



Serial Review: The powerhouse takes control of the cell:  
The role of mitochondria in signal transduction  
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# Kinase signaling cascades in the mitochondrion: a matter of life or death<sup>☆</sup>

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## Abstract

In addition to powering energy needs of the cell, mitochondria function as pivotal integrators of cell survival/death signals. In recent years, numerous studies indicate that each of the major kinase signaling pathways can be stimulated to target the mitochondrion. These include protein kinase A, protein kinase B/Akt, protein kinase C, extracellular signal-regulated protein kinase, c-Jun N-terminal kinase, and p38 mitogen-activated protein kinase. Although most studies focus on phosphorylation of pro- and antiapoptotic proteins (BAD, Bax, Bcl-2, Bcl-xL), kinase-mediated regulation of complex I activity, anion and cation channels, metabolic enzymes, and Mn-SOD mRNA has also been reported. Recent identification of a number of scaffold proteins (AKAP, PICK, Sab) that bring specific kinases to the cytoplasmic surface of mitochondria further emphasizes the importance of mitochondrial kinase signaling. Immunogold electron microscopy, subcellular fractionation, and immunofluorescence studies demonstrate the presence of kinases within subcompartments of the mitochondrion, following diverse stimuli and in neurodegenerative diseases. Given the sensitivity of these signaling pathways to reactive oxygen and nitrogen species, in situ activation of mitochondrial kinases may represent a potent reverse-signaling mechanism for communication of mitochondrial status to the rest of the cell. © 2004 Elsevier Inc. All rights reserved.

**Keywords:** Mitochondria; Protein kinases; Programmed cell death; Protein trafficking/translocation; Scaffold proteins; Oxidative stress; Parkinson's/Lewy body disease; Cancer; Free radical

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**Abbreviations:** AKAP, A-kinase anchoring protein; Akt/PKB, protein kinase B; DAG, diacylglycerol; ERK, extracellular signal-regulated protein kinase; GSK3 $\beta$ , glycogen synthase kinase 3 $\beta$ ; IP<sub>3</sub>, inositol triphosphate; JNK/SAPK, c-Jun N terminal kinase/stress-activated protein kinase; MAPK, mitogen-activated protein kinases; MAPKK, MAPK kinase; MEK 1/2, MAPK/ERK kinase, a MAPKK; MKK, MAPK kinase or MAPKK; Mn-SOD, manganese superoxide dismutase or SOD2; NF- $\kappa$ B, nuclear factor  $\kappa$ B; p38 MAPK, p38 mitogen activated protein kinase; PICK, protein that interacts with C-kinase; PKA, protein kinase A; PKC, protein kinase C; PP2a, protein phosphatase 2a; RACK, receptor for activated C-kinase; RICK, receptor for inactive C-kinase; ROS, reactive oxygen species; Sab, SH3BP5, Src homology 3-binding protein 5, a JNK-interacting protein; VDAC, voltage-dependent anion channel.

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## Introduction

Dynamic networks of signaling cascades mediate the communication of localized events to other regions of the cell, allowing appropriate cellular and tissue responses to opportunities or stresses in the larger environment. The translocation of activated signaling proteins from the cell membrane to the nucleus, where the rate of transcription of specific genes is altered, is easily the most familiar form of signal transduction. However, it is by no means the only route that signaling molecules can take. Localization of activated protein kinases to specific cytoplasmic subcompartments mediates important processes such as cell motility [1], and signaling endosomes may facilitate long distance communication in neurons [2]. In addition to classic hormone- or growth factor-initiated signaling cascades, recent advances in redox regulation of signaling pathways adds to the complexity of signals that must be integrated to produce a functional outcome. The mitochondrion is ideally suited as a point of integration for these signaling cascades due to its pivotal role in cellular metabolism, redox biochemistry, and survival–death decisions.

