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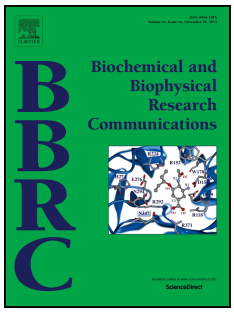

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TITLE

Shaping mitochondrial dynamics: the role of cAMP signalling

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ABSTRACT

In recent years, our idea of mitochondria evolved from “mere” energy and metabolite producers to key regulators of many cellular functions. In order to preserve and protect their functional status, these organelles engage a number of dynamic processes that allow them to decrease accumulated burden and maintain their homeostasis. Indeed, mitochondria can unite (fusion), divide (fission), position themselves strategically in the cell (motility/trafficking) and if irreversibly damaged or dysfunctional eliminated (mitophagy). These dynamic processes can be controlled both by mitochondrial and cellular signalling pathways, hence allowing mitochondria to tune their function to the cellular needs. Among the regulatory mechanisms, reversible phosphorylation downstream the cyclic AMP (cAMP) signalling cascade was shown to deeply influence mitochondrial dynamics. This review explores the emerging evidence suggesting that cAMP is a key player in the orchestration of mitochondrial fusion/fission, motility and mitophagy, extending the repertoire of this second messenger, which is now recognized as a major regulator of mitochondrial homeostasis.

Keywords

Mitochondria; cAMP; PKA; mitochondrial dynamics; mitophagy

1.Introduction

It is unnecessary to emphasize the importance of mitochondria for the eukaryotic cell. Indeed, these semi-independent organelles are entrusted with some of the most important cellular functions, such as energy generation and cell death regulation [1]; in addition, mitochondria generate metabolites and participate in cytosolic proteostasis [2]. All these actions strongly link mitochondrial function to cellular homeostasis. Being at the core of the cellular needs, it is imperative that these organelles continuously communicate with their host cell. In fact, in order to achieve a high level of communication with the other cellular components, mitochondria evolved into signalling hubs integrating themselves in virtually all the information networks that ensure cellular homeostasis. Thanks to the information gathered, mitochondria are able to adapt to the varying cellular needs, but also, at the same time, can communicate to the cell their bioenergetics status.

The information flow is continuous; indeed mitochondria can formulate important "messages" and deliver them to the cytosol to be decoded. For instance, release of cytochrome c from the mitochondrial inter-membrane space (IMS) to the cytosol is interpreted by the cell as a "death directive" and ultimately results in apoptosis [3], while an increase in the release of mitochondrial reactive oxygen species (ROS) can trigger specific transcription signatures in response to hypoxia [4-6]. On the other hand, and in order to closely assess cellular fitness, mitochondria have developed molecular "antennas" that allow them to intercept messages originating from the extracellular space or directly from the cell. Examples of this mechanism are the two main information-bearing molecules, calcium (Ca^{2+}) and cyclic AMP (cAMP). Indeed, albeit to different extent, mitochondria actively sense and participate in the signalling cascades of these second messengers.

At the steady state, mitochondrial Ca^{2+} levels are similar to those of the cytosol (i.e. ≈ 100 nM); however, these organelles are able to sense and uptake Ca^{2+} thanks to a multiproteic machinery, at the core of which is the 40 kDa mitochondrial Ca^{2+} uniporter (MCU) [7-9]. In addition, mitochondria can release Ca^{2+} back into the cytosol *via* efflux channels, such as the xNa^{+}/Ca^{2+} and the H^{+}/Ca^{2+} exchangers [7, 10]. Thanks to these characteristics, Ca^{2+} evolved to become a communicatory currency between mitochondria and their host, and is used to exchange information that influences the function of both sides. The effects of mitochondrial Ca^{2+} can be beneficial or detrimental, depending on the levels that Ca^{2+} reaches within the matrix [7, 10]. For instance, elevation of mitochondrial Ca^{2+} can trigger a beneficial increase in mitochondrial ATP production [10, 11]. However, if the levels of Ca^{2+} become too high, mitochondria may enter a state of increased permeability (termed permeability transition) that can lead to dissipation of their membrane potential and irreversible damage that eventually kills the host cell [12]. On the other hand, mitochondria are also major regulators of Ca^{2+} signalling. These organelles significantly influence intracellular Ca^{2+} levels by buffering it, while, by releasing Ca^{2+} previously accumulated they contribute to the generation of functionally distinct Ca^{2+} microdomains.

The relation of cAMP to mitochondria is not less complex than that of Ca^{2+}, and is certainly more debated. Mitochondria can “sense” cytosolic cAMP at their outer membrane (OMM) and IMS, however cAMP generated in the cytosol cannot permeate the inner mitochondrial membrane (IMM) to reach the innermost mitochondrial compartment [13, 14]. In fact, cAMP in the matrix is generated by a mitochondrial version of a soluble adenylyl cyclase (sAC), in response to metabolic stimuli [15-17]. Consequently, based on the source of cAMP, mitochondria host two distinct cAMP cascades, one that responds to cellular stimuli and another, confined in the matrix, that appears independent from the cytosol [18]**.** Each of these pathways has been associated with the regulation of distinct functions and may

differently affect mitochondrial homeostasis. cAMP in the matrix (mt-cAMP) was initially associated with the regulation of oxidative phosphorylation (OXPHOS) [16, 17, 19], albeit with some discordances, likely depending on different experimental procedures and reagents employed [20]. Nevertheless, as we will discuss later, recent experimental evidence suggests that the roles of mt-cAMP go beyond the control of OXPHOS. On the other hand, the cAMP cascade hosted at the OMM is involved in the control of programmed cell death and in the regulation of mitochondria dynamics [13, 21]. In line with their role in regulating Ca^{2+} levels, mitochondria were recently suggested to participate in the regulation of cAMP diffusion through a debated mechanism [22, 23]; furthermore, it remains unknown whether these organelles are able to modulate cAMP levels by releasing messenger produced in the matrix.

Four main processes are responsible for the characteristic dynamic nature of mitochondria: a) *fusion*, the process through which distinct mitochondria join to form a new organelle; b) *fission,* the opposite of fusion, where a mitochondrion divides into separate organelles; c) *motility*, where mitochondria engage the microtubule network to be transported to specific intracellular sites; and d) *mitophagy*, the process through which dysfunctional mitochondria are eliminated. These dynamic behaviours are extremely important for mitochondria and cellular health and, expectedly, alterations of all four processes have been associated with severe pathological conditions [21, 24]. Given the importance of mitochondrial dynamics, it is not surprising that mitochondria and host cells developed a number of multi-layered regulatory mechanisms in order to ensure the fine-tuning of these processes. Amongst these mechanisms, reversible phosphorylation downstream cAMP has been proposed to participate, at least to some extent, in the control of virtually all the actions that compose mitochondrial dynamics. In this review, we discuss how the cAMP signalling cascade regulates mitochondrial fusion, fission, mitophagy and

motility, showcasing the players and possible therapeutic possibilities that emerge by the crossing of an ancient organelle with an equally ancient second messenger.

2. cAMP machinery

Intracellular cAMP concentrations are determined by the balance between the processes of synthesis, degradation, and export from the cell. Ten distinct adenylyl cyclases (ACs), nine transmembrane (tmACs) and a soluble one (sAC), are responsible for cAMP production in mammals [25-27]. To contrast their actions, there are the phosphodiesterases (PDEs), a class of enzymes constituted by 11 families, eight of which have the ability to hydrolyse cAMP [28, 29]. Finally, albeit somewhat underappreciated as regulatory modality, cAMP can be exported from the cell *via* a number of ATP binding cassette (ABC) proteins, in particular the multi-drug resistance proteins (MRP) MRP4 and MRP5 [30]. Both PDE-dependent cAMP degradation and MRP-related cAMP export counteract cAMP synthesis, and are crucial for the maintenance of low cAMP levels in resting cells and for the termination of the cAMP cascade in stimulated ones.

The cAMP pathway is usually triggered by the activation of ACs, followed by cAMP diffusion and binding to its receptor proteins. To date, a number of cAMP effectors have been identified: cyclic-nucleotide-gated (CNG) channels were among the first to be identified, while the members of the Popeye-domain containing family [31, 32] are the newest discovered. Nevertheless, despite intense efforts to identify novel cAMP-binding proteins, it is widely accepted that the major cAMP effectors are the exchange proteins directly activated by cAMP (Epac) and, most importantly, protein kinase A (PKA) [33].

PKA is a serine/threonine-specific kinase responsible for most of the cellular functions induced by cAMP. Indeed, cells rely on the cAMP/PKA axis for the control of many,

(sometimes contradictory) tasks, raising the need for a regulatory network that would confer specificity to the actions of this soluble molecule. In order to achieve specificity of action, the cAMP signalling pathway is organised into microdomains, i.e. spatially defined functional units that respond independently to cAMP elevations. Usually, these domains are built around an A-kinase anchoring protein (AKAP), serving as a scaffold, and use PKA as effector [33, 34]**.** Mitochondria, amazingly, host more than one fully independent cAMP microdomains. Hereafter we will provide a brief description of the cAMP signalling cascades hosted at different mitochondrial compartments.

3. cAMP signalling at the mitochondrial core

A paramount characteristic of mitochondria is their strict compartmentalization. These organelles present several compartments, and at least three of them, the OMM, the IMS and the mitochondrial matrix, contain distinct cAMP signalling microdomains.

Nearly a decade ago, the group of Giovanni Manfredi, using classic biochemical approaches, made the important observation that cAMP produced in the cytosol is unable to permeate the IMM and to reach the matrix, and proposed that cAMP signalling in this compartment is maintained by a resident form of sAC and a local pool of PKA [16]. Later, two separate studies using matrix-specific cAMP-sensitive FRET-based sensors, confirmed that cytosolic cAMP cannot enter the inner mitochondrial compartment [17, 18]**,** except in particular conditions such as mitochondrial permeability transition [18]. A similar cAMP pathway, confined to mitochondria, was later discovered also in yeast [35]. In contrast to these findings, Zhang and colleagues proposed that, in *Drosophila*, cAMP produced in the cytosol can reach the mitochondrial matrix unopposed, providing evidence of direct communication between tmACs and matrix cAMP effectors [36]. These findings raise the challenging question of how the negatively charged cAMP is able to overcome

the opposing force of the mitochondrial membrane potential (≈180 mV, negative inside), opening the exciting possibility of a cAMP transporter located in the IMM. Therefore, it would appear that in *Drosophila,* where sAC is not expressed and consequently a matrix cAMP source is absent, mitochondria respond to cytosolic cAMP and lost their ability to generate cAMP according to their needs in a cell-independent manner.

