protects against apoptosis [46].

The impact of these two mitochondrial cAMP microdomains on PKA activity is not clear. Acin-Perez et al. first proposed that sAC modulates OXPHOS through PKA-dependent phosphorylation of complex IV subunits [47]. Another study using FRET-based assays revealed that increases of cAMP in the matrix do not activate mtPKA [45]. These discrepant results illustrate the necessity of a better characterization of cAMP/PKA signaling and microdomains inside mitochondria.

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