Following development of the endosymbiotic theory of mitochondrial origin, characterization of enzymes in carbohydrate, lipid, amino acid, and nucleotide metabolism, and the elucidation of the Krebs cycle and electron transport chain, the mitochondrion has reemerged as a central mediator of cell death signaling [3]. Aside from extensive work with Bcl-2 family members and release of mitochondrial death mediators [4–7], relatively little is known about how this organelle communicates with the rest of the cell. Even in healthy nondying cells, regulation of mitochondrial numbers in relation to cellular needs would require coordinated transcription of nuclear and mitochondrial genes and the genesis or trafficking of mitochondria to appropriate regions of high-energy utilization [8]. Likewise, mechanisms for signaling autophagic degradation of aged or damaged mitochondria also remain to be elucidated [9–11].

In recent years, numerous studies have consistently demonstrated that certain components of well-known kinase signaling cascades are specifically targeted to mitochondria, where they modulate mitochondrial activity and the release of mitochondrial products that ultimately affect the entire cell. While the majority of these studies have focused on the mitochondrion as a recipient and integrator of cell survival/death signals, components of the respiratory chain are also regulated by phosphorylation [12–14]. Additionally, several of these kinase pathways are subject to regulation by reactive oxygen and nitrogen species. Specific mechanisms by which redox tone can regulate cell signaling pathways

have been previously reviewed [15–19]. The following discussion focuses on kinase regulation of mitochondrial function and studies that demonstrate localization of activated kinases within mitochondrial subcompartments. As reactive oxygen/nitrogen species are typically short-lived, definitive mitochondrial localization of kinases suggests additional mechanisms for reverse signaling from mitochondria to the rest of the cell.

## Protein kinase A

The protein kinase A (PKA) signaling pathway mediates a multitude of responses to hormonal stimulation which are often cell type specific (for review, see [20]). The classic PKA pathway involves the binding of an extracellular molecule to a G protein-coupled receptor, which catalyzes the formation of intracellular cyclic AMP through the activation of adenylate cyclase. Cyclic AMP then binds to the two regulatory subunits of PKA, thereby releasing the two catalytic subunits to phosphorylate serine and threonine residues on target proteins. These subunits enter the nucleus and phosphorylate transcription factors such as CREB and NF- $\kappa$ B. In addition, a growing role for localized PKA signaling in specific subcellular compartments has been recognized with the discovery of specific anchoring scaffold proteins.

PKA activity has been identified within the mitochondria in a wide variety of species, including human (e.g., see [21,22]). Although these studies typically relied on differential centrifugation techniques, which can be subject to cytoplasmic contamination, the more recent elucidation of A-kinase anchoring proteins (AKAPs) has led to major paradigm shifts concerning mechanisms by which activation of a common signaling pathway can lead to divergent cellular responses. Certain AKAPs serve to specifically recruit PKA isoforms to the cytoplasmic side of the outer mitochondrial membrane [23–28]. Moreover, tissue specific D-AKAP1 splice variants result in differential targeting to either mitochondria or the endoplasmic reticulum [29]. As AKAPs also bind other kinases and phosphatases, and in some cases may not actually recruit PKA [30], this group of proteins could also function in a larger role to mediate signaling cross talk between different kinase pathways (reviewed in [31]).

Mitochondrially targeted PKA activity tends to have positive effects on the mitochondria and on the cell as a whole. PKA localized to the inner membrane and matrix of mitochondria phosphorylates and promotes the activity of complex I [12]. AKAP-mediated targeting of activated PKA to the cytoplasmic surface of mitochondria results in

phospho-inhibition of the proapoptotic protein BAD, enhancing cell survival [25,28]. A peripheral benzodiazepine receptor-associated protein functions as an AKAP that promotes mitochondrial steroidogenesis [32]. Another novel role proposed for AKAP-121 includes targeting of Mn-superoxide dismutase mRNA to the mitochondria for localized translation of this important antioxidant [33]. Moreover, the small G-protein Rab32, which regulates mitochondrial fission, appears to function as a mitochondrially targeted AKAP [34]. Thus, mitochondrial targeting of PKA appears to be involved in regulating most major mitochondrial functions, promoting respiration, antagonizing cell death, and regulating mitochondrial protein expression and biogenesis (Fig. 1).