Recently, using a mitochondrial matrix localized FRET-based PKA activity sensor, we proved that, contrary to the original observation by Acin-Perez et al. [16], the endogenous PKA activity in this compartment is undetectable. Moreover, several groups documented the presence of Epac1, the other major cAMP effector, in the mitochondrial matrix, further fuelling the debate on the identity of matrix-resident cAMP binding proteins. Importantly, these studies attributed to Epac1 activity most of the cAMP-dependent mitochondrial responses [37-39].

The IMM and OMM define the IMS, another domain hosting the components needed for a functional cAMP-signalling cascade that can be fuelled by cytosolic cAMP, freely permeating the OMM. In line with a classical cAMP microdomain, the IMS contains an AKAP, called sphingosine kinase-interacting protein (SKIP), which specifically tethers PKA type I, the most cAMP-sensitive between the PKA isoforms [40]. SKIP mediates PKA-dependent phosphorylation of ChChd3, a scaffolding protein that participates in the MICOS complex (MItochondrial COntact Site and Cristae Organizing System) [41, 42], and is important for the maintenance of cristae integrity and mitochondrial function [43]. A sensitive PKA localized just outside the mitochondrial matrix could also allow the IMS to sense small cAMP amounts leaking from this compartment under stress conditions, characterised by mitochondrial permeability transition pore (MPTP) flickering [18]. This, in turn, may

contribute to PKA-mediated strengthening of the cristae and stress recovery. In line with this possibility, ChChd3 depletion results in extensive mitochondrial fragmentation [43].

cAMP signalling in the matrix and IMS has been involved in a number of mitochondrial functions, including OXPHOS [16], regulation of ATP synthesis [16, 17], production of aldosterone [44], regulation of cell death [38, 39], sepsis induced heart dysfunction [45], memory regulation [46], and regulation of mitochondrial DNA synthesis and transcription [36, 47]; however, a direct link connecting cAMP-mediated events in the inner mitochondrial compartments with the machineries that regulate mitochondrial dynamics is still missing.

4. cAMP signalling at the mitochondrial surface

The mitochondrial compartment most involved in mitochondrial dynamics is the OMM. This permeable membrane is the first line of separation between mitochondria and the cytosol of hosting cells, and contains many of the molecular determinants involved in mitochondrial fission/fusion, motility and mitophagy. Therefore, it is not a surprise that the OMM harbours the signalling pathways that regulate these processes. Indeed, the OMM is widely accepted as a site hosting significant PKA activity [18, 33, 48]. We recently showed that the PKA activity at the OMM persists longer than in the cytosol, thanks to a yet unidentified mechanism that may rely on phosphatases [18]**.** PKA tethering at the OMM is granted by several AKAPs [33, 49-51], and it is well accepted that the cAMP**/**PKA axis activity at the OMM regulates several processes, such as mitochondrial protein import [52, 53], apoptosis [50, 54, 55], autophagy [56, 57], mitophagy [58, 59] and mitochondrial fission and fusion [13, 21].

5. cAMP regulation of mitochondrial morphology

The relationship between form and function is a biological dogma well reflected by the importance of mitochondrial dynamics in mitochondrial function and homeostasis. Indeed,

size, shape, number and interconnectivity of mitochondria change continuously, tuning key mitochondrial functions (such as ATP production, intermediary metabolism, Ca^{2+} signalling, free radical homeostasis, mitochondrial biogenesis and apoptosis) with cellular needs [60, 61]. Variations in mitochondrial size depend on the balance between two highly regulated and evolutionarily conserved processes, fusion and fission [61, 62]. Mitochondrial fusion is a fast merging event that allows the exchange of matrix content between adjoining mitochondria. On the other hand, mitochondrial fission is a regulated dissection process that, starting from a single organelle, can produce one or more uneven daughter mitochondria. Both these processes favor the maintenance of a healthy mitochondrial population; in fact, thanks to fusion events, stressed mitochondria can decrease their burden (e.g. mutated mitochondrial DNA, toxic ROS species) by sharing it with neighboring healthy organelles [63, 64]; on the other side, thanks to fission, irreversibly damaged organelles, or parts of, are isolated from the healthy mitochondrial population and eliminated by mitophagy (*figure 1*) [65]. Therefore, it does not come as a surprise that unbalanced mitochondrial fission or fusion leads to pathological conditions [66, 67].

Fission and fusion are dynamic and reversible processes that depend on the coordination of a number of proteins and can occur rapidly in response to specific stimuli [68, 69]. The fast timing of fusion and fission is not compatible with transcriptional regulation of their machineries; indeed, these processes are mainly regulated by post-translational modifications [70]. In particular, an important regulatory mechanism is the reversible phosphorylation downstream the two main second messengers, Ca^{2+} and cAMP.

A number of proteins have been identified as key players of mitochondrial fusion. Mitofusin 1 (Mfn1) and 2 (Mfn2), both necessary for canonical OMM fusion, are large GTPases localized at the OMM, where they can initiate the interaction of two adjacent mitochondria [71]. Another protein essential to fusion is optic atrophy 1 (OPA1), a conserved GTPase of

the dynamin family, localized at the IMM [72]. OPA1 exerts a number of important functions, from stabilizing mitochondria cristae to mediate IMM fusion [61].

Mitochondrial fission is mainly driven by dynamin-related protein 1 (Drp1), a cytosolic GTPase that, in response to specific stimuli, accumulates on the OMM, where it forms homopolymeric structures at the constriction points of the separating mitochondria. Several receptor proteins may participate in the recruitment of activated Drp1 to the OMM: mitochondrial fission protein 1 (Fis1), mitochondrial fission factor (Mff), mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51), to cite some. Fis1 is uniformly localized at the OMM and was the first to be proposed as Drp1 receptor; however the role of Fis1 in Drp1-dependent mitochondrial fission was challenged and is still debated [73-77]. Mitochondrial constriction and division occur at sites which are in contact with the endoplasmic reticulum, with the concerted contribution of the cytoskeletal machinery [78]. At these sites, Drp1 is organized into a ring-like complex that restricts, bringing the lipid bilayers of the two membranes in close proximity [79], although not close enough to allow membrane fission [80, 81]. The final step of fission is performed by the classical dynamin-2 (Dyn-2), recruited to the fission sites by Drp1 [81].

While Dyn-2 is the final effector of the fission event, the first, and probably most important, regulatory node of this process is Drp1. This protein is the main target of several signalling pathways regulating fission: it undergoes many types of post-translational modifications (phosphorylation, S-nitrosylation, SUMOylation, ubiquitination, and O-GlcNAcylation), each of these processes affecting distinct steps of mitochondrial fission. Among them, reversible phosphorylation is probably the most effective mechanism for differentially regulating Drp1 activity. Indeed, Drp1 phosphorylation at multiple serine residues (S600, S616, S637) by different kinases (PKA, CaMKIα, CDK/Cyclin B, ERK1/2, PKCδ) has distinct and sometimes opposing effects on fission (reviewed in [82]).

PKA activation results in the phosphorylation of a conserved S637 residue (S656 in rat splice variant 1 [83]), located at N-terminus of the Drp1 GTPase effector domain (GED). Drp1 S637 phosphorylation regulates its GTPase activity [83, 84], as well as its localization: Drp1 phosphorylated at S637 is not recruited at mitochondria but retained in the cytosol, thus inhibiting mitochondrial fission, leaving fusion unopposed, and eventually resulting in elongated organelles [83] . While phosphorylation of Drp1 S637 is under the control of cAMP, its dephosphorylation can be induced by Ca^{2+}. Indeed, high cytosolic Ca^{2+} levels result in the activation of calcineurin (CaN), a Ca^{2+}- and calmodulin-dependent protein phosphatase, which dephosphorylates Drp1 inducing mitochondrial fission [83, 85]. At a functional level, the crosstalk between cAMP and Ca^{2+} goes beyond modulating mitochondrial shape, and significantly impacts mitochondrial and cellular homeostasis. Indeed, CaN activation results in Drp1 activation, mitochondrial fission and consequently promotes mitophagy and, in some cases, apoptosis [83, 85]. On the contrary, activation of PKA or genetic ablation of CaN results in inhibition of mitochondrial fission, elongation of mitochondria, increase in mitochondrial respiration [86] and increased cell resistance and survival [25, 87].

While it is well established that PKA is tethered at the OMM thanks to AKAPs [13, 33], it is not entirely clear which PKA pool, the OMM-bound or the cytosolic one, is responsible for Drp1 regulation. A possible scenario would be that OMM-bound PKA phosphorylates Drp1 *in situ* facilitating its release from mitochondria, while cytosolic PKA ensures that Drp1 stays in its inactive status until a fission-inducing dephosphorylation becomes dominant. Strong evidence supports this possibility, as, for instance, depletion of AKAP1, the main tether of PKA at the OMM, by specific knock down [88, 89] or in response to hypoxia [89], results in Drp1 dephosphorylation and mitochondrial fission. As we will discuss later, a similar effect was also observed by delocalizing PKA from AKAP1 through overexpression

of PINK1 [59]. Accordingly, AKAP1 was identified as a neuroprotective and mitochondria-stabilizing factor in neuronal cells [88].

True to its ambiguous and pleiotropic nature, the cAMP signalling cascade has been recently proposed to induce also mitochondrial fragmentation. Indeed, Wikstrom and colleagues demonstrated that PKA-dependent phosphorylation of Drp1 at S637 in response to adrenergic stimulation, when occurring in concomitance with increased cellular free fatty acids, results in mitochondrial fragmentation in primary brown adipocytes [90]. This was proposed as the mechanism through which brown adipocytes would shift mitochondria to a more energy consuming and heat producing mode of function [90]. The mechanistic involvement of PKA-dependent phosphorylation of Drp1 at S637 into mitochondrial fragmentation is not well understood. Nevertheless, phosphorylation of Drp1 at the same site by another kinase, CaM kinase I alpha (CaMKIα), was also observed to fragment mitochondria in hippocampal neurons [91].

To date, very few data are available on the role of cAMP/PKA signalling on the molecular players of the other major shape-defining event, fusion. PKA can phosphorylate Mfn2 on S442, leading to cell growth arrest in rat vascular smooth muscle cells [92]. For its part, OPA1 was suggested to act as an AKAP targeting PKA on lipid droplets, in order to facilitate lipolysis in response to cAMP elevations downstream beta adrenergic activity [93]. However, despite the involvement of mitochondrial shaping proteins, these effects seem to be independent of mitochondrial morphology. Recently, Signorile et al. showed that a decrease in mt-cAMP led to a reduction in the levels of the deacetylase sirtuin 3 (Sirt3), resulting in hyperacetylation and proteolytic processing of OPA1, leading to mitochondrial fission and eventually apoptosis [94]. While these reports open the possibility of a role for cAMP in the process of fusion, strong experimental evidence is still

lacking; it may be, however, challenging to dissect a possible pro-fusion effect from the well studied anti-fission actions of the cAMP/PKA axis.

