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The basics of mitochondrial cAMP signalling: Where, when, why

Giulietta Di Benedetto [a,b,*], Konstantinos Lefkimmiatis [b,c], Tullio Pozzan [a,b,d]

[a] Neuroscience Institute, National Research Council of Italy (CNR), 35121 Padova, Italy
[b] Veneto Institute of Molecular Medicine, Foundation for Advanced Biomedical Research, 35129 Padova, Italy
[c] Department of Molecular Medicine, University of Pavia, 27100 Pavia, Italy
[d] Department of Biomedical Sciences, University of Padova, 35121 Padova, Italy

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ABSTRACT

Cytosolic cAMP signalling in live cells has been extensively investigated in the past, while only in the last decade the existence of an intramitochondrial autonomous cAMP homeostatic system began to emerge. Thanks to the development of novel tools to investigate cAMP dynamics and cAMP/PKA-dependent phosphorylation within the matrix and in other mitochondrial compartments, it is now possible to address directly and in intact living cells a series of questions that until now could be addressed only by indirect approaches, in isolated organelles or through subcellular fractionation studies. In this contribution we discuss the mechanisms that regulate cAMP dynamics at the surface and inside mitochondria, and its crosstalk with organelle Ca^{2+} handling. We then address a series of still unsolved questions, such as the intramitochondrial localization of key elements of the cAMP signaling toolkit, e.g., adenylate cyclases, phosphodiesterases, protein kinase A (PKA) and Epac. Finally, we discuss the evidence for and against the existence of an intramitochondrial PKA pool and the functional role of cAMP increases within the organelle matrix.

1. Introduction

Mitochondria are ubiquitous organelles present in practically all eukaryotic cells [1] characterized by a unique structure made by two closely apposed membranes, the Inner Mitochondrial Membrane, IMM, highly and dynamically folded in structures called cristae [2], and the Outer Mitochondrial Membrane, OMM, that encircles the IMM. Mitochondria were the subject of very intensive studies until the middle of the 20th century, that led to the discovery of their central role in the production of energy (in the form of ATP) through oxidation of carbohydrate metabolites and fatty acids, culminating with the development of the chemiosmotic model [3], the theory that eventually explained the mechanism of energy transduction, not only in mitochondria but also in chloroplasts and bacteria.

After some decades of diminished interest due to the wrong impression that the most important mitochondrial secrets had been revealed, at the end of the last century the interest in these organelles was strongly rejuvenated. This was due to two fundamental breakthrough findings, namely the discovery that mitochondria are key players in controlled forms of cell death, in particular apoptosis[4][5], and the finding that these organelles regulate cellular calcium (Ca^{2+}) signalling [6,7]. Nowadays more than ever mitochondria are on stage, under different spotlights, in particular as metabolic and signalling hubs, and are increasingly recognized as pivotal regulators in almost every aspect of cell pathophysiology. Indeed, responsive, efficient and fit mitochondria are not only necessary for cellular health, but mitochondrial dysfunctions appear causally involved in various types of diseases, from metabolic to immunological, from oncological to neurodegenerative [8,9]. Given their "steering committee" role, it is not surprising that mitochondria are required to continuously communicate with their host cell. Thanks to a finely tuned and bidirectional information-exchange machinery (that is still to be fully identified in molecular detail), mitochondria adapt to the varying cellular needs, whilst at the same time, they communicate to the cell their bioenergetics status. For example, among the messages delivered to the cytosol, the release of cytochrome *c* from the mitochondrial inter-membrane space (IMS) is interpreted by the cell as a death directive that ultimately results in apoptosis[5], while an increase in the production of reactive oxygen species (ROS) can activate transcription of specific genes in response to hypoxia [10–12]. On the other hand, mitochondria possess molecular "antennas", monitoring and sensing messages originating from the cytoplasm or from the extracellular space. In addition, mitochondria actively participate in the

* Corresponding author at: Neuroscience Institute, National Research Council of Italy (CNR), 35121 Padova, Italy.
E-mail address: giulietta.dibenedetto@cnr.it (G. Di Benedetto).

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signalling cascades of the two main cellular second messengers, Ca^{2+} and cyclic AMP (cAMP), which are both "sensed" and (at least Ca^{2+}) forwarded back to the cell to dispatch information.

The capacity of mitochondria to accumulate Ca^{2+} at the expense of energy consumption was discovered in the 50 s and was extensively investigated until the late 70 s. Throughout the 80 s, however, mitochondrial Ca^{2+} uptake was considered of modest physiological relevance, until it was demonstrated that, in intact live cells, mitochondria are able to sense physiological increases in cytosolic Ca^{2+} and to rapidly uptake it into the matrix [13–15]. Only more recently, the multiproteic machinery responsible for mitochondrial Ca^{2+} uptake [16], at the core of which is the so called MCU (mitochondrial Ca^{2+} uniporter) [17,18], has been unravelled. Ca^{2+} accumulated by mitochondria is released back into the cytosol via efflux mechanisms, such as the xNa^{+}/Ca^{2+} and the H^{+}/Ca^{2+} exchangers [15,19,20], suggesting that this messenger acts as "communication currency" between mitochondria and the rest of the cell, conveying information that influences the function of both sides. The effects of Ca^{2+} on mitochondria can be positive or negative [14,15,20]. Elevation of matrix Ca^{2+} fosters ATP production through the activation of matrix dehydrogenases [20–23], but if this increase is too large or too prolonged, mitochondria enter a state of increased IMM permeability (called "permeability transition") that leads to dissipation of their membrane potential ($\Delta\psi$) and to irreversible damage, which eventually kills the cell [24]. On the other hand, mitochondria significantly impinge upon intracellular Ca^{2+} dynamics, contributing to the shaping of intracellular functionally distinct Ca^{2+} microdomains.

The relation of the other major second messenger, cAMP, with mitochondria has been unveiled only more recently and remains less defined and more debated. This is somehow surprising since cAMP is known to control a variety of key functions in prokaryotes, from which mitochondria derive [25]. Indeed, cAMP mediates microbial metabolic flexibility, *i.e.*, the catabolite repression response, and represents a master regulator of microbial virulence, modulating different aspects of host–pathogen interaction [26]. However, despite its broad use since early evolution of life, a role for cAMP in mitochondrial pathophysiology has rarely been considered until recently. This possibly depended on the lack of evidence of mitochondrial cAMP transporters, and of mitochondria-targeting sequences in components of the cAMP signalling machinery. Nevertheless, thanks to the effort of several laboratories, it is now clear that the effects of cAMP on mitochondria converge on two major organelle compartments, the OMM (the cytosolic surface in particular), and the matrix/IMM. Starting with the outermost mitochondrial compartment, the OMM, the presence of all the components necessary to form functional units of cAMP-mediated signalling is firmly established. On the contrary, the existence of a cAMP signalling machinery inside mitochondria (matrix and IMM) started being deeply investigated only in the last decade, albeit sparse evidence dating back to the 80 s exists. Thus, the role of matrix cAMP (mt-cAMP) in mitochondrial physiology has just started to be clarified, and a number of features have still to be defined and, very likely, discovered.