### PI3K/Akt/PKB

The serine/threonine kinase Akt (protein kinase B) plays a major role in cell proliferation and survival in many cell types. Akt is classically activated by phosphoinositide-

dependent kinases following recruitment to the plasma membrane by products of the type I phosphoinositide 3-kinase [35]. Antiapoptotic effects of nitric oxide may be partially mediated through cGMP-dependent activation of phosphoinositide 3-kinase and Akt [36]. In addition to direct effects of Akt in phospho-inactivating the proapoptotic protein BAD [37], Akt can recruit Raf-1 to the mitochondria [38] and influence expression of proteins involved in the mitochondrial permeability transition [39], which precedes necrotic and apoptotic cell death [9]. Finally, Akt can promote cell survival through regulation of forkhead transcription factors [40].

In neuroblastoma and human embryonic kidney cells, insulin-like growth factor 1 results in rapid translocation of phospho-Akt into mitochondrial subcellular fractions [41]. However, this effect may be cell type specific, as Akt was not observed in mitochondria of mesangial cells stimulated by insulin-like growth factor 1 [42]. Activated mitochondrial Akt resulted in phosphorylation of the  $\beta$  subunit of ATP synthase and of glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) [41]. GSK3 $\beta$  has been localized by immunoelectron

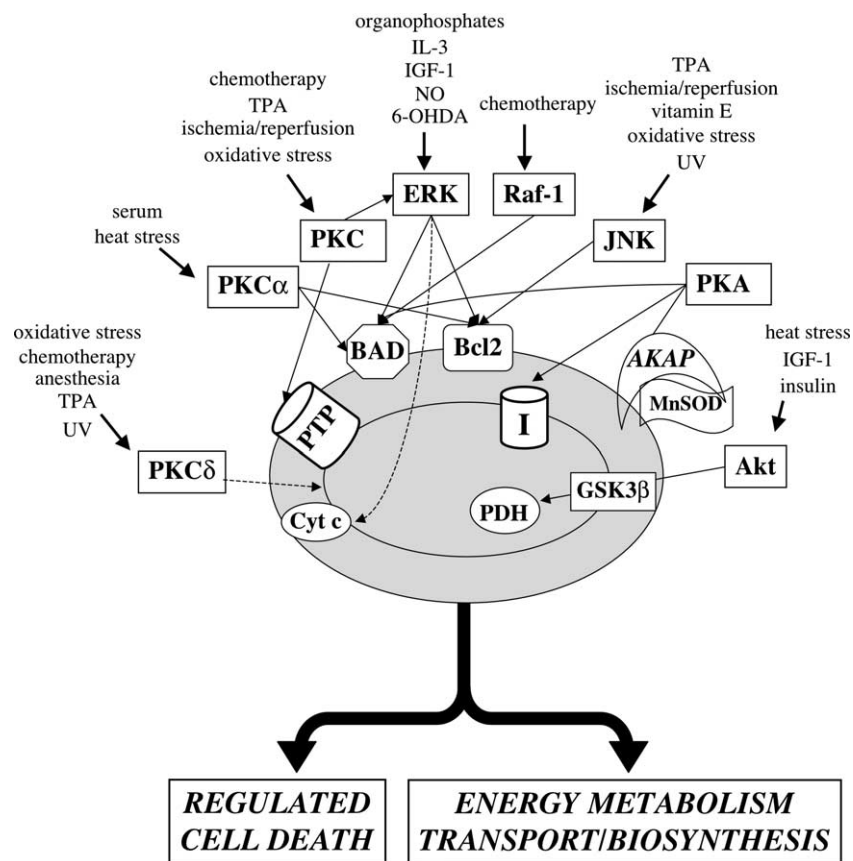


Fig. 1. Schematic summarizing major kinase pathways that converge on the mitochondrion. A growing body of data indicate that activated versions of each of these kinases (rectangles) are targeted directly to mitochondria, resulting in phosphorylation of mitochondrial proteins that regulate cell death (PTP, BAD, Bcl-2) and metabolic function (complex I, GSK3 $\beta$ , PDH). Phospho-ERK and PKC may also influence cytochrome *c* (Cyt *c*) release or membrane potential through other mechanisms (dotted arrows). In addition, kinases and mitochondrial anchoring proteins may participate in a novel mechanism for regulating mitochondrial protein expression, as illustrated by PKA- and AKAP-dependent targeting of MnSOD mRNA to the mitochondrion for local translation. Abbreviations not defined elsewhere: IGF-1, insulin-like growth factor 1; IL-3, interleukin-3; NO, nitric oxide; PDH, pyruvate dehydrogenase; PTP, permeability transition pore; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; UV, ultraviolet radiation; 6-OHDA, 6-hydroxydopamine.

microscopy to the mitochondria, where it functions to phosphorylate and inhibit mitochondrial pyruvate dehydrogenase activity [43] and to promote apoptosis [44]. Based on accessibility to proteases, Akt also appears to be localized within the mitochondria rather than on its surface, predominantly in mitochondrial membrane fractions and to a lesser degree in the matrix [41]. Interestingly, disruption of the mitochondrial proton gradient inhibited mitochondrial Akt accumulation, suggestive of specific import mechanisms.

