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Organelles in focus

# The complex crosstalk between mitochondria and the nucleus: What goes in between?☆

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ABSTRACT

Mitochondria are critical metabolic hubs in which catabolic and anabolic cellular processes converge and are integrated. To perform their function, mitochondria also need to respond to signals that monitor their function and send continuous feedback to the nucleus and other organelles to trigger the required expression programs (for example, stabilization of hypoxia-inducible factor 1 – α). Unsurprisingly, mitochondrial dysfunction results in wide range of disorders. Understanding how cells adapt to changes in mitochondrial function is critical for the evaluation of mitochondrial disorders and the development of potential treatments. Each type of mitochondrial dysfunction results in a unique transcriptional response. Here we review the role of nuclear-encoded factors in the response to changes in mitochondrial function and discuss their relevance to metabolic homeostasis, outlining the diverse and complex ways in which nuclei adapt to maintain mitochondrial homeostasis.

This article is part of a Directed Issue entitled: Mitochondrial Diseases.



**Organelle facts:**

- Mitochondrial dysfunction activates regulatory pathways that induce changes in nuclear gene expression able to monitor the organelle status.
- Mitochondrial function is connected to cell signaling pathways through changes in redox and phosphate pairs (NAD/NADH; CoQH2/CoQ and ATP/ADP vs. AMP), critical metabolite concentrations (succinate, aK-glutarate, Acetyl-CoA, etc.), and reactive oxygen species (ROS) production.
- Variations in mitochondrial status modulate specific transcriptional programs.
- The process that transduces the information required for the cell to adapt to a mitochondrial challenge is called "retrograde signaling".

## 1. Introduction

Mitochondria are well known for their role of producing energy by oxidative phosphorylation, but these organelles also make critical contributions to other areas of cell metabolism, information flux (calcium, ROS, etc.) and cell-death cascades (apoptosis). The first clinical report of a genuine mitochondrial dysfunction was published by Rolf Luft in 1959 (Ernster et al., 1959). Since then, a number of diseases have been linked to mitochondrial dysfunction, and current figures show that 1 in every 5000 individuals are affected by a mitochondrial disorder (Pfeffer et al., 2012).

The wide range of pathologies caused by mitochondrial dysfunction include lactic acidosis, skeletal myopathy, deafness, neurodegenerative diseases, muscular disorders, cardiomyopathy, diabetes and cancer (Vafai and Mootha, 2012). The varied symptoms and the involvement of multiple tissues make mitochondrial disorders hard to diagnose and treat, and diagnosis is best achieved by identifying the underlying genetic alteration.

Mitochondrial dysfunction can alter cell signaling because of its primary role in synthesizing critical metabolites (NADH/$NAD^+$, ATP/ADP, ATP/AMP, succinate/a-ketoglutarate, etc.). Mitochondrial dysfunction can thus affect sirtuin-mediated signaling (NADH/$NAD^+$), AMPK signaling (ATP/AMP), mTOR signaling (ATP/ADP) or Hif1a signaling (succinate/a-ketoglutarate), and can

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also impact signaling mediated by reactive oxygen species (ROS) or $Ca^{2+}$ (Jones et al., 2012). Depending on the cell type and type of mitochondrial dysfunction, one or several of these paths might be especially affected. Understanding the detailed signaling response to mitochondrial dysfunctions will help to generate a better understanding of the complex puzzle of mitochondrial disorders.

## 2. Organelle function

In addition to these signaling molecules, which monitor cell metabolic status and thus mitochondrial performance, information about mitochondrial quality is also transduced to the cell via specific mitochondria-derived pathways, among which the mitochondrial unfolding protein response (mtUPR) is gaining much attention (Mottis et al., 2014). It has also been suggested that mitochondria-to-nucleus retrograde signaling can be envisioned as a complementary mechanism to these mitochondrial quality control systems (Jazwinski, 2013).

Changes in nuclear gene expression to maintain mitochondrial homeostasis are not limited to nuclear-encoded mitochondrial proteins. The retrograde response also changes the global nuclear gene expression pattern. Identifying the components of these changes was the first question to be addressed by research into mitochondria-nuclear interactions in the late 1980s.

Communication between the mitochondrial and nuclear genomes was first postulated in 1987 in yeast (Parikh et al., 1987). The first factors implicated in retrograde signaling (including COX VI, CIT2 and RTG proteins) were also identified in yeast (Butow et al., 1988; Jia et al., 1997; Liao et al., 1991; Liu and Butow, 2006; Rothermel et al., 1997) (Table 1). Further analysis of Rtg proteins (Rtg1–3) showed that these proteins are normally present in the cytoplasm and translocate to nucleus upon retrograde signaling (Sekito et al., 2000). Subsequent studies in yeast also characterized more factors and also signaling pathways such as RAS2 and the TOR signaling pathway (Butow and Avadhani, 2004; Kirchman et al., 1999; Liu and Butow, 2006) (Table 1). The TOR pathway has also being linked to Rtg proteins in the context of retrograde signaling (Breitkreutz et al., 2010; Dilova et al., 2004; Dilova et al., 2002; Giannattasio et al., 2005; Komeili et al., 2000). Furthermore, yeast studies have shown that dysfunctional mitochondria inhibit TORC1 (Kawai et al., 2011).