6. cAMP/PKA regulation of mitophagy and autophagy

Autophagy is the process through which cells disassemble cellular components to use them as an alternative source of energy at critical times, as during nutrient deprivation. This process is also an important housekeeping mechanism in clearing damaged cellular components, from misfolded proteins to entire organelles. Autophagy can be either a general or a selective process. Non-selective autophagy allows tissue remodelling during development [95, 96] and is activated during starvation, providing the cells with energy metabolites used to survive under stress conditions. Selective autophagy, on the other hand, is important for the degradation of protein aggregates and dysfunctional or superfluous organelles. Damaged mitochondria are eliminated through a specific type of selective autophagy called mitophagy, a process of paramount importance, being the core mechanism for mitochondria quality and quantity control. Mitophagy can be ubiquitylation- or receptor-mediated. The first eliminates damaged organelles while the second is responsible for hypoxia- [97] or developmental-induced [98-100] mitochondrial clearance.

Autophagy starts with the recognition of the components to be eliminated and the formation, around them, of a double membrane-bound vesicle named autophagosome. In receptor-induced mitophagy, this step depends on a number of receptors (NIX [101]; BNIP3 [97]; FUNDC1 [102]) that directly interact with the autophagosome membrane. On the other hand, for the ubiquitylation-dependent pathway this step is controlled by the crosstalk between the PTEN-induced putative kinase 1 (PINK1), a mitochondrial protein that accumulates selectively on the surface of depolarized mitochondria [103], and an E3 ubiquitin ligase called Parkin. PINK1-dependent recruitment of Parkin on mitochondria

triggers the extensive ubiquitylation and the subsequent degradation of several OMM proteins, resulting in the impairment of mitochondrial fusion [104, 105]. Subsequently, pro-fission proteins such as Drp1 [65] and autophagy receptors [106, 107] are recruited to complete the fragmentation and elimination of the targeted organelle.

The cAMP/PKA axis can regulate mitophagy through modulation of the activity of the pro-fission protein Drp1 [108]. As we discussed previously, PKA phosphorylates Drp1 at S637, shifting the balance between fusion and fission, ultimately favouring mitochondrial elongation [83-85]. While mitochondrial morphology *per se* does not dictate whether an organelle will undergo mitophagy [108], it has been shown that inhibiting fission or promoting fusion decreases mitophagy, whereas enhanced fission precedes and facilitates it [65]. Accordingly, the activation of the cAMP/PKA pathway is often associated with an inhibitory effect on mitophagy (*figure 1*). That being said, regulating mitochondrial size through Drp1 phosphorylation is not the only signalling node between the cAMP pathway and mitophagy.

In a recent report, activation of PKA resulted in the phosphorylation of components of MICOS, a multiproteic complex involved in the formation and maintenance of mitochondrial cristae [109]. Upon PKA-dependent phosphorylation, two MICOS proteins, MIC60 and MIC19, were able to destabilize PINK1, reducing its level on depolarized mitochondria and consequently preventing the recruitment of Parkin and the degradation of these organelles [58]. Thanks to this pathway, PKA may be part of a mechanism that protects mitochondria with low membrane potential from being degraded. Such process could be important in specific circumstances, including axonal transport of mitochondria in neurons [110], or, as we will discuss later, during nutrient starvation [56, 57].

Further evidence of the importance of PKA in inhibiting mitophagy was recently provided by the finding that artificial targeting of PINK to healthy and fully polarized mitochondria disturbed the binding of PKA to its OMM tether AKAP1. Displacement of PKA from the OMM resulted in a marked decrease in Drp1 S637 phosphorylation and induction of mitochondrial fragmentation [59]. It can be envisioned that PKA expulsion from the OMM of PINK1-positive organelles confers a high level of selectivity towards damaged segments of the mitochondrial network versus healthy ones. In fact, an alternative marker for mitochondrial depolarization could be Ca^{2+} release from the compromised organelle, although this signal would rapidly diffuse throughout the cytosol, making the recognition of damaged organelles challenging. Taken together these findings indicate that the cAMP/PKA signalling at the OMM is a key component of the pathways that control mitochondrial recycling.

Equally important to the elimination of damaged mitochondria is to safeguard healthy organelles from degradation processes induced by starvation, such as autophagy. Many decades ago it was observed that during starvation mitochondria enlarge and display increased cristae and matrix density [111, 112]. This behaviour, that at the time seemed paradoxical, represents an important escape strategy of mitochondria from starvation-induced autophagy and, interestingly, depends on PKA. Indeed, it was recently demonstrated that starvation triggers a rise in cAMP levels, which, through PKA activation, leads to phosphorylation of Drp1 at S637, with consequent inhibition of fission and larger organelles [56, 57]. Elongated mitochondria exhibit increased density of cristae and higher dimerization of the mitochondrial ATP synthase, and consequently display higher efficiency of energy production. On the contrary, mitochondria that fail to elongate during starvation consume cellular ATP to maintain their membrane potential, rapidly leading the cell to a bioenergetic crisis, which culminates with death [56].

Thanks to these studies, mitochondrial elongation is now recognised as a stereotypical response to limited nutrient supply, when cells need to maximize the efficiency of energy production. Under these conditions energy production relies mainly on internal substrates, such as amino acid and fatty acid (FA) catabolism. During starvation, autophagy replenishes lipid droplets with FAs, which can then be efficiently transferred only to elongated mitochondria [113]. Elongated mitochondria are crucial for the efficient progression of the autophagic process, not only because of their ability to use FAs, but also because they provide the membranes necessary for the formation of the autophagosome [114]. In line with these findings, it was reported that glicolytic metabolism is a prerequisite for Parkin recruitment and mitophagy, a process that does not affect efficiently respiring mitochondria [115, 116].

In starving conditions, a decrease of ATP is matched by an increase in AMP, followed by activation of 5' AMP-activated protein kinase (AMPK) [117]. Interestingly, in response to mitochondrial damage AMPK was shown to phosphorylate Mff resulting in mitochondrial recruitment of Drp1 and consequent fragmentation [118]. It is therefore worth to note that during starvation the cAMP/PKA-dependent mitochondrial elongation counteracts the AMPK-driven fission. It is tempting to speculate that cAMP is the extra signal that may enable the cell to distinguish between damage and energetic demand. In support to this idea, PKA was found to phosphorylate and inhibit the activation of AMPK in adipocytes during β-adrenergic-induced lipolysis [119], and in hepatic cancer cells upon both glucagon administration [120] and glucose starvation [121]. Activation of PKA in response to glucose starvation may counteract AMPK-induced apoptosis. Indeed Palorini and colleagues, exploiting thorough omics approaches, showed that the survival of cancer cells in glucose limiting conditions requires the cAMP/PKA axis activation, and is mediated

by induction of autophagy and glutamine metabolism [122]. A direct connection of these phenotypes with mitochondrial function, and how nutrient deprivation translates in a cAMP signal, is not yet demonstrated; however there is plenty of evidence to allow, or better, dictate such working hypothesis.

7. cAMP and mitochondrial motility

The ability of a cell to perform simultaneously different tasks largely depends on the intrinsic properties of cellular structure and morphology (e.g. lengths and diameters) that physically define the sites where distinct events take place. In addition to a spatial platform, these locations have to provide the necessary elements for their designated activity, including energy and metabolites. Being important energy and signalling regulators, mitochondria participate in the creation of such intracellular niches and this is reflected in the elaborated mechanisms that cells developed for controlling mitochondrial recruitment in the sites of interest [123]. Indeed, despite being continuously trafficked around the cell, mitochondria display a well-organised distribution pattern that, if disturbed, impair many key cellular processes.

The neuronal cell represents a prototypical example of the importance that mitochondria can assume for the task-specificity of subcellular domains. Neurons are high-energy demanding cells with well-defined structural domains, each with diverse needs and functions [124]. Mitochondria have to be present in high numbers not only at the cell soma, but also at distal synapses that are connected to the cellular body through long and tight axonal processes. Mitochondria can reach these sites thanks to several proteins acting as adaptors and molecular motors. These complexes are controlled by signalling events that determine the direction, velocity and disengagement of the organelle from its trafficking apparatus [125]. Once mitochondria become stationary, they integrate themselves to the

local environment, contributing energy, metabolites and participating to the local signalling (e.g. buffering Ca^{2+}). Once their job is done, or whether damage occurs, mitochondria become motile again, in order to reach the next site of interest or to engage their degradation machinery [124, 126].

Mitochondrial trafficking involves the coordinated actions of motor proteins associated with the microtubular network. Microtubules are rigid structures with clear polarity, as their “plus end” points invariably to the periphery of the cell. A large number of molecular motors associate with microtubules, however mitochondria are propelled mainly by two groups of motor proteins, the minus end-directed dynein and the large family of plus end-directed kinesins [127]. In neurons, kinesins promote mitochondrial trafficking versus the synapse (anterograde movement), while dynein pushes towards the opposite direction (retrograde movement). Mitochondria engage kinesin/dynein motors with the aid of adaptor proteins that mediate the interaction between the motor and mitochondrial membrane receptors. In mammals, Trafficking Kinesin Protein (TRAK) 1 and 2 are the main adaptor proteins that bridge the OMM-embedded receptor protein Miro, and the molecular motors of the KIF5 cargo-binding domain and dynein [125, 128, 129]. While Miro recruits KIF5 via its binding with TRAK 1/2, another mitochondrial receptor protein, syntabulin, is able to link directly KIF5 to mitochondria [130, 131]. Once mitochondria reach their destination, they have to become stationary and join the local pool of organelles. This can be done by disengaging the transport machinery, or thanks to anchoring mechanisms able to halt the motor-driven transport. One of such anchor proteins is syntaphilin, an axon-targeted OMM protein that can act as an anchor and immobilize mitochondria in axons [132, 133].

As all cellular transport processes, mitochondrial motility and transport are under the strict control of signalling pathways [134, 135]. A classic example of mitochondrial movement

control is the Ca^{2+} sensitivity of Miro, achieved through its Ca^{2+}-binding EF-hands [136]. When mobile mitochondria enter a microenvironment of elevated Ca^{2+} concentration, such as an active synapse, Ca^{2+} binds to the Miro-EF hands and immobilizes the organelle by impacting on the KIF5-Miro-TRAK complex through a debated mechanism [129, 137-139].