### Protein kinase C

The protein kinase C (PKC) family consists of multiple isozymes with distinct distribution patterns in different tissues [45]. Binding of an extracellular ligand to a receptor tyrosine kinase or G protein-coupled receptor activates phospholipase C, which produces inositol triphosphate (IP<sub>3</sub>) and diacylglycerol (DAG). Calcium liberated by IP<sub>3</sub> causes PKC to bind to membranes, where DAG then activates it. Activated PKC phosphorylates many targets, including c-Fos and NF- $\kappa$ B. It is important to note, though, that the isozymes of PKC differ not only in their localization but also in their responsiveness to IP<sub>3</sub>, DAG, and calcium. There are three major subgroups of PKC isoforms, conventional, novel, and atypical, classified by virtue of their responsiveness to these regulators [46].

Nearly 10 years ago, the  $\alpha$  and  $\beta$  isoforms of PKC were detected in a subset of mitochondria in carp retinal Müller cells [47]. These immunoelectron microscopy studies showed that the kinase was associated with the inner membrane and cristae. Since that time, a large, growing body of research indicates that PKC isoforms play a direct role in regulating mitochondrial function.

Quite frequently, activated PKC isoforms that translocate to the mitochondria are proapoptotic or inhibitory to mitochondrial function. For example, renal proximal tubular cells respond to oxidative stress by trafficking activated PKC $\epsilon$  to the mitochondria, which inhibits the electron transport chain, ATP production, and Na<sup>+</sup> transport, likely in part through direct phosphorylation of Na<sup>+</sup>-K<sup>+</sup>-ATPase [48]. Treatment of various neoplastic cells with phorbol esters, H<sub>2</sub>O<sub>2</sub>, or anticancer agents such as cisplatin and etoposide causes PKC $\delta$  to travel to the mitochondria, where it triggers the release of cytochrome *c* and the subsequent induction of apoptosis [49–52]. A similar process occurs in keratinocytes, in which exposure to UV radiation triggers PKC $\delta$  activation and mitochondrial translocation, followed by disruption of the mitochondrial membrane potential, caspase release, and apoptosis [53]. Overexpression of PKC $\delta$  promotes apoptosis in both normal and neoplastic keratinocytes by targeting the mitochondria and altering its membrane potential [54]. Indeed, a failure of PKC $\delta$  activity has been suggested as a mechanism of both carcinogenesis and chemotherapy resistance [50,52].

