Trends in Biochemical Sciences

CellPress

Opinion

Mitochondrial Proteins Moonlighting in the Nucleus

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Mitochondria function as cellular energy generators, producing the fuel required to drive biological processes. The response of cells to mitochondrial activity or dysfunction regulates their survival, growth, proliferation, and differentiation. Several proteins that contain mitochondrial-targeting sequences (MTS) also reside in the nucleus and there is increasing evidence that the nuclear translocation of mitochondrial proteins represents a novel pathway by which mitochondria signal their status to the cell. Here, we discuss the different mechanisms that control the dual mitochondrial and nuclear localisation of proteins and propose that these nuclear moonlighters represent a widespread regulatory circuit to maintain mitochondrial homeostasis.

Trends

An increasing number of mitochondrial proteins have been reported to reside in the nucleus and act as mediators of direct mitochondria-to-nucleus communication. These proteins may perform similar functions in both compartments or have distinct activities.

Mitochondrial protein import is responsive to mitochondrial activity and this represents a key regulatory point to determine the balance between mitochondrial and nuclear localisation.

Active mitochondrial enzyme complexes may translocate from the mitochondrial matrix to nuclei.

Metabolic enzymes can associate with chromatin and regulate gene expression.

Mitochondrial Communication with the Nucleus

Mitochondria host many metabolic processes, including the generation of cellular energy in the form of ATP by **oxidative phosphorylation** (see Glossary). Although they contain their own genome, most mitochondrial proteins are encoded in the nucleus. It is essential for nuclei to sense changes in mitochondrial metabolism and mount an appropriate response to restore **homeostasis** [1–3]. Disrupted communication between mitochondria and nuclei is implicated in metabolic diseases, cancer, neurodegeneration, and other ageing processes. The role of mitochondria in apoptosis is well characterised [4], but under nonapoptotic conditions, **retrograde signalling** pathways from mitochondria to nuclei are triggered by changes in metabolite levels or altered **proteostasis** [2,3,5]. Commonly, metabolites, including **reactive oxygen species** (**ROS**), act as **second messengers** to regulate cytoplasmic pathways [2,3,5]. However, a new paradigm is emerging whereby proteins that harbour an **MTS** can localise to nuclei and, in some cases, act as direct signals from mitochondria to regulate nuclear events. We propose that, by acting as signalling intermediaries between mitochondria and nuclei, these proteins promote a rapid response to changes in mitochondrial function and may directly link metabolic activity to genome integrity and gene expression.

Direct Mitochondria-to-Nucleus Signalling

Conceptually, the translocation of mitochondrial proteins to nuclei represents the simplest and most direct means of retrograde communication between the two organelles. These proteins can be responsive to a variety of stimuli and may perform a similar function in both compartments or have distinct mitochondrial and nuclear roles. Below, we discuss some of the mechanisms involved.

Nuclear Redirection of Transcription Factors in Response to Disrupted Mitochondrial Function

Transcription factors can be targeted to mitochondria yet primed to be redirected to the nucleus in response to mitochondrial stress. For example, mammalian nuclear factor erythroid 2-related factor 2 (NRF2), which lacks an MTS, is sequestered in a complex with Kelch-like ECH-associated protein 1 (KEAP1) and the MTS-containing phosphatase phosphoglycerate mutase

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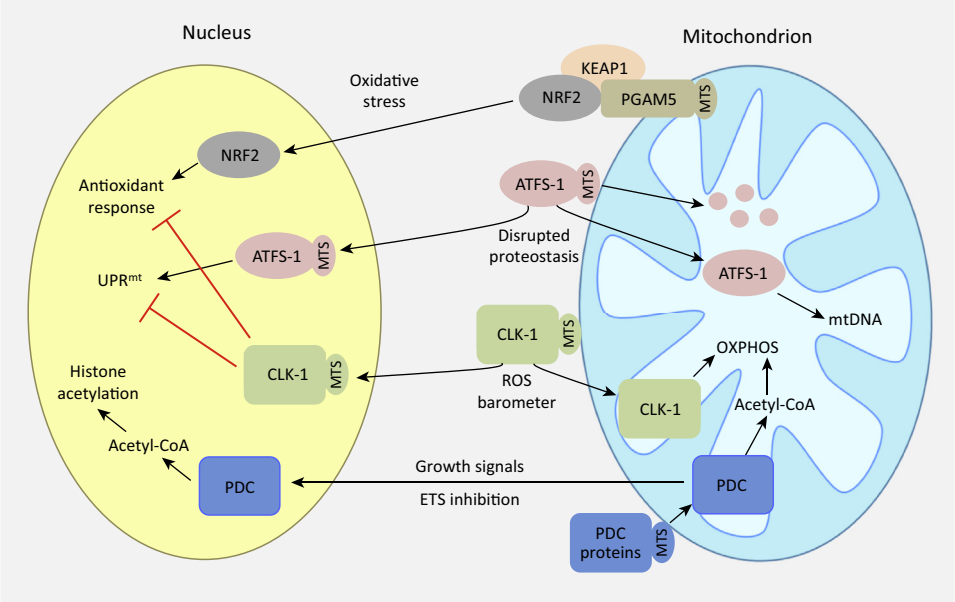