Another critical regulator of mitochondrial transport is reversible phosphorylation, and PKA is one of the kinases proposed to come into play. Interestingly, the cAMP signalling pathway regulates many of the proteins involved in mitochondrial transport. Indeed, PKA has been shown to phosphorylate members of the kinesin family [134, 135], as well as dynein [140] and syntaphilin [141], while cAMP-dependent activation of its other major effector Epac2 results in phosphorylation of syntabulin [142]. Despite clear biochemical evidence of their cAMP-dependent phosphorylation, none of these proteins has been associated to the effects of cAMP in mitochondrial movement. However, as discussed later, since cAMP was observed to both promote and inhibit mitochondrial transport, it would not be a surprise if these proteins are at the core of its opposing effects.

The effects of cAMP in mitochondrial motility in mouse brainstem neurons were first observed using two-photon microscopy. When respiratory neurons were treated with the phosphatase inhibitor calyculin A, mitochondria movement was strongly inhibited, suggesting an important role of reversible phosphorylation in this process. In the same study, inhibition of MAP kinase or tyrosine kinase had no effect while the cAMP-increasing agents forskolin (a non-specific activator of tmACs) and 3-isobutyl-1-methylxanthine (IBMX, a broad-range PDE inhibitor), strongly, and reversibly, reduced mitochondrial movement [143]. Similarly, in hippocampal neurons IBMX reduced mitochondrial movement through a mechanism that may involve the Akt-GSK3β signalling pathway [144]. In contrast with these reports, Xu and colleagues measured mitochondrial transport

in zebrafish M-cells and found that treatment with the cell permeant cAMP analog db-cAMP augmented mitochondrial motility and increased the speed of their anterograde-movement [145]. The authors argue that db-cAMP-dependent amelioration of mitochondrial movement contributes to the well-documented regenerative actions of db-cAMP [146, 147]. However, it is important to note that db-cAMP is a metabolically activatable PKA agonist that, when applied, releases butyrate due to intracellular and extracellular esterase action. Since butyrate was shown to have distinct biological effects independent of cAMP [148], experiments using other cAMP analogs or different means to increase cellular cAMP (e.g forskolin or IBMX) would be needed to consolidate these findings.

Recently, Ogawa and colleagues found that a multiproteic complex involving Miro, TRAK1, Disrupted In Schizophrenia 1 (DISC1), the dynein regulator NDE1 and the kinase GSK3β participates in mitochondrial trafficking [149]. Since NDE1 can be phosphorylated by PKA at T131 in a DISC1/PDE4-dependent manner [150]**,** the authors hypothesized a role of the cAMP/PKA axis in the regulation of this complex, and consequently on mitochondrial movement. The phosphomimetic NDE1 T131E mutant abolished retrograde mitochondrial movement, while the phosphodead NDE1 T131A did not, suggesting PKA-dependent inhibition of mitochondrial retrograde movement. However, the authors were unable to replicate the effects of NDE1 T131E mutant by raising intracellular cAMP levels. Surprisingly, treatment of neuronal cell lines with a mixture of forskolin and IBMX resulted in a significant increase in retrograde-moving mitochondria [149]. Although the molecular mechanism remains unclear, these data suggest an involvement of cAMP in directional mitochondrial motility. Based on clear evidence suggesting that in neurons cAMP concentrations vary drastically between the cell body, axon and boutons [151, 152]**,** travelling mitochondria will come in contact with gradients of cAMP which may differently

affect their motility. Given the importance of both mitochondrial movement and cAMP in psychiatric disorders, it would be of primary importance to understand the molecular mechanisms underlying the involvement of cAMP in mitochondrial trafficking [153, 154].

8. Concluding remarks

Several lines of evidence suggest that mitochondrial fission, fusion, motility and mitophagy are crucial for mitochondrial homeostasis and strictly regulated. Indeed, identifying the targets of the signalling pathways that control these processes would enable us to manipulate mitochondrial behaviour and consequently modulate mitochondrial pathophysiology [24, 155]. The cAMP signalling pathway presents a number of characteristics that would make it an optimal candidate for the exogenous regulation of mitochondrial homeostasis. As showcased in this review, cAMP is involved in the regulation of mitochondrial dynamics at different levels and, interestingly, its actions are consistently beneficial both for mitochondria and the host cell. As a matter of fact, activation of PKA at the OMM is a well-recognised pro-survival signal [54, 88], while, thanks to the cAMP/PKA axis, mitochondria elongate to escape unnecessary degradation [56, 57]. In addition, the cAMP cascade opposes non-selective mitophagy by phosphorylating MICOS components and destabilizing PINK1 [108, 109]. Finally, recent experimental evidence suggests that the cAMP/PKA axis may participate in the re-distribution of damaged mitochondria from the axons to the soma of neurons, hence facilitating their degradation [149]. Despite this promising evidence, our understanding of how cAMP signalling events are integrated and regulate mitochondrial dynamics remains incomplete. For starters, it is not clear which PKA pools (the ones present at the OMM or those free in the cytosol) are responsible for the regulation of each dynamic process [18]. In addition, it remains obscure whether specific cAMP-generating stimuli aiming to specifically manipulate mitochondrial dynamics can be triggered by the cell or the

organelles. Finally, while it is conceivable that PKA phosphorylates a different cohort of targets during the regulation of each process (fission/fusion, mitophagy and transport), most of these proteins remain unknown. We believe that combining live cell imaging [156, 157] to molecular and biochemical approaches [158-161] will facilitate the identification of the molecular mechanisms and targets through which cAMP exerts its regulatory actions on mitochondrial dynamics. The employment of such multidisciplinary approach promises to generate a wealth of information that will pave the road to novel therapeutic lines against mitochondrial-related disease.

9. Conflict of interest

The authors declare no conflict of interest.

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11. References

[1] H. Vakifahmetoglu-Norberg, A.T. Ouchida, E. Norberg, The role of mitochondria in metabolism and cell death, Biochem Biophys Res Commun, 482 (2017) 426-431.

[2] L. Ruan, C. Zhou, E. Jin, A. Kucharavy, Y. Zhang, Z. Wen, L. Florens, R. Li, Cytosolic proteostasis through importing of misfolded proteins into mitochondria, Nature, 543 (2017) 443-446.

[3] X. Luo, I. Budihardjo, H. Zou, C. Slaughter, X. Wang, Bid, a Bcl2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors, Cell, 94 (1998) 481-490.

[4] N.S. Chandel, D.S. McClintock, C.E. Feliciano, T.M. Wood, J.A. Melendez, A.M. Rodriguez, P.T. Schumacker, Reactive oxygen species generated at mitochondrial complex III stabilize hypoxia-inducible factor-1alpha during hypoxia: a mechanism of O2 sensing, J Biol Chem, 275 (2000) 25130-25138.

[5] N.S. Chandel, E. Maltepe, E. Goldwasser, C.E. Mathieu, M.C. Simon, P.T. Schumacker, Mitochondrial reactive oxygen species trigger hypoxia-induced transcription, Proc Natl Acad Sci U S A, 95 (1998) 11715-11720.

[6] G.S. McElroy, N.S. Chandel, Mitochondria control acute and chronic responses to hypoxia, Exp Cell Res, (2017).

[7] D. De Stefani, R. Rizzuto, T. Pozzan, Enjoy the Trip: Calcium in Mitochondria Back and Forth, Annu Rev Biochem, 85 (2016) 161-192.

[8] D. De Stefani, A. Raffaello, E. Teardo, I. Szabò, R. Rizzuto, A forty-kilodalton protein of the inner membrane is the mitochondrial calcium uniporter, Nature, 476 (2011) 336-340.

[9] J.M. Baughman, F. Perocchi, H.S. Girgis, M. Plovanich, C.A. Belcher-Timme, Y. Sancak, X.R. Bao, L. Strittmatter, O. Goldberger, R.L. Bogorad, V. Koteliansky, V.K. Mootha, Integrative genomics identifies MCU as an essential component of the mitochondrial calcium uniporter, Nature, 476 (2011) 341-345.

[10] R. Rizzuto, D. De Stefani, A. Raffaello, C. Mammucari, Mitochondria as sensors and regulators of calcium signalling, Nat Rev Mol Cell Biol, 13 (2012) 566-578.

[11] L.S. Jouaville, P. Pinton, C. Bastianutto, G.A. Rutter, R. Rizzuto, Regulation of mitochondrial ATP synthesis by calcium: evidence for a long-term metabolic priming, Proc Natl Acad Sci U S A, 96 (1999) 13807-13812.

[12] V. Giorgio, S. von Stockum, M. Antoniel, A. Fabbro, F. Fogolari, M. Forte, G.D. Glick, V. Petronilli, M. Zoratti, I. Szabó, G. Lippe, P. Bernardi, Dimers of mitochondrial ATP synthase form the permeability transition pore, Proc Natl Acad Sci U S A, 110 (2013) 5887-5892.

[13] K. Lefkimmiatis, cAMP signalling meets mitochondrial compartments, Biochem Soc Trans, 42 (2014) 265-269.

[14] F. Valsecchi, L.S. Ramos-Espiritu, J. Buck, L.R. Levin, G. Manfredi, cAMP and mitochondria, Physiology (Bethesda), 28 (2013) 199-209.

[15] F. Valsecchi, C. Konrad, G. Manfredi, Role of soluble adenylyl cyclase in mitochondria, Biochim Biophys Acta, 1842 (2014) 2555-2560.

[16] R. Acin-Perez, E. Salazar, M. Kamenetsky, J. Buck, L.R. Levin, G. Manfredi, Cyclic AMP produced inside mitochondria regulates oxidative phosphorylation, Cell Metab, 9 (2009) 265-276.

[17] G. Di Benedetto, E. Scalzotto, M. Mongillo, T. Pozzan, Mitochondrial Ca^{2+} uptake induces cyclic AMP generation in the matrix and modulates organelle ATP levels, Cell Metab, 17 (2013) 965-975.

[18] K. Lefkimmiatis, D. Leronni, A.M. Hofer, The inner and outer compartments of mitochondria are sites of distinct cAMP/PKA signaling dynamics, J Cell Biol, 202 (2013) 453-462.

[19] G. Di Benedetto, D. Pendin, E. Greotti, P. Pizzo, T. Pozzan, Ca2+ and cAMP cross-talk in mitochondria, J Physiol, 592 (2014) 305-312.

[20] R. Covian, S. French, H. Kusnetz, R.S. Balaban, Stimulation of oxidative phosphorylation by calcium in cardiac mitochondria is not influenced by cAMP and PKA activity, Biochim Biophys Acta, 1837 (2014) 1913-1921.