In eukaryotes, cytosolic cAMP is involved in many cellular functions such as gene transcription, metabolism, cell migration and death, and in systemic processes as diverse as hormone signal transduction, memory formation and control of heart beating [27]. Such a variety of cAMP-regulated processes and functions, sometimes opposite, suggested long ago that cAMP could be compartmentalized inside the cell, acting in independent microdomains (Buxton & Brunton, 1983), an idea that is now largely accepted [28–30]. When the existence of cAMP signalling microdomains close to mitochondria was tested, it was revealed that these organelles evolved the tools to detect cytosolic cAMP at their OMM. Moreover, while it is expected that cAMP synthetized in the cytosol will be permeable through the OMM, data from several laboratories agree that cAMP cannot permeate the IMM to reach the mitochondrial matrix [31–35]. Cyclic AMP, however, can be generated within the matrix by a mitochondrial form of soluble adenylate cyclase (sAC), in response to metabolic stimuli and Ca^{2+} increases [32,33,36,37]. Consequently, depending on the cAMP source, mitochondria are subjected to two distinct cAMP cascades, one responding to cytosolic and extracellular stimuli and another confined in the matrix, but linked to the cytosol by Ca^{2+} signalling [32]. These segregated, but not sealed, pathways impinge on the regulation of distinct functions and differentially affect mitochondrial homeostasis. It is, however, worth noting that elevation of cAMP levels in response to cell stimulation is only one of the prerequisites for the effect of this second messenger on mitochondrial functions; cAMP effectors (*e.g.*, cAMP activated kinases) need to be present as well in the different mitochondrial compartments; this topic is presently still quite debated and it will be briefly discussed below.

The best characterized mitochondrial functions modulated by the cAMP cascade hosted at the OMM are apoptosis and mitochondrial dynamics [38–42]. On the other hand, cAMP in the matrix (mt-cAMP) was initially suggested to regulate oxidative phosphorylation (OXPHOS) [32,36,43], although with some discordances, likely depending on different experimental procedures and timescale employed [44]. Subsequent experimental evidence, however, suggested that the roles of mt-cAMP go beyond the control of OXPHOS, and the discovery of an increasing number of functions is gradually illuminating and justifying the presence of a complex machinery such as that of cAMP signalling in the core of the organelle. The discovery of a secluded cAMP-dependent pathway, and the demonstration of its crosstalk with Ca^{2+}, opened the way to a re-evaluation of mitochondria as integrators of multiple second messenger cascades. Studies over the last decade revealed that mitochondria can now be regarded as signalling hubs, involving not only Ca^{2+} (as previously well established), but also cAMP [32,33,36,43,45,46], cGMP [47] and other small metabolites as signals [48].

2. Overview of the mitochondrial cAMP signalling machinery

Intracellular cAMP concentrations depend on the balance between synthesis, degradation, and export from the cell, performed by distinct components of the cAMP machinery. In addition, a number of scaffolding proteins [49], can act as platforms for the establishment of "signalosomes", functional units defining cAMP micro- or even nano-domains [50,51].

Cyclic AMP is synthesized by Adenylate cyclases (ACs). Mammals express ten distinct ACs, nine transmembrane (tmACs) [52] and a soluble one (sAC) [53,54]. Phosphodiesterases (PDEs) are the enzymes that degrade cAMP, and they are classified in 11 families, eight of which have the ability to hydrolyse cAMP [55,56]. Finally, cAMP can be extruded from the cell by ATP binding cassette (ABC) proteins, in particular the multi-drug resistance proteins MRP4 and MRP5 [57]. Both cAMP degradation and export counteract cAMP synthesis and are key to the maintenance of low cAMP levels in the cytosol under resting conditions, and to the termination of the cAMP signals after stimulation. Despite strong efforts to identify novel cAMP-binding proteins, the known cAMP effectors belong to a few families. Cyclic nucleotide-gated (CNG) channels have been identified decades ago [58], while the members of the Popeye-domain containing family are the last discovered [59]. The most studied and best characterized cAMP effectors, however, are the serine/threonine-specific Protein Kinase A (PKA) [60–62] and Epac (Exchange Proteins directly Activated by cAMP) [63,64]. PKA is responsible for the vast majority of the cAMP-dependent functions known to date. Signals conveyed by PKA are terminated by phosphatases, which dephosphorylate PKA targets [65].

The cAMP signalling pathway controls many, sometimes contradictory, tasks, and this pleiotropy clearly suggests the existence of mechanisms guaranteeing specificity between the triggering signals and activated effectors; indeed, it is underpinned by a compartmentalized organization into micro- and nano-domains [50,51]. Such domains may depend on local differences in cAMP levels (owing to proximity of cAMP production and/or degradation elements) or on proximity or differential activity of cAMP effectors, targets and signal terminators (i.e. phosphatases). The scaffolds that nucleate cAMP signalosomes are called

A-kinase anchoring proteins (AKAPs) [49]. Mitochondria host several AKAPs [35,66], mostly associated with the OMM and at least one (called SKIP, sphingosine kinase interacting protein) suggested to be localized within the IMM [67], albeit the majority of SKIP is present soluble in the cytosol [68]. To our knowledge, no AKAPs have been identified in the matrix, to date.

3. cAMP signalling at the outer casing

Mitochondria possess a characteristic dynamic nature, owing to three main processes. First of all, fusion and fission, through which distinct mitochondria join to form a new organelle, or divide into more separate ones. Second, motility, in which mitochondria exploit the microtubule network to migrate and reach specific intracellular sites. Finally, the quality control process, called mitophagy, which eliminates dysfunctional organelles. All these processes are fundamental for mitochondrial and cellular health, and alterations in any of them are associated with severe pathological conditions [41,69]. To ensure the proper control of such vital events, mitochondria developed complex and stringent regulatory mechanisms, that guarantee their function and fine-tuning. One of them relies on reversible PKA-dependent phosphorylation, that participates extensively in the control of several aspects of mitochondrial dynamics.