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Figure 1. Mitochondrial Proteins Directly Signal to the Nucleus to Regulate Gene Expression. In mammalian cells, the transcription factor NRF2 associates with the outer mitochondrial membrane as part of a complex with KEAP1 and PGAM5, but dissociates from the complex upon oxidative stress and translocates to the nucleus, where it targets the promoters of genes that contribute to antioxidant defences [6–8]. The *Caenorhabditis elegans* transcription factor ATFS-1 is imported into the mitochondrial matrix and degraded by proteolysis [9], while CLK-1 and components of the PDC are imported into mitochondria and their N-terminal MTSs cleaved [16,20]. CLK-1 is required for the synthesis of ubiquinone and PDC generates acetyl-CoA, both of which contribute to oxidative phosphorylation (OXPHOS) [15,22]. ATFS-1 and CLK-1 are redirected from mitochondria to nuclei in response to disrupted proteostasis and physiological ROS production, respectively [9,16]. ATFS-1 mediates the UPR^{mt} and the expression of mitochondrial-encoded genes in *C. elegans* [9,12], while CLK-1 acts to limit stress responses in both *C. elegans* and human cells [16]. PDC is proposed to translocate from mitochondria to nuclei as an intact complex in human cells in response to growth signals or impaired oxidative phosphorylation. Similar to its mitochondrial activity, nuclear PDC generates acetyl-CoA and this is used as a co-factor for histone acetylation [20]. Abbreviations: ATFS-1, activating transcription factor associated with stress 1; CLK-1, CLOCK-1; CoA, coenzyme A; ETS, electron transport system; KEAP1, Kelch-like ECH-associated protein 1; MTS, mitochondrial-targeting sequence; NRF2, nuclear factor erythroid 2-related factor 2; OXPHOS, oxidative phosphorylation; PDC, pyruvate dehydrogenase complex; PGAM5, phosphoglycerate mutase 5; ROS, reactive oxygen species.

5 (PGAM5) at the outer mitochondrial membrane [6,7]. Upon mitochondrial stress, NRF2 dissociates from the complex and translocates to the nucleus to activate its target genes [6] (Figure 1). This close proximity with the primary site of cellular ROS production allows NRF2 to rapidly mobilise antioxidant defences when mitochondrial oxidative stress occurs [8].

In contrast to NRF2, the nuclear localisation of the *Caenorhabditis elegans* transcription factor Activating Transcription Factor associated with Stress 1 (ATFS-1) is regulated by the efficiency of its mitochondrial import [9]. ATFS-1 is a component of the **mitochondrial unfolded protein response** (**UPR^{mt}**), which is triggered by disrupted proteostasis [10,11]. Normally, ATFS-1 is imported into mitochondria, where it undergoes proteolytic degradation; however, upon UPR^{mt} induction, it is stabilised within the mitochondria and interacts with the mitochondrial genome to limit the accumulation of mitochondrially encoded mRNAs [9,12]. Concurrently, mitochondrial import of ATFS-1 is impaired and a pool is redirected to the nucleus, where it regulates genes encoding proteins required for maintaining proteostasis and oxidative phosphorylation [9,12] (Figure 1). ATFS-1 is able to localise to both organelles because it contains an MTS and a nuclear localisation signal; it is the coordinated mitochondrial stabilisation and nuclear localisation of

Glossary

Echoforms: identical forms of a protein at different subcellular locations.
Eclipsed distribution: the uneven distribution of a protein between two cellular compartments.
Endosymbiosis: the theory that organelles, such as mitochondria, originated as a symbiosis between two distinct prokaryotic cells.
Homeostasis: the maintenance of a constant internal environment in cells or organisms to maintain functioning by compensating for changing conditions.
Mitochondrial targeting sequence (MTS): a short amino acid sequence usually found near the N terminus of nuclear-encoded mitochondrial proteins that can interact with the import machinery located within the inner and outer mitochondrial membranes.
Mitochondrial unfolded protein response (UPR^{mt}): a mitochondria-to-nucleus signalling pathway that responds to mitochondrial stress, particularly the accumulation of misfolded or unfolded proteins in mitochondria or an imbalance between mitochondrial and nuclear encoded proteins.
Mitophagy: the selective degradation of damaged mitochondria by autophagy.
Moonlighting protein: a protein with more than one function.
Oxidative phosphorylation (OXPHOS): the process by which electrons are transferred to oxygen by the electron transport chain located at the mitochondrial inner membrane to produce energy in the form of ATP.
Proteostasis: the coordinated regulation of proteins including their translation, folding, movement, and degradation. Cells try to maintain proteostasis, particularly in response to stress.
Reactive oxygen species (ROS): chemically reactive molecules that contain oxygen. Mitochondria are the major site of ROS generation in cells because ROS are a by-product of oxidative phosphorylation.
Retrograde signalling: in the context of this article, this refers to signalling from mitochondria to the nucleus. Signalling from the nucleus to other organelles is termed anterograde signalling.