[21] K.H. Flippo, S. Strack, Mitochondrial dynamics in neuronal injury, development and plasticity, J Cell Sci, 130 (2017) 671-681.

[22] S.R. Agarwal, C.E. Clancy, R.D. Harvey, Mechanisms Restricting Diffusion of Intracellular cAMP, Sci Rep, 6 (2016) 19577.

[23] M. Richards, O. Lomas, K. Jalink, K.L. Ford, R.D. Vaughan-Jones, K. Lefkimmiatis, P. Swietach, Intracellular tortuosity underlies slow cAMP diffusion in adult ventricular myocytes, Cardiovasc Res, 110 (2016) 395-407.

[24] M. Liesa, M. Palacín, A. Zorzano, Mitochondrial dynamics in mammalian health and disease, Physiol Rev, 89 (2009) 799-845.

[25] Y. Chen, M.J. Cann, T.N. Litvin, V. Iourgenko, M.L. Sinclair, L.R. Levin, J. Buck, Soluble adenylyl cyclase as an evolutionarily conserved bicarbonate sensor, Science, 289 (2000) 625-628.

[26] B.S. Jaiswal, M. Conti, Calcium regulation of the soluble adenylyl cyclase expressed in mammalian spermatozoa, Proc Natl Acad Sci U S A, 100 (2003) 10676-10681.

[27] J.H. Zippin, Y. Chen, S.G. Straub, K.C. Hess, A. Diaz, D. Lee, P. Tso, G.G. Holz, G.W. Sharp, L.R. Levin, J. Buck, CO2/HCO3(-)- and calcium-regulated soluble adenylyl cyclase as a physiological ATP sensor, J Biol Chem, 288 (2013) 33283-33291.

[28] M. Brescia, M. Zaccolo, Modulation of Compartmentalised Cyclic Nucleotide Signalling via Local Inhibition of Phosphodiesterase Activity, Int J Mol Sci, 17 (2016).

[29] K. Kokkonen, D.A. Kass, Nanodomain Regulation of Cardiac Cyclic Nucleotide Signaling by Phosphodiesterases, Annu Rev Pharmacol Toxicol, 57 (2017) 455-479.

[30] A.M. Hofer, K. Lefkimmiatis, Extracellular calcium and cAMP: second messengers as "third messengers"?, Physiology (Bethesda), 22 (2007) 320-327.

[31] R.F. Schindler, C. Scotton, J. Zhang, C. Passarelli, B. Ortiz-Bonnin, S. Simrick, T. Schwerte, K.L. Poon, M. Fang, S. Rinné, A. Froese, V.O. Nikolaev, C. Grunert, T. Müller, G. Tasca, P. Sarathchandra, F. Drago, B. Dallapiccola, C. Rapezzi, E. Arbustini, F.R. Di Raimo, M. Neri, R. Selvatici, F. Gualandi, F. Fattori, A. Pietrangelo, W. Li, H. Jiang, X. Xu, E. Bertini, N. Decher, J. Wang, T. Brand, A. Ferlini, POPDC1(S201F) causes muscular dystrophy and arrhythmia by affecting protein trafficking, J Clin Invest, 126 (2016) 239-253.

[32] R.F. Schindler, T. Brand, The Popeye domain containing protein family--A novel class of cAMP effectors with important functions in multiple tissues, Prog Biophys Mol Biol, 120 (2016) 28-36.

[33] K. Lefkimmiatis, M. Zaccolo, cAMP signaling in subcellular compartments, Pharmacol Ther, 143 (2014) 295-304.

[34] J.L. Esseltine, J.D. Scott, AKAP signaling complexes: pointing towards the next generation of therapeutic targets?, Trends Pharmacol Sci, 34 (2013) 648-655.

[35] K.C. Hess, J. Liu, G. Manfredi, F.A. Mühlschlegel, J. Buck, L.R. Levin, A. Barrientos, A mitochondrial CO2-adenylyl cyclase-cAMP signalosome controls yeast normoxic cytochrome c oxidase activity, FASEB J, 28 (2014) 4369-4380.

[36] F. Zhang, Y. Qi, K. Zhou, G. Zhang, K. Linask, H. Xu, The cAMP phosphodiesterase Prune localizes to the mitochondrial matrix and promotes mtDNA replication by stabilizing TFAM, EMBO Rep, 16 (2015) 520-527.

[37] J. Qiao, F.C. Mei, V.L. Popov, L.A. Vergara, X. Cheng, Cell cycle-dependent subcellular localization of exchange factor directly activated by cAMP, J Biol Chem, 277 (2002) 26581-26586.

[38] Z. Wang, D. Liu, A. Varin, V. Nicolas, D. Courilleau, P. Mateo, C. Caubere, P. Rouet, A.M. Gomez, G. Vandecasteele, R. Fischmeister, C. Brenner, A cardiac mitochondrial

cAMP signaling pathway regulates calcium accumulation, permeability transition and cell death, Cell Death Dis, 7 (2016) e2198.

[39] L. Fazal, M. Laudette, S. Paula-Gomes, S. Pons, C. Conte, F. Tortosa, P. Sicard, Y. Sainte-Marie, M. Bisserier, O. Lairez, A. Lucas, J. Roy, B. Ghaleh, J. Fauconnier, J. Mialet-Perez, F. Lezoualc'h, Multifunctional Mitochondrial Epac1 Controls Myocardial Cell Death, Circ Res, 120 (2017) 645-657.

[40] C.K. Means, B. Lygren, L.K. Langeberg, A. Jain, R.E. Dixon, A.L. Vega, M.G. Gold, S. Petrosyan, S.S. Taylor, A.N. Murphy, T. Ha, L.F. Santana, K. Tasken, J.D. Scott, An entirely specific type I A-kinase anchoring protein that can sequester two molecules of protein kinase A at mitochondria, Proc Natl Acad Sci U S A, 108 (2011) E1227-1235.

[41] V. Kozjak-Pavlovic, The MICOS complex of human mitochondria, Cell Tissue Res, 367 (2017) 83-93.

[42] C. Ott, E. Dorsch, M. Fraunholz, S. Straub, V. Kozjak-Pavlovic, Detailed analysis of the human mitochondrial contact site complex indicate a hierarchy of subunits, PLoS One, 10 (2015) e0120213.

[43] M. Darshi, V.L. Mendiola, M.R. Mackey, A.N. Murphy, A. Koller, G.A. Perkins, M.H. Ellisman, S.S. Taylor, ChChd3, an inner mitochondrial membrane protein, is essential for maintaining crista integrity and mitochondrial function, J Biol Chem, 286 (2011) 2918-2932.

[44] D. Katona, A. Rajki, G. Di Benedetto, T. Pozzan, A. Spät, Calcium-dependent mitochondrial cAMP production enhances aldosterone secretion, Mol Cell Endocrinol, 412 (2015) 196-204.

[45] R. Neviere, F. Delguste, A. Durand, J. Inamo, E. Boulanger, S. Preau, Abnormal Mitochondrial cAMP/PKA Signaling Is Involved in Sepsis-Induced Mitochondrial and Myocardial Dysfunction, Int J Mol Sci, 17 (2016).

[46] E. Hebert-Chatelain, T. Desprez, R. Serrat, L. Bellocchio, E. Soria-Gomez, A. Busquets-Garcia, A.C. Pagano Zottola, A. Delamarre, A. Cannich, P. Vincent, M. Varilh, L.M. Robin, G. Terral, M.D. García-Fernández, M. Colavita, W. Mazier, F. Drago, N. Puente, L. Reguero, I. Elezgarai, J.W. Dupuy, D. Cota, M.L. Lopez-Rodriguez, G. Barreda-Gómez, F. Massa, P. Grandes, G. Bénard, G. Marsicano, A cannabinoid link between mitochondria and memory, Nature, 539 (2016) 555-559.

[47] B. Lu, J. Lee, X. Nie, M. Li, Y.I. Morozov, S. Venkatesh, D.F. Bogenhagen, D. Temiakov, C.K. Suzuki, Phosphorylation of human TFAM in mitochondria impairs DNA binding and promotes degradation by the AAA+ Lon protease, Mol Cell, 49 (2013) 121-132.

[48] A. Carlucci, L. Lignitto, A. Feliciello, Control of mitochondria dynamics and oxidative metabolism by cAMP, AKAPs and the proteasome, Trends Cell Biol, 18 (2008) 604-613.

[49] N.M. Alto, J. Soderling, J.D. Scott, Rab32 is an A-kinase anchoring protein and participates in mitochondrial dynamics, J Cell Biol, 158 (2002) 659-668.

[50] N.N. Danial, C.F. Gramm, L. Scorrano, C.Y. Zhang, S. Krauss, A.M. Ranger, S.R. Datta, M.E. Greenberg, L.J. Licklider, B.B. Lowell, S.P. Gygi, S.J. Korsmeyer, BAD and glucokinase reside in a mitochondrial complex that integrates glycolysis and apoptosis, Nature, 424 (2003) 952-956.

[51] A. Feliciello, M.E. Gottesman, E.V. Avvedimento, cAMP-PKA signaling to the mitochondria: protein scaffolds, mRNA and phosphatases, Cell Signal, 17 (2005) 279-287.

[52] O. Schmidt, A.B. Harbauer, S. Rao, B. Eyrich, R.P. Zahedi, D. Stojanovski, B. Schönfisch, B. Guiard, A. Sickmann, N. Pfanner, C. Meisinger, Regulation of mitochondrial protein import by cytosolic kinases, Cell, 144 (2011) 227-239.

[53] M. Opalińska, C. Meisinger, Metabolic control via the mitochondrial protein import machinery, Curr Opin Cell Biol, 33 (2015) 42-48.

[54] H. Harada, B. Becknell, M. Wilm, M. Mann, L.J. Huang, S.S. Taylor, J.D. Scott, S.J. Korsmeyer, Phosphorylation and inactivation of BAD by mitochondria-anchored protein kinase A, Mol Cell, 3 (1999) 413-422.

[55] D. Moujalled, R. Weston, H. Anderton, R. Ninnis, P. Goel, A. Coley, D.C. Huang, L. Wu, A. Strasser, H. Puthalakath, Cyclic-AMP-dependent protein kinase A regulates apoptosis by stabilizing the BH3-only protein Bim, EMBO Rep, 12 (2011) 77-83.

[56] L.C. Gomes, G. Di Benedetto, L. Scorrano, During autophagy mitochondria elongate, are spared from degradation and sustain cell viability, Nat Cell Biol, 13 (2011) 589-598.

[57] A.S. Rambold, B. Kostelecky, N. Elia, J. Lippincott-Schwartz, Tubular network formation protects mitochondria from autophagosomal degradation during nutrient starvation, Proc Natl Acad Sci U S A, 108 (2011) 10190-10195.