The OMM is the mitochondrial border, and, keeping solutes over ≈ 5 kDa outside the IMS [70–72], it represents the first filter between the organelles and the cytosol. This outer casing hosts several independent cAMP-driven functional units [73,74], known to regulate mitochondrial fission and fusion [34,41], motility [42,75] and mitophagy [76,77], but also autophagy [78,79], apoptosis [38,80,81] and mitochondrial protein import. The latter has been studied mainly in yeast [82], with some interesting hints also in mammals. Indeed, it was shown in mice that PKA-dependent phosphorylation of mitochondrial precursors, such as GSTA4−4, CYP2B1, CYP2E1 and NDUFS4, increases their association with cytosolic chaperones, eventually promoting import [83–85]. A very recent study [86] indicated, on the contrary, that phosphorylation within or near the mitochondrial targeting sequence of multiple proteins could disrupt their import rates and matrix processing. The authors speculated that dephosphorylation after import would be required for proper processing and maturation of such proteins, a model already proposed for phosphorylated chloroplast precursor proteins [87]. They suggested also that selected mitochondrial proteins could be subjected to the action of cytosolic kinases, including PKA, unveiling a so far underappreciated signalling mechanism, conserved from yeast to plants and to mammals, serving to direct proteins to mitochondria or to alter their import rates [86].

The generation on the OMM of cAMP signaling microdomains has been carefully investigated by employing selectively targeted FRET-based cAMP- and PKA phosphorylation-sensitive sensors. No evidence was obtained of significant differences between the cAMP concentration on the OMM surface and the cytosol [33,88,89]; notwithstanding, local signalosomes on the mitochondrial surface exist and depend on the local expression of several AKAPs, and on the differential localization of phosphatases between the bulk cytosol and the mitochondrial surface [33,88,89].

A number of AKAPs have been reported to tether PKA to the OMM: Rab32 [90], AKAP121 and its isoforms (AKAP149, D-AKAP1 and S-AKAP84) [73], WAVE-1 [91] and AKAP10 (also called D-AKAP2). Despite this remarkable presence, a study exploiting isolated mitochondria attributed to the OMM only 9% of the total mitochondrial PKA activity [92]. However, recent evidence suggests that PKA tethered on the mitochondrial surface responds better to cAMP elevations than its cytosolic counterpart [33,88,89].

AKAP10 was found localized, although not exclusively, at mitochondria, indicating the possible existence of multiple pools and a possible dynamic regulatory nature of this AKAP [93]; however its mitochondrial localization was not confirmed by subsequent studies [94].

The AKAP Rab32 was originally characterized as participating in both mitochondrial dynamics and anchoring of PKA [90,95]. Subsequently, it was found localized at MAMs (Mitochondria-Associated Membranes), the interfaces between mitochondria and endoplasmic reticulum (ER) membranes [96]. There Rab32 is thought to modulate ER Ca^{2+} handling and PKA tethering, impinging on the phosphorylation status of two important (see below) PKA targets, BAD and Drp1, and ultimately, exerting a delaying effect on apoptosis.

AKAP121, the most extensively studied among OMM-associated AKAPs, has a key role in mitochondrial fitness; indeed, when mutated and unable to bind PKA it promotes apoptosis [97], whereas when overexpressed it is protective [98]. In neurons, axonal mitochondria with normal membrane potential ($\Delta\psi$) are transported anterogradely toward the synapse, whereas those with low $\Delta\psi$ are transported back to the cell body [99], where lysosomes are predominantly localized [100]. Recent evidence indicates that AKAP121-tethered PKA is stabilized by PINK1 (PTEN-induced kinase-1) and governs the mitochondrial trafficking in dendrites through the phosphorylation of Miro-2 [101]. Indeed, cAMP actions were previously associated to neuronal mitochondrial retrograde movements, and several proteins involved in mitochondrial transport, as kinesins, dynein and syntaphilin, have been known for years to be phosphorylated by PKA [102]. Accumulating evidence indicates a previously underestimated link between mitochondrial mobility and mitophagy in neurons [103]. One of the AKAP121-tethered PKA targets is Drp1 (dynamin-1-like protein), a GTPase with a strong impact on mitochondrial dynamics. Drp1 is subjected to complex post-translational modifications involving both cAMP- and Ca^{2+}-dependent pathways, with sometimes opposite effects [104]. Recently, Drp1 has been implicated also as a partner of ACTR10 (actin-related protein 10), to promote mitochondrial retrograde transport in axons [105]. Drp1 is in dynamic equilibrium between cytosol and mitochondria, where, once recruited, it polymerizes and promotes fission; however, upon PKA phosphorylation, Drp1 translocation to OMM is inhibited, leaving mitochondrial fusion unopposed, hence promoting mitochondrial elongation [39,106]; on the opposite side, Drp1 dephosphorylation by the Ca^{2+}-activated phosphatase calcineurin results in mitochondrial fission [107]. This is a notable example of the cell-pervading cross-talk between cAMP and Ca^{2+}, which, in this case, exert opposite actions on the mitochondrial shape and, eventually, on many shape-linked processes. Mitochondrial fission is indeed linked to mitophagy and apoptosis [39,107], whereas fusion positively affects mitochondrial bioenergetics [108] and, consequently, several processes, such as neuronal morphogenesis, mitochondrial adaptation to hypoxia [109], and, in general, cell resistance and survival [110,111].

Among the cell survival strategies, a key role is played by autophagy [112], a general self-degradation process put in place at critical times, e.g. limited nutrients, or to clear damaged proteins and organelles. Damaged mitochondria clearing is named mitophagy and represents the mechanism ultimately responsible for mitochondria quality and quantity control. The general (macro) and the specific autophagy forms are linked to mitochondrial shape and dynamics in opposite ways. Macro-autophagy is accompanied by elongation, triggered by PKA phosphorylation of Drp1, a stereotypical response necessary to sustain cellular ATP levels and viability [106]. On the contrary, mitochondrial fission precedes and facilitates mitophagy, which is jointly controlled by PINK1, which accumulates selectively on the OMM of depolarized mitochondria [113] and by Parkin, an E3 ubiquitin ligase recruited by PINK1 [114]. PKA impinges on mitophagy both modulating Drp1 activity [115] and phosphorylating MIC60 and MIC19, components of the MICOS complex (MItochondrial COntact Site and Cristae Organizing System) [116]. Once phosphorylated by PKA, these two proteins destabilize PINK1 from depolarized mitochondria, preventing mitophagy [76]. On the opposite side, if PINK1 is overexpressed specifically at OMM, it phosphorylates AKAP121 altering its PKA association; as a consequence, Drp1 phosphorylation decreases and mitochondria

fragment [77].

Finally, WAVE-1-thetered PKA affects mitochondrial movements [117] and negatively regulates apoptosis, partly through the control of Bcl-2 localization and phosphorylation [118] and by promoting autophagy through the Beclin1/Bcl-2 and Beclin1/PI3K complex-dependent pathways [119].