These studies were followed by others that examined retrograde signaling in more depth and also in other cell types and organisms. Understanding the conservation of the retrograde response between species is very important and therefore studies different organisms are important, especially regarding the differences in mitochondrial homeostasis between yeast and animal cells, particularly during mitochondrial biogenesis (Heddi et al., 1993; Jazwinski, 2013; Poyton and McEwen, 1996).

In mammalian cells, the first proteins implicated in retrograde signaling (Cox-Va, b-actin, myc, GAPDH, EF-1) were characterized after the studies carried out in yeast (Marusich et al., 1997; Wang and Morais, 1997) (Table 1). Several studies subsequently revealed the diverse nature of mammalian retrograde signaling, including activation of NFAT, ATF2, NFKb, MAPK, PKC, Egr-1 and CEBP, and CamKIV-mediated activation of CREB (Amuthan et al., 2002; Arnould et al., 2002; Biswas et al., 1999, 2003; Butow and Avadhani, 2004). It should be noted that NFKb has roles in mitochondrial biogenesis and the response to ROS (Srinivasan et al., 2010).

### 2.1. Conservation and diversity in retrograde signaling

Several microarray analyses in yeast showed that mitochondria-to-nucleus communication is not limited to a handful of factors but is instead a global response alters the expression levels of different sets of genes depending on the type of mitochondrial dysfunction (Epstein et al., 2001; McCammon et al., 2003; Traven et al., 2001). Consistent with the yeast studies, the mTOR pathway has been implicated in retrograde signaling in mammalian cells, confirming the conserved nature of retrograde signaling between species (Komeili et al., 2000; Laplante and Sabatini, 2012).

Although the retrograde signaling response has yet to be resolved in full, nuclear response elements commonly involved in mitochondrial dysfunction along with more specific ones have been identified. Genome-wide microarray transcriptome studies have been especially important in identifying genes that are differentially expressed upon mitochondrial dysfunction. These studies had performed using different cell lines; one of the earliest studies used a mtDNA depleted human breast cancer cell line (Delsite et al., 2002). However, there is no consensus in the published data. The type of mitochondrial dysfunction seems to have a strong influence on the observed pattern of nuclear gene expression. This has been shown by comparing the expression profiles of Rho0 (mtDNA-depleted) cells and cells carrying the A3243G mutation, which suggests partially distinct multiple pathways of retrograde signaling (Jahangir Tafrechi et al., 2005). Furthermore, RT-PCR and GeneChip microarray analyses consistently show non-identical gene expression patterns in different Rho0 cells lines (Miceli and Jazwinski, 2005; Mineri et al., 2009).

### 2.2. Key players in the transcriptional response

Nonetheless, some signaling pathways are repeatedly reported to be involved in retrograde signaling: mTOR, NFKB, c-JUN/JNK and RXRA, NFATs, PKC, CamK IV, PI3K/AKT, Sirt1, No/CO (Jones et al., 2012). The importance of these pathways is further supported by the implication of defined transcription factors such as MYC, CREB, CEBP, FOXO-1, Egr-1, NRF-1, TFAM, ATF2, ctBP1, and PGC-1a/PRC (Jones et al., 2012).

## 3. Cell physiology

### 3.1. Implications for metabolism

Cells affected by mitochondrial dysfunction have to adapt to the sub-optimal energy metabolism. The most common adaptive response to decreased mitochondrial ATP production is increased glycolytic flux to lactate (von Kleist-Retzow et al., 2007). In yeast, the metabolic adaptation to an incomplete TCA cycle requires production of metabolites such as glutamate (Butow and Avadhani, 2004). Therefore cell survival in these circumstances can be helped by the use of alternative and more varied carbon sources. Common mechanisms observed in yeast are increased glyoxylate cycle activity and fatty acid β-oxidation (Jazwinski, 2013), mechanisms also triggered by nutrient deprivation (Wang et al., 2010). In addition, microarray studies of mtDNA-depleted cells revealed that TCA cycle and glyoxylate cycle genes are controlled similarly (Epstein et al., 2001). These metabolic changes in the switch from OXPHOS to glycolysis were corroborated by transcriptomic analysis in *Drosophila melanogaster* OXPHOS mutants (Freije et al., 2012). However, cells cannot depend solely on glyoxylate cycle for survival, and must therefore activate additional mechanisms.

### 3.2. Mitochondrial biogenesis, capacity and clearance

The purpose of nuclear–mitochondrial cross-talk is to achieve a fine-tuned and functional mitochondrial population. The cell should have the required amount of healthy mitochondria and clear any unhealthy organelles. Mitochondrial quality control is the term usually used to describe the set of events and processes geared

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