[58] S. Akabane, M. Uno, N. Tani, S. Shimazaki, N. Ebara, H. Kato, H. Kosako, T. Oka, PKA Regulates PINK1 Stability and Parkin Recruitment to Damaged Mitochondria through Phosphorylation of MIC60, Mol Cell, 62 (2016) 371-384.

[59] K.R. Pryde, H.L. Smith, K.Y. Chau, A.H. Schapira, PINK1 disables the anti-fission machinery to segregate damaged mitochondria for mitophagy, J Cell Biol, 213 (2016) 163-171.

[60] K.L. Cerveny, Y. Tamura, Z. Zhang, R.E. Jensen, H. Sesaki, Regulation of mitochondrial fusion and division, Trends Cell Biol, 17 (2007) 563-569.

[61] D.C. Chan, Mitochondrial fusion and fission in mammals, Annu Rev Cell Dev Biol, 22 (2006) 79-99.

[62] B. Westermann, Mitochondrial fusion and fission in cell life and death, Nat Rev Mol Cell Biol, 11 (2010) 872-884.

[63] H. Chen, A. Chomyn, D.C. Chan, Disruption of fusion results in mitochondrial heterogeneity and dysfunction, J Biol Chem, 280 (2005) 26185-26192.

[64] H. Chen, J.M. McCaffery, D.C. Chan, Mitochondrial fusion protects against neurodegeneration in the cerebellum, Cell, 130 (2007) 548-562.

[65] G. Twig, A. Elorza, A.J. Molina, H. Mohamed, J.D. Wikstrom, G. Walzer, L. Stiles, S.E. Haigh, S. Katz, G. Las, J. Alroy, M. Wu, B.F. Py, J. Yuan, J.T. Deeney, B.E. Corkey, O.S. Shirihai, Fission and selective fusion govern mitochondrial segregation and elimination by autophagy, EMBO J, 27 (2008) 433-446.

[66] A.B. Knott, G. Perkins, R. Schwarzenbacher, E. Bossy-Wetzel, Mitochondrial fragmentation in neurodegeneration, Nat Rev Neurosci, 9 (2008) 505-518.

[67] S.B. Ong, S. Subrayan, S.Y. Lim, D.M. Yellon, S.M. Davidson, D.J. Hausenloy, Inhibiting mitochondrial fission protects the heart against ischemia/reperfusion injury, Circulation, 121 (2010) 2012-2022.

[68] A. Pyakurel, C. Savoia, D. Hess, L. Scorrano, Extracellular regulated kinase phosphorylates mitofusin 1 to control mitochondrial morphology and apoptosis, Mol Cell, 58 (2015) 244-254.

[69] T. Shutt, M. Geoffrion, R. Milne, H.M. McBride, The intracellular redox state is a core determinant of mitochondrial fusion, EMBO Rep, 13 (2012) 909-915.

[70] D.J. Pagliarini, J.E. Dixon, Mitochondrial modulation: reversible phosphorylation takes center stage?, Trends Biochem Sci, 31 (2006) 26-34.

[71] E. Schrepfer, L. Scorrano, Mitofusins, from Mitochondria to Metabolism, Mol Cell, 61 (2016) 683-694.

[72] C. Frezza, S. Cipolat, O. Martins de Brito, M. Micaroni, G.V. Beznoussenko, T. Rudka, D. Bartoli, R.S. Polishuck, N.N. Danial, B. De Strooper, L. Scorrano, OPA1 controls apoptotic cristae remodeling independently from mitochondrial fusion, Cell, 126 (2006) 177-189.

[73] Y.J. Lee, S.Y. Jeong, M. Karbowski, C.L. Smith, R.J. Youle, Roles of the mammalian mitochondrial fission and fusion mediators Fis1, Drp1, and Opa1 in apoptosis, Mol Biol Cell, 15 (2004) 5001-5011.

[74] S. Koirala, Q. Guo, R. Kalia, H.T. Bui, D.M. Eckert, A. Frost, J.M. Shaw, Interchangeable adaptors regulate mitochondrial dynamin assembly for membrane scission, Proc Natl Acad Sci U S A, 110 (2013) E1342-1351.

[75] O.C. Losón, Z. Song, H. Chen, D.C. Chan, Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission, Mol Biol Cell, 24 (2013) 659-667.

[76] Q. Shen, K. Yamano, B.P. Head, S. Kawajiri, J.T. Cheung, C. Wang, J.H. Cho, N. Hattori, R.J. Youle, A.M. van der Bliek, Mutations in Fis1 disrupt orderly disposal of defective mitochondria, Mol Biol Cell, 25 (2014) 145-159.

[77] L.C. Gomes, L. Scorrano, High levels of Fis1, a pro-fission mitochondrial protein, trigger autophagy, Biochim Biophys Acta, 1777 (2008) 860-866.

[78] K.J. De Vos, V.J. Allan, A.J. Grierson, M.P. Sheetz, Mitochondrial function and actin regulate dynamin-related protein 1-dependent mitochondrial fission, Curr Biol, 15 (2005) 678-683.

[79] S. Hoppins, L. Lackner, J. Nunnari, The machines that divide and fuse mitochondria, Annu Rev Biochem, 76 (2007) 751-780.

[80] Y. Yoon, K.R. Pitts, M.A. McNiven, Mammalian dynamin-like protein DLP1 tubulates membranes, Mol Biol Cell, 12 (2001) 2894-2905.

[81] J.E. Lee, L.M. Westrate, H. Wu, C. Page, G.K. Voeltz, Multiple dynamin family members collaborate to drive mitochondrial division, Nature, 540 (2016) 139-143.

[82] C. Hu, Y. Huang, L. Li, Drp1-Dependent Mitochondrial Fission Plays Critical Roles in Physiological and Pathological Progresses in Mammals, Int J Mol Sci, 18 (2017).

[83] J.T. Cribbs, S. Strack, Reversible phosphorylation of Drp1 by cyclic AMP-dependent protein kinase and calcineurin regulates mitochondrial fission and cell death, EMBO Rep, 8 (2007) 939-944.

[84] C.R. Chang, C. Blackstone, Cyclic AMP-dependent protein kinase phosphorylation of Drp1 regulates its GTPase activity and mitochondrial morphology, J Biol Chem, 282 (2007) 21583-21587.

[85] G.M. Cereghetti, A. Stangherlin, O. Martins de Brito, C.R. Chang, C. Blackstone, P. Bernardi, L. Scorrano, Dephosphorylation by calcineurin regulates translocation of Drp1 to mitochondria, Proc Natl Acad Sci U S A, 105 (2008) 15803-15808.

[86] P.T. Pfluger, D.G. Kabra, M. Aichler, S.C. Schriever, K. Pfuhlmann, V.C. García, M. Lehti, J. Weber, M. Kutschke, J. Rozman, J.W. Elrod, A.L. Hevener, A. Feuchtinger, M. Hrabě de Angelis, A. Walch, S.M. Rollmann, B.J. Aronow, T.D. Müller, D. Perez-Tilve, M. Jastroch, M. De Luca, J.D. Molkentin, M.H. Tschöp, Calcineurin Links Mitochondrial Elongation with Energy Metabolism, Cell Metab, 22 (2015) 838-850.

[87] A.S. Dickey, S. Strack, PKA/AKAP1 and PP2A/Bβ2 regulate neuronal morphogenesis via Drp1 phosphorylation and mitochondrial bioenergetics, J Neurosci, 31 (2011) 15716-15726.

[88] R.A. Merrill, R.K. Dagda, A.S. Dickey, J.T. Cribbs, S.H. Green, Y.M. Usachev, S. Strack, Mechanism of neuroprotective mitochondrial remodeling by PKA/AKAP1, PLoS Biol, 9 (2011) e1000612.

[89] H. Kim, M.C. Scimia, D. Wilkinson, R.D. Trelles, M.R. Wood, D. Bowtell, A. Dillin, M. Mercola, Z.A. Ronai, Fine-tuning of Drp1/Fis1 availability by AKAP121/Siah2 regulates mitochondrial adaptation to hypoxia, Mol Cell, 44 (2011) 532-544.

[90] J.D. Wikstrom, K. Mahdaviani, M. Liesa, S.B. Sereda, Y. Si, G. Las, G. Twig, N. Petrovic, C. Zingaretti, A. Graham, S. Cinti, B.E. Corkey, B. Cannon, J. Nedergaard, O.S.

Shirihai, Hormone-induced mitochondrial fission is utilized by brown adipocytes as an amplification pathway for energy expenditure, EMBO J, 33 (2014) 418-436.

[91] X.J. Han, Y.F. Lu, S.A. Li, T. Kaitsuka, Y. Sato, K. Tomizawa, A.C. Nairn, K. Takei, H. Matsui, M. Matsushita, CaM kinase I alpha-induced phosphorylation of Drp1 regulates mitochondrial morphology, J Cell Biol, 182 (2008) 573-585.

[92] W. Zhou, K.H. Chen, W. Cao, J. Zeng, H. Liao, L. Zhao, X. Guo, Mutation of the protein kinase A phosphorylation site influences the anti-proliferative activity of mitofusin 2, Atherosclerosis, 211 (2010) 216-223.

[93] M. Rogne, K. Taskén, Compartmentalization of cAMP signaling in adipogenesis, lipogenesis, and lipolysis, Horm Metab Res, 46 (2014) 833-840.

[94] A. Signorile, A. Santeramo, G. Tamma, T. Pellegrino, S. D'Oria, P. Lattanzio, D. De Rasmo, Mitochondrial cAMP prevents apoptosis modulating Sirt3 protein level and OPA1 processing in cardiac myoblast cells, Biochim Biophys Acta, 1864 (2017) 355-366.

[95] D.L. Berry, E.H. Baehrecke, Growth arrest and autophagy are required for salivary gland cell degradation in Drosophila, Cell, 131 (2007) 1137-1148.

[96] Y. Imagawa, T. Saitoh, Y. Tsujimoto, Vital staining for cell death identifies Atg9a-dependent necrosis in developmental bone formation in mouse, Nat Commun, 7 (2016) 13391.

[97] H. Zhang, M. Bosch-Marce, L.A. Shimoda, Y.S. Tan, J.H. Baek, J.B. Wesley, F.J. Gonzalez, G.L. Semenza, Mitochondrial autophagy is an HIF-1-dependent adaptive metabolic response to hypoxia, J Biol Chem, 283 (2008) 10892-10903.