The links between PKA-dependent phosphorylation of mitochondrial proteins and apoptosis are complex and not completely clarified. For example, PKA anchored to the OMM through AKAP121, WAVE-1, and possibly also Rab32 [90,95], is thought to antagonize apoptosis by phosphorylating and inactivating the pro-apoptotic protein BAD [38,80,120]. An interesting case is represented by glucose- and GLP-1-stimulated beta-cells, in which the rise in cAMP is mediated in part by GPCR-coupled tmACs and in part by Ca^{2+} induced sAC activation [121]. The ensuing cAMP reaches the OMM-tethered PKA, becoming involved in the anti-apoptotic game against BAD.

An opposite, pro-apoptotic effect, of cAMP increase has been proposed during ischemia or acidosis. In this case, the cAMP produced by sAC appears to activate a PKA pool that facilitates the translocation of the pro-apoptotic BAX to mitochondria [122,123,124]. To explain these two opposite effects of PKA-dependent phosphorylation on apoptosis, it can be envisaged that during ischemia or acidosis the PKA pool engaged by sAC is different from that activated by glucose or GLP-1 that inhibit BAD action.

This example highlights the complex role of AKAPs: acting as anchoring platforms, they allow to exploit the same few molecular players to obtain very different and sometimes opposite effects. One could hypothesize that such a setting has been evolutionary favoured as an energy saving solution; indeed, for each single molecular component added, several essential regulatory elements should also be added, exponentially increasing the number of proteins, mRNAs and eventually genes needed. The evolution of tethering platforms appears to allow sparing elements in return for compartmentalizing capacity.

Interestingly, sAC, which is the more divergent, and the more evolutionary ancient among all mammalian ACs [53], does not appear tethered to any AKAP. sAC is unique in being not anchored to plasma membrane, in being found in many different subcellular locations (including sub-mitochondrial compartments) [125] and in being subjected to complex and still poorly known alternative splicing of its mRNA [126] and probably also to post-translational processing [127]. In its longer form, in addition to the classical cyclase domains, sAC includes about 1200 aminoacids, very likely with regulatory functions, the details of which are mostly unknown [127]. This huge regulatory region could be envisaged as coding the necessary domain toolkit to regulate such a freelance enzyme.

As mentioned above, an additional mechanism that allows the establishment of PKA-dependent phosphorylation microdomains depends on the activity of phosphatases. We recently showed [88,89] that, upon indistinguishable increases in cytosolic or OMM cAMP levels in rat cardiac myocytes and primary fibroblasts (elicited by either β-adrenergic receptors or direct ACs stimulation), the response of a PKA phosphorylation-sensitive sensor located on the OMM surface is much higher and sustained than that of the same probe free in the cytosol. We demonstrated that this localized microdomain of high PKA-dependent phosphorylation depends on a lower dephosphorylation rate on the OMM than in the cytosol, due to limited access of phosphatases to OMM targets. These data unravel a novel mechanism that can generate a functional cAMP-activated microdomain, independent from second messenger heterogeneity (Fig. 1).

4. cAMP signalling in the core

4.1. cAMP and PKA in the IMS

The OMM is characterized by high permeability to molecules of molecular weight up to about 5 kDa [70–72], due to the presence of a non-selective channel named VDAC, while even small proteins such as cytochrome *c* (~12 kDa) are impermeant, except during exceptional conditions such as the opening of the so called permeability transition pore (PTP), a huge mitochondrial channel whose molecular components only recently began to emerge (see *e.g.* [128,129]). Being smaller than 5 kDa, cAMP produced in the cytosol should have free access to the IMS. On the contrary, both the regulatory (R) and the catalytic (C) subunits of PKA should be excluded from the IMS, given the absence of classical mitochondrial targeting sequences in these proteins. Evidence for the presence of PKA subunits and of AKAPs in the IMS has however been reported. In particular, it has been suggested that the AKAP SKIP is localized in the IMS, specifically tethering PKA type I and thus facilitating phosphorylation of ChChd3 [67,130]. This latter protein is localized at the IMM surface facing the IMS [131] and participates in the MICOS complex [132], which is important for the maintenance of cristae integrity. Another IMM/IMS protein that has been suggested to function as an AKAP is OPA1, a dynamin-related GTPase essential for normal mitochondrial morphology; OPA1 was found also associated

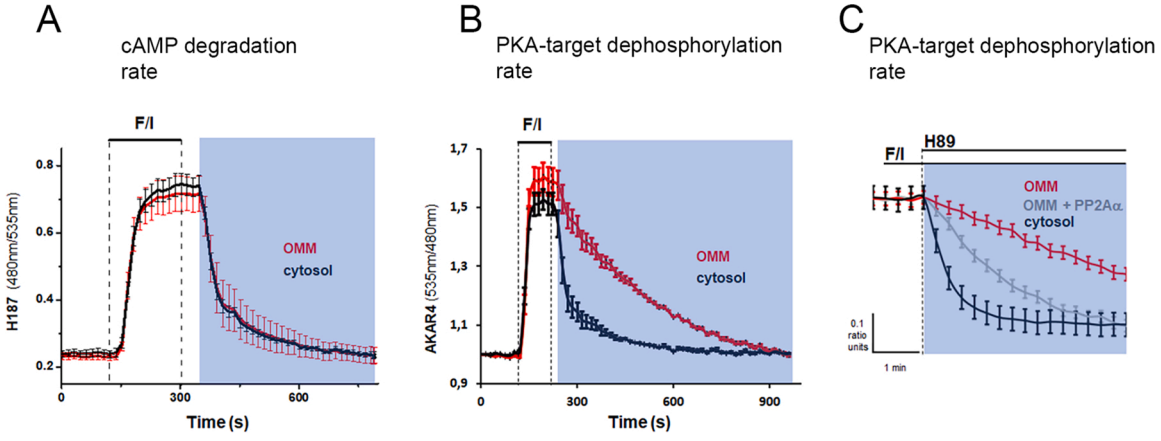

Fig. 1. Phosphatases are responsible for the existence of different microdomains of PKA phosphorylation between the cytosol and the mitochondrial surface: (**A**) Maximal cAMP levels (likely leading to sensor saturation) were achieved using high levels of forskolin (to activate ACs) in combination to IBMX (to block PDEs) (F/I). When these drugs were rinsed away the rate of PDE-dependent cAMP degradation was revealed and was indistinguishable between the cytosol and the OMM. Despite that, the rate of dephosphorylation of a PKA-dependent phosphorylation sensitive sensor, which depends on phosphatases, is much slower at the OMM (**B**). This is due to limited access of phosphatases to the PKA targets present at the OMM. Indeed, the overexpression of a phosphatase increases the dephosphorylation rate at the OMM (**C**). Such a mechanism generates a functional cAMP/PKA-dependent microdomain at the mitochondrial surface, although in the absence of different cAMP levels from the rest of the cell. For details, see Burdyga et al. (2018).

with lipid droplets (LDs), and here functioning as an AKAP [133,134].

