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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☆

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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.

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

Contents

Abbreviations: AKAP, A-kinase anchoring protein; Akt/PKB, protein kinase B; DAG, diacylglycerol; ERK, extracellular signal-regulated protein kinase; GSK3β, glycogen synthase kinase 3β; IP_3, 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-κB, nuclear factor κB; 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.

☆ This article is part of a series of reviews on "The Powerhouse Takes Control of the Cell." The full list of papers may be found on the home page of the journal.

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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-κB. 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