In other systems, some of these same PKC isoforms also mediate prosurvival functions. PKC $\alpha$  phosphorylates mitochondrial Bcl-2 in several cell types, thereby reducing apoptosis, enhancing survival after heat shock, or producing resistance to chemotherapy [55,56]. In rat cardiac myocytes PKC $\delta$  was shown to move to the mitochondria in response to anesthetic exposure or ischemia/reperfusion. PKC $\delta$  then appears to activate mitochondrial K<sub>ATP</sub> channels, which in turn promote cardioprotection [57]. PKC $\epsilon$  also promotes cardioprotection following ischemia/reperfusion through a different mechanism, phosphorylating the voltage-dependent anion channel (VDAC) component of the mitochondrial permeability transition pore [58]. This prevents mitochondrial swelling, outer membrane rupture, release of apoptogenic factors, and decreases in ATP production. Also, PKC $\epsilon$  and extracellular signal-regulated kinases (ERKs) appear to physically interact at the mitochondria to inactivate the proapoptotic protein BAD in cardiac myocytes [59]. Inactivation of the proapoptotic protein Bax by PKC $\epsilon$  in prostate cancer cells renders these cells resistant to androgen-deprivation therapy [60].

As PKC isoforms translocate from one cell compartment to another, these conflicting responses to PKC signaling may be mediated in part by association with specific anchoring scaffold proteins, receptors for activated C kinase (RACKs) and receptors for inactive C kinase (RICKs) [61]. In particular, a protein that interacts with C kinase (PICK1) was recently described that specifically targets PKC $\alpha$  to mitochondria [62]. Mechanisms by which divergent scaffold protein expression may impact the outcome of PKC signaling in a cell type- and/or stimulus-dependent manner remain to be elucidated.

### Raf-MEK-ERK

The extracellular signal regulated protein kinases (ERK1/2) are integrally involved in regulating pivotal processes including proliferation, differentiation, adaptation (i.e., cell motility, long term potentiation), survival, and even cell death. The three-tiered ERK signaling module involves sequential activation of Raf (MAPKKK), MEK1/2 (MAPKK), and ERK1/2 (MAPK). Depending on its intracellular localization and pathway of activation, Raf-1 can affect apoptosis by different mechanisms [38,63]. Likewise, ERK signaling can mediate apparently opposite responses to injury even within the same general cell type (see [64,65] for review), which likely reflect differences in activation mechanism and/or subcellular targeting.

The recognition that the antiapoptotic protein Bcl-2 plays an important role in targeting Raf-1 to the mitochondria, resulting in phosphorylation of BAD, provided early evidence for distinct signaling roles for subpopulations of plasma membrane-targeted versus mitochondrially targeted Raf proteins [66]. Furthermore, signaling modules consisting of Raf-1, MEK1, and the adapter protein Grb10 have been

localized to mitochondrial membranes [67]. The antiapoptotic effects of mitochondrially localized Raf-1 are independent of ERK activity in myeloid cells [38], although MEK/ERK signaling does mediate antiapoptotic effects of B-Raf in fibroblasts [68]. Interestingly, phosphorylation of S338 and S339 on Raf-1 promotes mitochondrial translocation and protection of endothelial cells from the intrinsic pathway of apoptosis, whereas Src mediated phosphorylation of Y340 and Y341 and MEK/ERK activity are important for protection from death receptor-initiated cell death [63].

Many studies using pharmacologic inhibitors of MEK have indicated that ERK can modulate mitochondrial functions, particularly those associated with cell death. For example, ERK signaling appears to promote mitochondrial ATP synthase function in glucose-deprived astrocytes [69], to maintain mitochondrial membrane potential and prevent cytochrome *c* release [70], and to inactivate the proapoptotic protein BAD [71]. In contrast to these cytoprotective effects, ERK has also been implicated in promoting oxidative neuronal injuries [64] and in neurodegenerative diseases [72–77]. MEK/ERK promotes organophosphate-elicited mitochondrial vacuolation [78], apoptotic translocation of Bax to the mitochondria [79], and nonapoptotic programmed cell death [80]. As pro- and antideath effects of MEK/ERK signaling could be mediated by downstream targets or at the transcriptional level [81], these studies do not necessarily indicate mitochondrial targeting of ERK.