[98] K. Ito, R. Turcotte, J. Cui, S.E. Zimmerman, S. Pinho, T. Mizoguchi, F. Arai, J.M. Runnels, C. Alt, J. Teruya-Feldstein, J.C. Mar, R. Singh, T. Suda, C.P. Lin, P.S. Frenette, Self-renewal of a purified Tie2+ hematopoietic stem cell population relies on mitochondrial clearance, Science, 354 (2016) 1156-1160.

[99] H.H. Pua, J. Guo, M. Komatsu, Y.W. He, Autophagy is essential for mitochondrial clearance in mature T lymphocytes, J Immunol, 182 (2009) 4046-4055.

[100] H. Sandoval, P. Thiagarajan, S.K. Dasgupta, A. Schumacher, J.T. Prchal, M. Chen, J. Wang, Essential role for Nix in autophagic maturation of erythroid cells, Nature, 454 (2008) 232-235.

[101] R.L. Schweers, J. Zhang, M.S. Randall, M.R. Loyd, W. Li, F.C. Dorsey, M. Kundu, J.T. Opferman, J.L. Cleveland, J.L. Miller, P.A. Ney, NIX is required for programmed mitochondrial clearance during reticulocyte maturation, Proc Natl Acad Sci U S A, 104 (2007) 19500-19505.

[102] L. Liu, D. Feng, G. Chen, M. Chen, Q. Zheng, P. Song, Q. Ma, C. Zhu, R. Wang, W. Qi, L. Huang, P. Xue, B. Li, X. Wang, H. Jin, J. Wang, F. Yang, P. Liu, Y. Zhu, S. Sui, Q. Chen, Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells, Nat Cell Biol, 14 (2012) 177-185.

[103] R.J. Youle, D.P. Narendra, Mechanisms of mitophagy, Nat Rev Mol Cell Biol, 12 (2011) 9-14.

[104] A.M. Pickrell, R.J. Youle, The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease, Neuron, 85 (2015) 257-273.

[105] J.P. Bernardini, M. Lazarou, G. Dewson, Parkin and mitophagy in cancer, Oncogene, 36 (2017) 1315-1327.

[106] W.X. Ding, H.M. Ni, M. Li, Y. Liao, X. Chen, D.B. Stolz, G.W. Dorn, X.M. Yin, Nix is critical to two distinct phases of mitophagy, reactive oxygen species-mediated autophagy induction and Parkin-ubiquitin-p62-mediated mitochondrial priming, J Biol Chem, 285 (2010) 27879-27890.

[107] M. Lazarou, D.A. Sliter, L.A. Kane, S.A. Sarraf, C. Wang, J.L. Burman, D.P. Sideris, A.I. Fogel, R.J. Youle, The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy, Nature, 524 (2015) 309-314.

[108] M. Song, G.W. Dorn, Mitoconfusion: noncanonical functioning of dynamism factors in static mitochondria of the heart, Cell Metab, 21 (2015) 195-205.

[109] M. van der Laan, S.E. Horvath, N. Pfanner, Mitochondrial contact site and cristae organizing system, Curr Opin Cell Biol, 41 (2016) 33-42.

[110] K.E. Miller, M.P. Sheetz, Axonal mitochondrial transport and potential are correlated, J Cell Sci, 117 (2004) 2791-2804.

[111] J.W. WILSON, E.H. LEDUC, Mitochondrial changes in the liver of essential fatty acid-deficient mice, J Cell Biol, 16 (1963) 281-296.

[112] N.A. Ratcliffe, P.E. King, Ultrastructural changes in the mitochondria of the acid gland of Nasonia vitripennis (Walker) (Pteromalidae: Hymenoptera) induced by starvation, Z Zellforsch Mikrosk Anat, 99 (1969) 459-468.

[113] A.S. Rambold, S. Cohen, J. Lippincott-Schwartz, Fatty acid trafficking in starved cells: regulation by lipid droplet lipolysis, autophagy, and mitochondrial fusion dynamics, Dev Cell, 32 (2015) 678-692.

[114] D.W. Hailey, A.S. Rambold, P. Satpute-Krishnan, K. Mitra, R. Sougrat, P.K. Kim, J. Lippincott-Schwartz, Mitochondria supply membranes for autophagosome biogenesis during starvation, Cell, 141 (2010) 656-667.

[115] M.K. McCoy, A. Kaganovich, I.N. Rudenko, J. Ding, M.R. Cookson, Hexokinase activity is required for recruitment of parkin to depolarized mitochondria, Hum Mol Genet, 23 (2014) 145-156.

[116] V.S. Van Laar, B. Arnold, S.J. Cassady, C.T. Chu, E.A. Burton, S.B. Berman, Bioenergetics of neurons inhibit the translocation response of Parkin following rapid mitochondrial depolarization, Hum Mol Genet, 20 (2011) 927-940.

[117] M.M. Mihaylova, R.J. Shaw, The AMPK signalling pathway coordinates cell growth, autophagy and metabolism, Nat Cell Biol, 13 (2011) 1016-1023.

[118] E.Q. Toyama, S. Herzig, J. Courchet, T.L. Lewis, O.C. Losón, K. Hellberg, N.P. Young, H. Chen, F. Polleux, D.C. Chan, R.J. Shaw, Metabolism. AMP-activated protein kinase mediates mitochondrial fission in response to energy stress, Science, 351 (2016) 275-281.

[119] N. Djouder, R.D. Tuerk, M. Suter, P. Salvioni, R.F. Thali, R. Scholz, K. Vaahtomeri, Y. Auchli, H. Rechsteiner, R.A. Brunisholz, B. Viollet, T.P. Mäkelä, T. Wallimann, D. Neumann, W. Krek, PKA phosphorylates and inactivates AMPKalpha to promote efficient lipolysis, EMBO J, 29 (2010) 469-481.

[120] D.K. Aw, R.A. Sinha, S.Y. Xie, P.M. Yen, Differential AMPK phosphorylation by glucagon and metformin regulates insulin signaling in human hepatic cells, Biochem Biophys Res Commun, 447 (2014) 569-573.

[121] A.C. Ferretti, F.M. Tonucci, F. Hidalgo, E. Almada, M.C. Larocca, C. Favre, AMPK and PKA interaction in the regulation of survival of liver cancer cells subjected to glucose starvation, Oncotarget, 7 (2016) 17815-17828.

[122] R. Palorini, G. Votta, Y. Pirola, H. De Vitto, S. De Palma, C. Airoldi, M. Vasso, F. Ricciardiello, P.P. Lombardi, C. Cirulli, R. Rizzi, F. Nicotra, K. Hiller, C. Gelfi, L. Alberghina, F. Chiaradonna, Protein Kinase A Activation Promotes Cancer Cell Resistance to Glucose Starvation and Anoikis, PLoS Genet, 12 (2016) e1005931.

[123] P. Mishra, D.C. Chan, Metabolic regulation of mitochondrial dynamics, J Cell Biol, 212 (2016) 379-387.

[124] E.L. Barnhart, Mechanics of mitochondrial motility in neurons, Curr Opin Cell Biol, 38 (2016) 90-99.

[125] M.A. Franker, C.C. Hoogenraad, Microtubule-based transport - basic mechanisms, traffic rules and role in neurological pathogenesis, J Cell Sci, 126 (2013) 2319-2329.

[126] A. Abeliovich, A.D. Gitler, Defects in trafficking bridge Parkinson's disease pathology and genetics, Nature, 539 (2016) 207-216.

[127] M.Y. Lin, Z.H. Sheng, Regulation of mitochondrial transport in neurons, Exp Cell Res, 334 (2015) 35-44.

[128] O.S. Koutsopoulos, D. Laine, L. Osellame, D.M. Chudakov, R.G. Parton, A.E. Frazier, M.T. Ryan, Human Miltons associate with mitochondria and induce microtubule-dependent remodeling of mitochondrial networks, Biochim Biophys Acta, 1803 (2010) 564-574.

[129] A.F. MacAskill, K. Brickley, F.A. Stephenson, J.T. Kittler, GTPase dependent recruitment of Grif-1 by Miro1 regulates mitochondrial trafficking in hippocampal neurons, Mol Cell Neurosci, 40 (2009) 301-312.

[130] Q. Cai, C. Gerwin, Z.H. Sheng, Syntabulin-mediated anterograde transport of mitochondria along neuronal processes, J Cell Biol, 170 (2005) 959-969.

[131] Q. Su, Q. Cai, C. Gerwin, C.L. Smith, Z.H. Sheng, Syntabulin is a microtubule-associated protein implicated in syntaxin transport in neurons, Nat Cell Biol, 6 (2004) 941-953.

[132] Y. Chen, Z.H. Sheng, Kinesin-1-syntaphilin coupling mediates activity-dependent regulation of axonal mitochondrial transport, J Cell Biol, 202 (2013) 351-364.

[133] J.S. Kang, J.H. Tian, P.Y. Pan, P. Zald, C. Li, C. Deng, Z.H. Sheng, Docking of axonal mitochondria by syntaphilin controls their mobility and affects short-term facilitation, Cell, 132 (2008) 137-148.

[134] K.D. Lee, P.J. Hollenbeck, Phosphorylation of kinesin in vivo correlates with organelle association and neurite outgrowth, J Biol Chem, 270 (1995) 5600-5605.

[135] R. Sato-Yoshitake, H. Yorifuji, M. Inagaki, N. Hirokawa, The phosphorylation of kinesin regulates its binding to synaptic vesicles, J Biol Chem, 267 (1992) 23930-23936.

[136] J.L. Klosowiak, P.J. Focia, S. Chakravarthy, E.C. Landahl, D.M. Freymann, S.E. Rice, Structural coupling of the EF hand and C-terminal GTPase domains in the mitochondrial protein Miro, EMBO Rep, 14 (2013) 968-974.

[137] M. Saotome, D. Safiulina, G. Szabadkai, S. Das, A. Fransson, P. Aspenstrom, R. Rizzuto, G. Hajnóczky, Bidirectional Ca2+-dependent control of mitochondrial dynamics by the Miro GTPase, Proc Natl Acad Sci U S A, 105 (2008) 20728-20733.

[138] T.T. Nguyen, S.S. Oh, D. Weaver, A. Lewandowska, D. Maxfield, M.H. Schuler, N.K. Smith, J. Macfarlane, G. Saunders, C.A. Palmer, V. Debattisti, T. Koshiba, S. Pulst, E.L. Feldman, G. Hajnóczky, J.M. Shaw, Loss of Miro1-directed mitochondrial movement results in a novel murine model for neuron disease, Proc Natl Acad Sci U S A, 111 (2014) E3631-3640.

[139] X. Wang, T.L. Schwarz, The mechanism of Ca2+ -dependent regulation of kinesin-mediated mitochondrial motility, Cell, 136 (2009) 163-174.