It should be stressed that the experimental evidence supporting the localization of PKA in the IMS is limited and largely based on subcellular fractionation experiments. Moreover, SKIP, suggested to function as an AKAP in the IMS, is primarily a cytosolic protein [68] and neither the mechanism that allows its penetration across the OMM nor the % of the total SKIP within mitochondria have been established. In conclusion, the mechanism allowing PKA localization in the IMS and its functional role remain somehow undefined, and more convincing evidence are necessary to support or exclude a PKA role in this compartment.

4.2. cAMP in the matrix

The existence of a cAMP axis located within the matrix and modulating mitochondrial functions is an appealing possibility, supported by a number of recent experimental data. At the same time, contradictory results argue for or against the existence of a matrix-located PKA and the controversy is still unsolved. We will discuss first the major recent findings related to the mechanism of cAMP homeostasis within the matrix and the main functional effects modulated by changes in its concentration. We will finally address the possible molecular targets of matrix cAMP and the evidence in favour and against the localization of PKA within mitochondria.

For many years, the general consensus was that cAMP did not have any role in the mitochondrial matrix; this belief was largely due to both the plasma membrane exclusive localization of classical tmACs and the supposed impermeability of the IMM towards the negatively-charged cytosolic cAMP. In the last decade, however, a number of reports suggested the existence of an autonomous cAMP signalling cascade inside mitochondria. The first study which attempted to directly test the dynamics of cAMP in the mitochondrial matrix of living cells using a fluorescent biosensor concluded that cAMP produced in the cytoplasm rapidly diffuses into the organelle matrix [135]. Unfortunately, in our hands this biosensor largely mis-localized in the cytosol, raising serious doubts about this conclusion [32]. A few years later, Acin-Perez et al., based on data obtained in isolated mitochondria, suggested that, while the IMM is impermeable to cytosolic cAMP, the organelles are endowed with an AC-cAMP-PKA-PDE signalling cascade, wholly contained in their matrix [31]. They also suggested that phosphorylation by matrix PKA of a cytochrome *c* oxidase (COX) subunit modulates the activity of COX. They proposed that cAMP is produced in the matrix by a mitochondrial form of sAC, sensitive to bicarbonate, either added exogenously or derived from the carbon dioxide produced by the tricarboxylic acid (TCA) cycle [31]. In a series of subsequent studies, the same group identified PDE2A2 as the resident cAMP-degrading enzyme [136], and Ser 58 of COX subunit IV-1 as the residue involved in the PKA-mediated tuning of O_2 consumption and ATP production [43]. A similar CO_2-sAC-cAMP-PKA axis regulating normoxic COX activity has been subsequently reported also in yeast mitochondria [137]. Using a newly generated FRET-based cAMP biosensor, that specifically and efficiently localizes in the mitochondrial matrix, we directly demonstrated in living cells that cytosolic cAMP does not diffuse from cytosol into the organelles, but it can be generated in the matrix by sAC [32,33], and degraded by a phosphodiesterase sensitive to IBMX and to a PDE2 specific inhibitor [32]. In addition, we uncovered that mitochondrial matrix cAMP (mt-cAMP) increases not only in response to bicarbonate, but also, and synergistically, upon mitochondrial Ca^{2+} elevations [32], accordingly with the known *in vitro* properties of sAC [138]. Then, using a mitochondria-targeted luciferase and a set of genetic and pharmacological tools, we directly showed in live cells that mt-cAMP contributes positively to the regulation of mitochondrial ATP production, in line with Acin-Perez et al. [32].

A distinctive and key feature of cytosolic signal transduction is the convergence of a very large variety of extracellular (via membrane receptors) and intracellular (via metabolic intermediates) stimuli onto a limited number of intracellular second messengers, *i.e.* Ca^{2+}, cAMP, cGMP, IP_3, NO and a few others. This complexity requires an elaborate signalling code, relying not only on concentration, but also on complex spatio-temporal dynamics of the second messenger, eliciting different outcomes depending on its oscillation frequency and subcellular compartmentalization. A similar temporal signalling code might work also in the mitochondrial compartments. For instance, a single Ca^{2+} transient, as elicited by ATP stimulation of HeLa cells, induces a transient mt-cAMP increase, whereas a more prolonged Ca^{2+} increase, as that induced by the same stimulus but in conditions of blunted matrix Ca^{2+} efflux, induces a more persistent mt-cAMP response. In cardiomyocytes, increased frequency and amplitude of the spontaneous Ca^{2+} oscillations in the cytosol and mitochondria elicit mt-cAMP rises that, contrary to the oscillatory Ca^{2+} changes, do not oscillate, but increase slowly and eventually reach a plateau level [32] (Fig. 2). This evidence unveils that the intra-mitochondrial cAMP machinery is capable of integrating an oscillatory Ca^{2+} signal into a prolonged cAMP increase [32,37], indicating mitochondria as integrators of signals differentially encoded by different second messengers.

Altogether, these results raised more questions than they answered. For example, endogenous CO_2 produced by increased TCA cycle flux has been suggested to be insufficient to increase mt-cAMP levels [139]; the localization of PDE2A2 in the matrix has been questioned, and it was rather proposed that it is exclusively localized in the IMS [140]. Other PDEs were suggested to localize in mitochondria such as PDE8A [141,142] and Prune, discovered in *Drosophila* [143]. In the latter case, its matrix localization was unveiled exploiting an elegant Bimolecular Fluorescence Complementation approach (BiFC). However, the matrix targeted FRET-based cAMP sensor used in this study responded well to cytosolic cAMP increases, suggesting a possible partial mistargeting of the sensor in these experiments.

4.3. PKA and Epac1 in the matrix

While in the last years data from a number of groups confirmed and extended the conclusion of the impermeability of IMM to cAMP and of the existence of an endogenous cAMP signalling toolkit within the mitochondrial matrix, the localization (and consequently the role) of PKA within this compartment remain highly controversial. Here we briefly mention the major evidence against and in favour of PKA localization and on its role within the mitochondrial matrix.