The first evidence supporting mitochondrial targeting of ERK signaling was derived from biochemical subcellular fractionation studies. In renal tubular cells, both activated ERK1/2 and PKC $\alpha$  are enriched in mitochondrial fractions during cisplatin injury, where they contribute to increased mitochondrial membrane potential, decreased oxidative phosphorylation, and increased caspase-3 activation and apoptosis [82]. Likewise, activities of ERK in phosphorylating both Bcl-2 [83] and BAD [42,59] are associated with increased levels of activated ERK colocalizing or co-immunoprecipitating with the Bcl-2 family members in mitochondria. Although mitochondrial fractions of normal rat brain homogenates show 10-fold lower levels of ERK1/2 than those observed in crude homogenates [84], the existence of a mitochondrial pool of ERK1/2 in normal as well as stressed tissues supports a potential physiologic role for ERK in mitochondrial regulation.

Two recent immuno-electron microscopy studies have established the presence of phosphorylated ERK1/2 within the mitochondrion [85,86]. Phospho-ERK was found at high labeling densities within a subset of mitochondria in degenerating neurons from patients with Parkinson's disease and Lewy body dementia [85,87], corresponding to a distinct granular cytoplasmic pattern of staining not observed in age-matched control patients [88]. Some of these mitochondria were within autophagosomes [85]. As ERK signaling promotes autophagy in colon cancer cells [89], this suggests the possibility of ERK-regulated mitochondrial turnover. Although passive accumulation in

damaged mitochondria is also possible, the normal distribution of ERK and phospho-ERK within mitochondria during brain development [86] lends further support for an important role for ERK in mitochondrial regulation.

Interestingly, rather than being tethered to the cytoplasmic face of the mitochondrial outer membrane as one may expect for a signaling protein transmitting extracellular and cytoplasmic signals to mitochondria, both ultrastructural studies showed ERK localized within the mitochondrion. Biochemical subfractionation studies indicated the strongest localization in association with the combined outer membrane/intermembrane space fraction, with significant levels of ERK also detected in the matrix fractions [86]. While it is possible that surface-associated ERK may be transient or fail to survive mitochondrial isolation, it is clear that ERK is present in an ideal location for modulating mitochondrial death mediators and respiratory or metabolic processes.

As the Raf–Mek–ERK axis is sensitive to redox regulation [64], mitochondrial localization of activated ERK could reflect localized ERK activation in addition to mitochondrial targeting of ERK activated elsewhere. Indeed, intact mitochondrial respiratory function is essential for ERK activation by hydrogen peroxide or during ischemia–reperfusion in cardiac myocytes [90,91]. Moreover, mitochondrial K<sub>ATP</sub> channel openers can activate ERK by a mechanism dependent on production of mitochondrial reactive oxygen species (ROS) [92]. Mitochondrial dependence of ERK activation could be due in part to inactivation of mitochondrially targeted phosphatases. Protein phosphatase 2A (PP2A) not only is targeted to mitochondria by splice variants of its regulatory subunit [93], but also is sensitive to redox regulation [94]. Indeed, mitochondrial PP2A may protect cells by opposing ERK-mediated Bcl-2 phosphorylation [95]. Likewise, overexpression of the antioxidant enzyme Mn superoxide dismutase (MnSOD) reduces pathologic ERK phosphorylation [96]. Thus, in addition to transmitting extracellular messages to mitochondria, a pool of ERK signaling proteins may be poised to communicate changes in mitochondrial metabolism to influence appropriate cellular responses (Fig. 2).

### JNK/SAPK and p38 MAPK

The two other major branches of the MAPK family, the p38 MAPKs and the c-Jun N-terminal kinase (JNK) or stress-activated protein kinase (SAPK) have both been extensively implicated in prodeath signaling (reviewed in [97]). Like ERK, p38 and JNK are activated by a MAP kinase kinase (MKK), which in turn is activated by a MAPKKK in response to a stimulus. The stimulus may include oxidative stress, irradiation, or proinflammatory cytokines such as tumor necrosis factor  $\alpha$ .