[140] J. Scherer, J. Yi, R.B. Vallee, PKA-dependent dynein switching from lysosomes to adenovirus: a novel form of host-virus competition, J Cell Biol, 205 (2014) 163-177.

[141] J. Boczan, A.G. Leenders, Z.H. Sheng, Phosphorylation of syntaphilin by cAMP-dependent protein kinase modulates its interaction with syntaxin-1 and annuls its inhibitory effect on vesicle exocytosis, J Biol Chem, 279 (2004) 18911-18919.

[142] Y. Ying, L. Li, W. Cao, D. Yan, Q. Zeng, X. Kong, L. Lu, M. Yan, X. Xu, J. Qu, Q. Su, X. Ma, The microtubule associated protein syntabulin is required for glucose-stimulated and cAMP-potentiated insulin secretion, FEBS Lett, 586 (2012) 3674-3680.

[143] M. Müller, S.L. Mironov, M.V. Ivannikov, J. Schmidt, D.W. Richter, Mitochondrial organization and motility probed by two-photon microscopy in cultured mouse brainstem neurons, Exp Cell Res, 303 (2005) 114-127.

[144] S. Chen, G.C. Owens, D.B. Edelman, Dopamine inhibits mitochondrial motility in hippocampal neurons, PLoS One, 3 (2008) e2804.

[145] Y. Xu, M. Chen, B. Hu, R. Huang, In vivo Imaging of Mitochondrial Transport in Single-Axon Regeneration of Zebrafish Mauthner Cells, Front Cell Neurosci, 11 (2017) 4.

[146] D.H. Bhatt, S.J. Otto, B. Depoister, J.R. Fetcho, Cyclic AMP-induced repair of zebrafish spinal circuits, Science, 305 (2004) 254-258.

[147] J. Qiu, D. Cai, H. Dai, M. McAtee, P.N. Hoffman, B.S. Bregman, M.T. Filbin, Spinal axon regeneration induced by elevation of cyclic AMP, Neuron, 34 (2002) 895-903.

[148] P. Feng, L. Ge, N. Akyhani, G. Liau, Sodium butyrate is a potent modulator of smooth muscle cell proliferation and gene expression, Cell Prolif, 29 (1996) 231-241.

[149] F. Ogawa, L.C. Murphy, E.L. Malavasi, S.T. O'Sullivan, H.S. Torrance, D.J. Porteous, J.K. Millar, NDE1 and GSK3β Associate with TRAK1 and Regulate Axonal Mitochondrial Motility: Identification of Cyclic AMP as a Novel Modulator of Axonal Mitochondrial Trafficking, ACS Chem Neurosci, 7 (2016) 553-564.

[150] N.J. Bradshaw, D.C. Soares, B.C. Carlyle, F. Ogawa, H. Davidson-Smith, S. Christie, S. Mackie, P.A. Thomson, D.J. Porteous, J.K. Millar, PKA phosphorylation of NDE1 is DISC1/PDE4 dependent and modulates its interaction with LIS1 and NDEL1, J Neurosci, 31 (2011) 9043-9054.

[151] I. Maiellaro, M.J. Lohse, R.J. Kittel, D. Calebiro, cAMP Signals in Drosophila Motor Neurons Are Confined to Single Synaptic Boutons, Cell Rep, 17 (2016) 1238-1246.

[152] S.R. Neves, P. Tsokas, A. Sarkar, E.A. Grace, P. Rangamani, S.M. Taubenfeld, C.M. Alberini, J.C. Schaff, R.D. Blitzer, Moraru, II, R. Iyengar, Cell shape and negative links in regulatory motifs together control spatial information flow in signaling networks, Cell, 133 (2008) 666-680.

[153] J.K. Millar, B.S. Pickard, S. Mackie, R. James, S. Christie, S.R. Buchanan, M.P. Malloy, J.E. Chubb, E. Huston, G.S. Baillie, P.A. Thomson, E.V. Hill, N.J. Brandon, J.C. Rain, L.M. Camargo, P.J. Whiting, M.D. Houslay, D.H. Blackwood, W.J. Muir, D.J. Porteous, DISC1 and PDE4B are interacting genetic factors in schizophrenia that regulate cAMP signaling, Science, 310 (2005) 1187-1191.

[154] F. Guan, C. Zhang, S. Wei, H. Zhang, X. Gong, J. Feng, C. Gao, R. Su, H. Yang, S. Li, Association of PDE4B polymorphisms and schizophrenia in Northwestern Han Chinese, Hum Genet, 131 (2012) 1047-1056.

[155] H. Manji, T. Kato, N.A. Di Prospero, S. Ness, M.F. Beal, M. Krams, G. Chen, Impaired mitochondrial function in psychiatric disorders, Nat Rev Neurosci, 13 (2012) 293-307.

[156] J.Y. Jiang, J.L. Falcone, S. Curci, A.M. Hofer, Interrogating cyclic AMP signaling using optical approaches, Cell Calcium, (2017).

[157] D. Pendin, E. Greotti, K. Lefkimmiatis, T. Pozzan, Exploring cells with targeted biosensors, J Gen Physiol, 149 (2017) 1-36.

[158] D.M. Embogama, M.K. Pflum, K-BILDS: A Kinase Substrate Discovery Tool, Chembiochem, 18 (2017) 136-141.

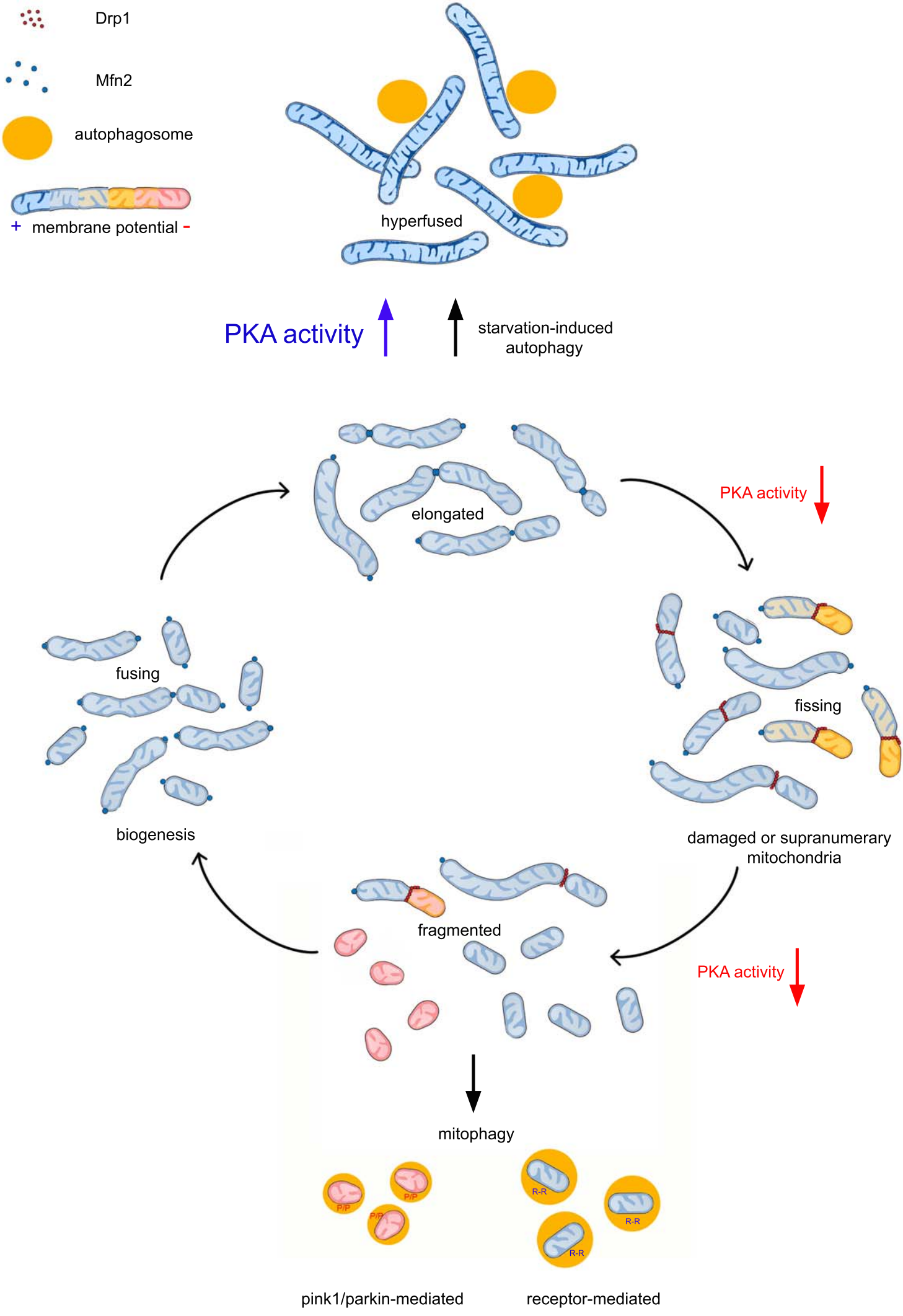
[159] P.M. Dedigama-Arachchige, M.K. Pflum, K-CLASP: A Tool to Identify Phosphosite Specific Kinases and Interacting Proteins, ACS Chem Biol, 11 (2016) 3251-3255.

[160] P. Giansanti, M.P. Stokes, J.C. Silva, A. Scholten, A.J. Heck, Interrogating cAMP-dependent kinase signaling in Jurkat T cells via a protein kinase A targeted immune-precipitation phosphoproteomics approach, Mol Cell Proteomics, 12 (2013) 3350-3359.

[161] P. Giansanti, T.T. Aye, H. van den Toorn, M. Peng, B. van Breukelen, A.J. Heck, An Augmented Multiple-Protease-Based Human Phosphopeptide Atlas, Cell Rep, 11 (2015) 1834-1843.

12. Figure Legends

Figure 1: Schematic representation of the involvement of the cAMP/PKA axis in the regulation of mitochondrial fission/fusion cycles and mitophagy.


Drp1
Mfn2
autophagosome
+ membrane potential -
hyperfused
PKA activity
starvation-induced autophagy
elongated
PKA activity
fusing
fissing
biogenesis
damaged or supranumerary mitochondria
fragmented
PKA activity
mitophagy
P/P
P/P
P/P
R-R
R-R
R-R
pink1/parkin-mediated
receptor-mediated

Highlights

- Mitochondrial dynamics are controlled by mitochondrial and cell signalling pathways
- Mitochondrial host cAMP/PKA signalling microdomains
- cAMP is a key player in the orchestration of mitochondrial dynamics
- PKA phosphorylation of mitochondrial targets regulates fission, mitophagy & motility