Traditionally, the main arguments against intramitochondrial PKA leaned on the fact that neither the C nor the R subunits of PKA contain a classical mitochondrial targeting sequence; moreover, the classical paradigm establishes that, for PKA to work properly, the C and R subunits must be present in identical concentrations, and this has never been proven in the matrix. Finally, a strong argument has been recently provided by Lefkimmiatis et al., who demonstrated that an increase in mt-cAMP does not induce any detectable phosphorylation of an artificial PKA substrate localized in the matrix [33]; the same artificial substrate, however, is rapidly phosphorylated if a Cα subunit targeted to the matrix is expressed.

In support of a possible matrix localization of PKA, despite the absence of classical targeting sequences in either C or R subunits, militates the fact that proteins can be targeted to the different mitochondrial compartments by mechanisms other than the classical one [144]; thus, one could envisage that both C and R subunits of PKA (and perhaps also AKAPs), have co-evolved one of these mechanisms to be targeted to the IMS/matrix; this possibility, however, has not been demonstrated and it remains at the moment just a speculation. Electron microscope evidence for the matrix localization of the C subunit has been repetitively presented [145–147]. On the other hand, *in vitro* experiments in which isolated COX was incubated with PKA, cAMP and radiolabeled ATP, resulted in the phosphorylation of several COX subunits, demonstrating that potentially PKA can phosphorylate COX peptides both on the IMS and matrix side [148,149,158,150–157]; moreover several groups have provided evidence supporting PKA-dependent phosphorylation of

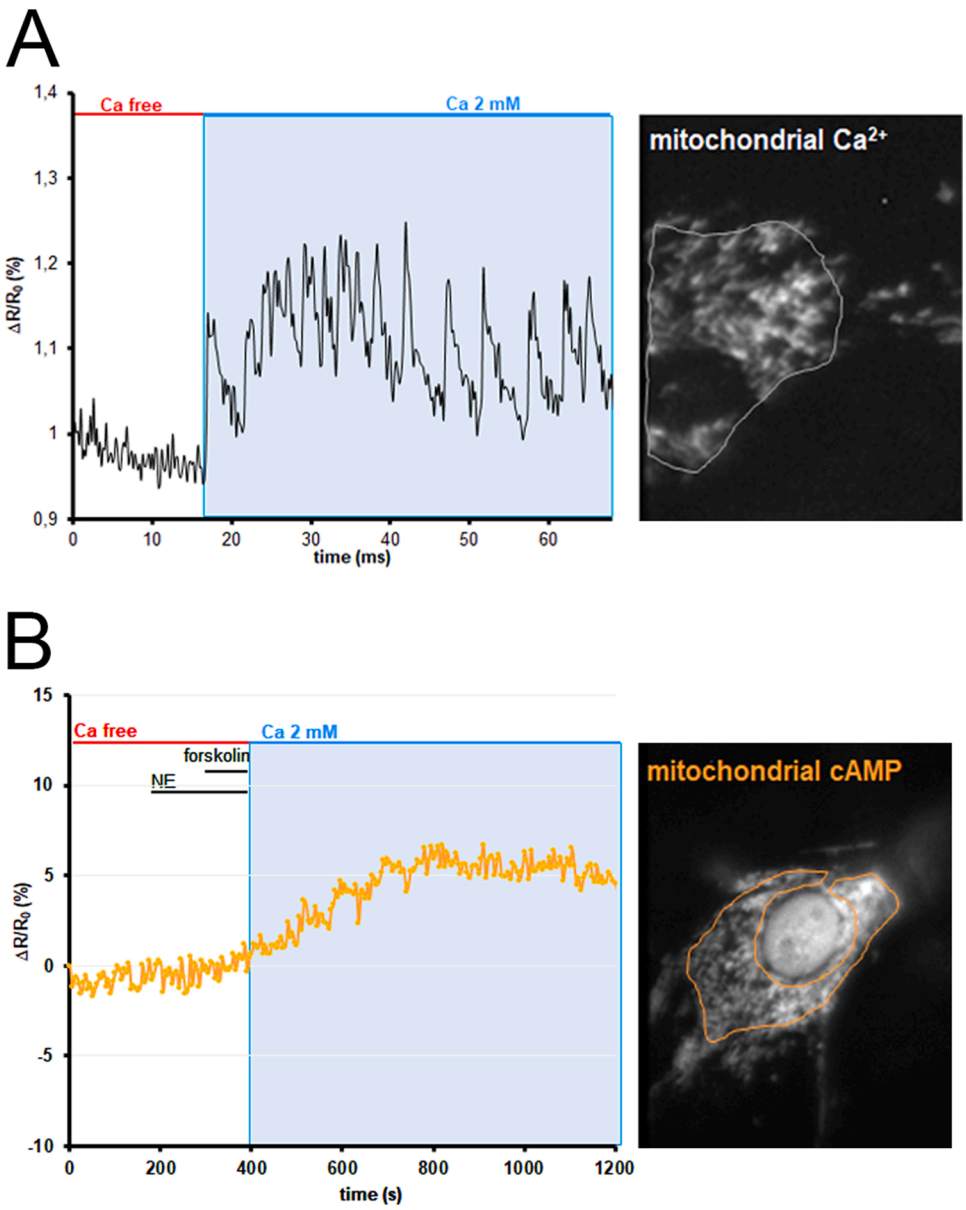

Fig. 2. Mitochondria can integrate an oscillatory Ca^{2+} signal into a prolonged cAMP increase: In the presence of extracellular Ca^{2+}, cardiomyocyte mitochondria uptake and release Ca^{2+} on a beat-to-beat basis. **(A)** Representative measures of Ca^{2+} kinetics in the mitochondria of a neonatal cardiomyocyte, first in the absence and then in the presence of external Ca^{2+}. In the latter condition, mitochondria display their typical oscillatory Ca^{2+} pattern, which is reflected in a sustained increase in mt-cAMP levels (**B**). These data suggest that Ca^{2+} oscillations are integrated by a mechanism that regulates mt-cAMP production. Of note, in the absence of Ca^{2+} neither adrenergic stimulation with norepinephrine (NE), nor direct activation of ACs with forskolin, both increasing cytosolic cAMP, resulted in mt-cAMP increases, illustrating that cytosolic cAMP does not enter mitochondria. For details, see Di Benedetto et al. (2013).

matrix or IMM proteins in isolated mitochondria of yeast, mammalian cell lines and tissues [145,146,161–168,148–151,155,156,159,160]. Most of these data, however, were based on the wrong assumption that cAMP could penetrate across the IMM. For example, in Sardanelli et al. [151] intact freshly isolated mitochondria incubated with cAMP (not permeable to the matrix), its analogue db-cAMP (membrane permeable) or PKA catalytic subunits gave similar phosphorylation patterns, suggesting that the PKA moiety involved (and/or the targets) were not localized in the organelle matrix. Finally, Prabu et al. [157] reported that, in *in vitro* perfused rabbit hearts after ischemia, there is a massive phosphorylation of COX subunits. Using the same approach they also identified by mass spectrometry the phosphorylated residues [158]. However, these sites not only lack a classical PKA consensus sequence but most of the conclusions were based on the use of the effective (but not selective [169]) PKA inhibitor H89.