Many studies indicate a role for p38 MAPK signaling in regulating events associated with cell death, including translocation of Bax from cytosolic to mitochondrial

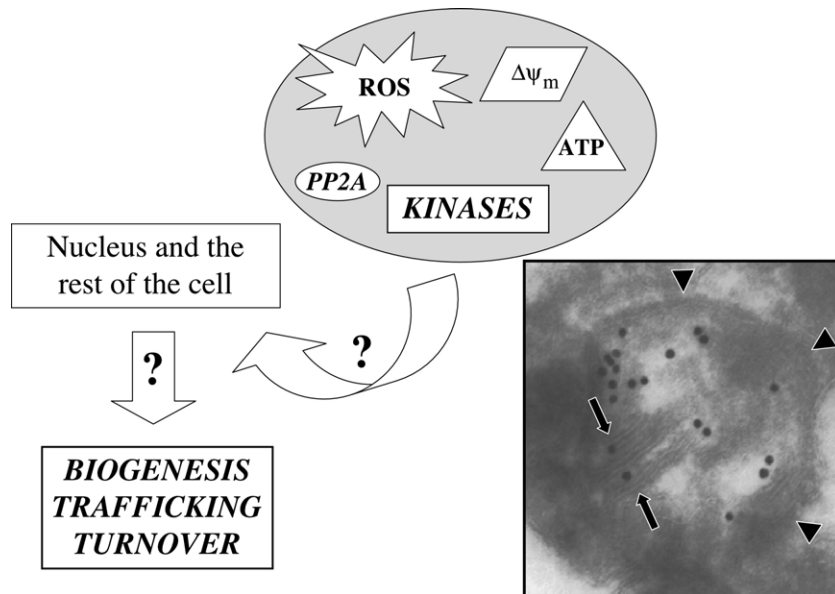


Fig. 2. The observation that kinases are localized within the mitochondrion supports a hypothetical mechanism for transmission of mitochondrially initiated messages. As activation of MAPK pathways in certain situations is dependent on mitochondrial ROS, membrane potential, and/or ATP production, in situ activation of mitochondrial kinases or inactivation of phosphatases (PP2A) could effectively communicate mitochondrial status to the rest of the cell, potentially influencing synthesis, trafficking, or turnover of mitochondrial components. Inset: Immunogold labeling (punctate dots) of phospho-ERK in association with mitochondrial cristae (arrows) and matrix in a neuron from a patient with Lewy body disease. Membranes appear as pale, unstained linear images in this uranyl-stained section, and the cytoplasmic surface of the mitochondrion is indicated with arrowheads.

compartments [98,99], caspase-independent potassium efflux [100], and transcriptional regulation of TR3, a steroid receptor-like protein that translocates from the nucleus to the mitochondria to initiate the intrinsic pathway of apoptosis [101]. Both p38 MAPK and JNK have been identified in signaling modules that also contain ERK and PKC $\epsilon$  in cardiac myocytes [59], and irradiation promotes translocation of both p38 and JNK1 to mitochondrial subcellular fractions [102].

Involvement of MAPKs in regulating the mitochondrial death pathway is particularly well documented for JNK, not simply through the activation of intermediates like Bax [103], but also by many subcellular fractionation studies showing localization of activated JNK to the mitochondria. In addition, recent identification of mitochondrially targeted scaffold proteins lends compelling evidence for the biologic relevance of mitochondrial JNK. For example, Sab (SH3BP5) is a JNK-binding protein that co-localizes with mitochondria [104], and may serve a function analogous to that of certain AKAPs in the localization of kinase activity to the mitochondria.