A few more recent papers support the existence of PKA in the mitochondrial matrix, in particular: i) phosphorylation of COX IV-1 involves a classical PKA consensus sequence [43]; ii) human (and yeast) TFAM, essential for mitochondrial DNA synthesis, expression and packaging, has been demonstrated to be phosphorylated by PKA *in vitro* [170] [171] or in intact cells by a transfected PKA C-subunit targeted to the mitochondrial matrix [170]. Notably, however, no direct evidence demonstrating that in intact (non transfected) cells TFAM phosphorylation depends on a PKA localized within mitochondria was provided. A recent study attempted to identify the interactome of PKA in the mitochondrial matrix. The authors overexpressed a matrix-targeted C-subunit and used a combination of proximity-dependent biotinylation, LC–MS/MS analysis and *in silico* phospho-site prediction, to identify 21 mitochondrial proteins potentially interacting with mt-PKA [172]. Noteworthy is that a number of previously suggested targets of matrix PKA (e.g. COX IV-1 [31,43], IF1 [173], NDUFS4 [149,174]) are missing.

It must be stressed that, with few exceptions (PDH and BCKDK kinases and phosphatases [175,176]), the kinases and phosphatases acting in the matrix are poorly characterized, and it is still unclear to what extent phosphorylation of mitochondrial matrix proteins occurs in the matrix itself or outside of mitochondria before or during import [86], although at least TFAM has been shown to be phosphorylated inside mitochondria [170].

In summary, although there are some evidence supporting the presence of PKA in the mitochondrial matrix (and IMS), the few data

obtained in intact living cells are unclear or even contradictory [32,33,170]. Altogether these findings indicate that PKA potentially can phosphorylate proteins located in the matrix or IMS, but at the same time do not exclude that in intact cells an enzyme distinct from PKA could be the cAMP-sensitive kinase of the mitochondrial matrix/IMS. This "non-canonical" PKA, if it exists, may share with cytosolic PKA some, but not all, features. We advanced this hypothesis when faced with the result that the mt-cAMP-dependent increase on mitochondrial ATP production was inhibited by a competitive inhibitor of cAMP binding to PKA and, importantly, by an overexpressed matrix-targeted PKI (the most specific PKA inhibitor). However, ATP production was not activated by membrane permeable cAMP analogs that are potent activators of the cytosolic enzyme [32]. The fact that PKA-phosphorylated residues on COX subunits I, IV, and Vb, identified by mass spectrometry, do not display the classical PKA consensus site [157], in conjunction with the failure of phosphorylation of a matrix localized PKA activity sensor upon mt-cAMP rise [33], and with the lack of evidence for interaction between a matrix-targeted PKA and any of the matrix proteins which have been previously found phosphorylated upon cAMP increase [172], might be interpreted along the same line.

The situation with matrix Epac1 is simpler than that of PKA. Epac1 in fact was discovered in 1998 [63,177] and the possibility of its presence in the matrix was first proposed by Qiao et al. [178], who also identified its mitochondrial targeting sequence. Surprisingly, this finding was not further explored for several years; however, once the existence of an intramitochondrial cAMP pool was unveiled, not only the interest in matrix Epac1 (mt-Epac1) pool increased, but it has been clearly shown that this protein mediates, at least in part, the effects of mt-cAMP [45,179,180]. In the heart, the presence in mitochondria of Epac1, as well as of that of the most active, truncated form of sAC (tsAC), has been directly demonstrated. Here a major role of this mitochondrial pathway would be protective, limiting mitochondrial Ca^{2+} entry through the MCU, and preventing the deleterious consequences of mitochondrial Ca^{2+} overload, such as the dissipation of $\Delta\Psi$ and the induction of PTP opening [179].

In the setting of ischemia/reperfusion (I/R) injury, instead, mt-Epac1 has been reported to have a deleterious action through two different mechanisms, favouring mitochondrial Ca^{2+} overload and increasing ROS effects [180]. The authors proposed that: i) I/R elicits cAMP production by sAC, that activates mt-Epac1, that in turn, via CaMKII, favours ER/mitochondria Ca^{2+} transfer, mitochondrial Ca^{2+} overload and finally PTP opening [180]; ii) CaMKII, by phosphorylating and inhibiting IDH2 activity, reduces NADPH production, and, accordingly, the antioxidant capability of cardiomyocytes [180].

Other groups have provided evidence for CaMKII association with mitochondria (or even intramitochondrial localization of the enzyme) [181–183] and, at variance with the work of Wang et al. [179], suggested that CaMKII-dependent phosphorylation increases mitochondrial Ca^{2+} influx via activation of the MCU complex [182–184]. The role of CaMKII in regulating mitochondrial Ca^{2+} uptake, however, has been recently very seriously criticized [185] and it has been demonstrated that knocking-out CaMKII in the heart has no effect on MCU-dependent Ca^{2+} uptake, either in isolated cardiac mitochondria, or in intact cardiomyocytes [186].

4.4. Mitochondrial cAMP levels and organelle functions

Finally, the most general question is the functional role of such a complex autonomous mt-cAMP signalling machinery, that appears to include all the molecular components necessary to convey different cAMP driven signals, albeit not an AKAP.

Although the effectors are still uncertain (Epac1, PKA?, another kinase?), a general consensus exists on the regulatory effect that mt-cAMP exerts in metabolic regulation, in particular mitochondrial respiratory chain activity and ATP production (see above).

Additional evidence supporting this metabolic role of mt-cAMP has been obtained recently. For example, sAC-KO MEFs are characterized by a major defect in OXPHOS activity; to partially compensate this deficit, the level of OXPHOS proteins is strongly increased [187]. The knock-out of the first ATP-binding site in the sAC gene, which should completely inactivate sAC (but this is a debated point; see [188–190]), was found to impair mitochondrial energy metabolism as well as growth in galactose medium, and to induce a shift towards glycolysis by causing a decline in the ETC complex I (CI) activity, COX activity, $\Delta\Psi$ and ATP production. On the whole, these sAC-KO MEFs display an energy deprivation response, as demonstrated also by increased AMP dependent Kinase (AMPK) phosphorylation and upregulation of PCG1α and NRF1, that increase mitochondrial biogenesis. Restoring sAC expression exclusively in the mitochondrial matrix rescued OXPHOS activity, normalized energy production and hampered mitochondrial biogenesis, suggesting that these phenotypes are specifically regulated by intramitochondrial sAC [187]. In line with this, the silencing of sAC resulted in decreased $\Delta\Psi$ [179], and sAC inhibition caused CI activity defects [191]. Notably, however, silencing and inhibition affect all forms of cellular sACs; their influence on mitochondrial function does not necessarily imply the action of mt-cAMP. In addition, as a cautionary note, it should be stressed that the sAC inhibitor KH7 employed in many of these experiments, and largely utilized in the past as well as currently (see, for example [31,191,192]), has been demonstrated to dramatically decrease the $\Delta\Psi$ and to acidify matrix pH [32,193,194], effects that *per se* impinge on normal mitochondrial functionality. Therefore, the conclusions drawn from papers exploiting KH7 as evidence for a role of mt-cAMP should be assessed prudently.

It has been proposed that, in cardiomyocytes, abnormal mt-cAMP/PKA signalling may participate in sepsis-induced mitochondrial dysfunction [195]. These authors claim that sepsisinduced OXPHOS defects can be attributed to abnormal mt-cAMP/PKA signalling through reduced Ser-58 phosphorylation of COXIV-1, and that inhibition of PDE2 improved both respiratory control ratio of cardiac fibers and myocardial efficiency in septic hearts [195]. However, their results were obtained exploiting exclusively pharmacological tools to inhibit PKA, PDE2 and sAC (including the above cited KH7), which necessary implies, once again, that the cAMP handled is not exclusively the intramitochondrial one.

Another recent work proposed that PKA phosphorylates ATPase Inhibitory Factor 1 (IF1) and inactivates its capacity to bind and inhibit mitochondrial ATP synthase in situations that compromise OXPHOS [173]. Dephosphorylated IF1 is present in hypoxia and in human carcinomas; upon its interaction with ATP synthase, both the synthetic and hydrolytic activities of this enzyme are inhibited. Thus, the phosphorylation status of IF1 regulates the flux of aerobic glycolysis and ATP production through OXPHOS in hypoxia and during the cell cycle [173]. Also in this work, however, the tools employed to manipulate the cAMP signalling cascade were exclusively pharmacological, and, given the undisputed matrix localization of IF1, it was assumed (although not directly tested) that phosphorylation of IF1 was due to a PKA localized in the mitochondrial matrix.

The first evidence for a cell-specific functional role of mt-cAMP was found in aldosterone-producing adrenal glomerulosa cells, where the involvement of mt-cAMP helped to explain an apparent paradox. In these cells, both angiotensin II (AngII) and corticotrophin (ACTH) increase aldosterone secretion, whilst acting in opposite directions on the average intracellular cAMP level. It was shown that, albeit AngII decreases cytosolic cAMP, it induces a cytosolic and mitochondrial Ca^{2+} increase that, through stimulation of mitochondrial sAC, results in a mt-cAMP rise [196]. Subsequently, the same group reported that, in addition to mitochondrial Ca^{2+} impinging on mt-cAMP, the reverse is also true: inducing a reduction of mt-cAMP formation resulted in a partial inhibition of mitochondrial Ca^{2+} accumulation; on the contrary, the treatment with a membrane-permeable cAMP analogue, the addition of a PDE2 inhibitor or the overexpression of sAC specifically in the mitochondrial matrix, increased Ca^{2+} uptake into the organelle. This

enhancing effect of mt-cAMP on Ca^{2+} uptake was independent from both the mitochondrial ΔΨ and Ca^{2+} efflux, but was sensitive to Epac1 activators/inhibitors [45]. The authors suggested the existence within mitochondria of a positive-feedback loop controlling mitochondrial Ca^{2+} handling; according to their model, Ca^{2+} triggers the formation of mt-cAMP that, in turn, recruits Epac1 and further enhances Ca^{2+} uptake. Although excessive function of this system may lead to cell death, it may have a role in emergency situations, when a rapid cellular response is required.

A unique mechanism was recently unveiled in hippocampal mitochondria through which mt-cAMP would regulate not only ATP synthesis and respiration, but also memory formation [192]. These authors proposed that the stimulation of cannabinoid-type 1 receptors (CB1R), found by them and by other groups localized on the OMM facing the IMS [192,197–200], inhibits the intra-mitochondrial sAC through the release of a Gαi protein associated with such receptors, thus inducing a decrease of mt-cAMP. This, in turn, would dampen the PKA-dependent phosphorylation of specific subunits of the ETC, eventually leading to decreased cellular respiration and an amnesic effect [192]. A further development of such mitochondrial CB1R signalling was recently reported by the same group, and it suggests that activation of mt-CB1R in astrocytes reduces PKA-dependent phosphorylation of mitochondrial complex I subunit NDUFS4, disrupting its assembly and activity [174]. This interesting signalling mechanism, however, has been heavily criticized (see for example [201]) and contains unexplored as well as contradictory points. For example: how could a Gαi bound to the inner surface of OMM reach and inhibit mt-sAC that is located in the matrix? How could Gαi inhibit mt-sAC which is the "not-G-protein-sensitive" adenylate cyclase *par excellence*? In which sub-mitochondrial compartment is PKA responsible for the ETC subunits phosphorylation? What is the mechanism of CB1R targeting and insertion in the OMM? At this stage, we believe it is fair to say that this mechanism remains fascinating but highly controversial.

CB1R is not the only GPCR found in mitochondria, and reports of mitochondrial localization of several other receptors (with associated G proteins) of this family have been recently published (purinergic [202], for serotonin [203], angiotensin II [204] and melatonin [205]). As for CB1R, additional data appear necessary to confirm these findings and their functional relevance.

Unlike for other mitochondrial functions, our understanding of the organelle cAMP signalling is still largely incomplete and sometimes even contradictory. For example, the localization of PKA within the matrix or the IMS is still debated and, if PKA is present within mitochondria, the mechanism that allows the post-translational import of the protein has not been identified; the nature of the intramitochondrial phosphatases that terminate the kinase-dependent phosphorylation is still largely unsolved and contradictory data are available as to the PDE(s) present within the matrix and IMS; the localization and targeting mechanism of receptors linked to cAMP production/degradation is a fascinating, but still debated finding. In summary, the study of the mitochondrial cAMP signalling toolkit is still in its infancy and novel approaches and experimental tools are necessary to solve the puzzle.

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CRediT authorship contribution statement

Giulietta Di Benedetto: Writing - original draft, Writing - review & editing. **Konstantinos Lefkimmiatis:** Writing - review & editing. **Tullio Pozzan:** Writing - review & editing.

Declaration of Competing Interest

None.

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