The effects of JNK on the mitochondria often involve stimulation of apoptosis. Treatment of isolated rat brain mitochondria with active JNK causes the inhibition of antiapoptotic Bcl-2 and Bcl-x<sub>L</sub>, promoting the release of cytochrome *c* and a decrease in  $\Delta\psi_m$  [105]. The mitochondrial pool of JNK is preferentially activated after oxidative stress in cardiac myocytes, and is responsible for the release of cytochrome *c* in those cells [106]. Treatment with phorbol esters or radiation-induced DNA damage triggers localization of JNK to the mitochondria in human U-937 leukemia cells, where it binds to and inhibits Bcl-x<sub>L</sub>, promoting apoptosis

[107,108]. In addition to releasing cytochrome *c*, mitochondrial JNK causes the release of Smac, the second mitochondria-derived activator of caspase that promotes caspase-9 activity [109]. JNK also mediates phosphorylation and oligomerization of proapoptotic BAD [110]. In ischemia-reperfusion injury, CA1 hippocampal neurons show increased levels of activated JNK that localize to the mitochondrial membrane prior to cell death [111]. Overexpression of a JNK-interacting protein (JIP-1) that sequesters JNK in the cytosol conferred protection against cardiac ischemia-reperfusion injury [112]. Thus, mitochondrial anchoring of JNK promotes phosphorylation of apoptotic regulators, triggering the release of mitochondrial death mediators.

Like the other kinases that regulate mitochondrial function, JNK signaling can yield paradoxical responses, promoting cell survival under some conditions. JNK can phospho-inactivate the pro-apoptotic protein BAD [113]. Activated JNK co-localizes with and phosphorylates Bcl-2 at Ser<sup>70</sup> in the mitochondrial membranes of interleukin-3-dependent hematopoietic cells. This occurs under conditions of stress or by exposure to interleukin-3, resulting in enhanced antiapoptotic activity of Bcl-2 [114]. Thus, the outcome of kinase signaling is often context dependent.

These studies indicate that diverse stimuli can trigger or prevent apoptosis through activation of JNK that is physically associated with the mitochondria. This may reflect mitochondrial translocation of JNK, perhaps mediated by assembly on Sab scaffolds, or it may reflect local activation of mitochondrial pools of JNK. It is interesting to note that mitochondrial ROS and the permeability transition have both been implicated upstream of JNK activation under both

physiologic and pathologic conditions [115,116]. Likewise, p38 MAPK is activated by mitochondrially derived ROS [117]. Thus, these kinases, like ERK, may signal in both directions to influence mitochondrial functions as well as to communicate mitochondrial messages to the rest of the cell.

## Conclusions

Mitochondrial alterations have been implicated in a wide variety of acute and chronic human conditions, including cancer, intoxication, neurodegenerative diseases, and aging [118–121]. For example, not only are there complex I deficiencies in sporadic Parkinson's disease [118], but also mutations in mitochondrially targeted proteins, including a putative kinase [122], have been recently identified in autosomal recessive forms of the disease [123,124]. Kinase signaling pathways impact major mitochondrial functions including sugar and lipid metabolism, oxidative phosphorylation, antioxidant protein expression, mitochondrial fission, and execution of survival–death decisions. Although, some of these kinase-associated effects could be indirect, mediated by downstream processes that in turn affect the mitochondria, a growing number of kinases are known to be directly targeted to the mitochondrial surface and/or compartments within.

Both biochemical and morphologic techniques support localization of kinases to mitochondria. Moreover, subfractionation of purified mitochondria and/or direct ultrastructural visualization indicates association of kinases with mitochondrial cristae and matrix, a distribution that fits with the predicted topology of certain kinase targets [14]. It is interesting to note that many of these kinase pathways respond to redox stimuli [15,16,19,64], raising the possibility of in situ activation of mitochondrial kinase cascades. In addition, the identification of specific mitochondrial anchoring proteins for PKA, PKC, and JNK lends compelling evidence for cytoplasmic to mitochondrial targeting of kinases. Although each kinase cascade elicits complex, sometimes paradoxical, effects on cell death/survival, new research directions based on molecular scaffolds and the potential redox sensitivity of their interactions with kinases, phosphatases, and structural proteins may illuminate new mechanisms of endosymbiotic communication under both physiologic and pathologic conditions.

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