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Review

Adaptation to metabolic dysfunction during aging: Making the best of a bad situation

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ABSTRACT

Mitochondria play a central role in energy metabolism in the process of oxidative phosphorylation. As importantly, they are key in several anabolic processes, including amino acid biosynthesis, nucleotide biosynthesis, heme biosynthesis, and the formation of iron-sulfur clusters. Mitochondria are also engaged in waste removal in the urea cycle. Their activity can lead to the formation of reactive oxygen species which have damaging effects in the cell. These organelles are dynamic, undergoing cycles of fission and fusion which can be coupled to their removal by mitophagy. In addition to these widely recognized processes, mitochondria communicate with other subcellular compartments. Various components of mitochondrial complexes are encoded by either the nuclear or the mitochondrial genome necessitating coordination between these two organelles. This article reviews another form of communication between the mitochondria and the nucleus, in which the dysfunction of the former triggers changes in the expression of nuclear genes to compensate for it. The most extensively studied of these signaling pathways is the retrograde response whose effectors and downstream targets have been characterized. This response extends yeast replicative lifespan by adapting the organism to the mitochondrial dysfunction. Similar responses have been found in several other organisms, including mammals. Declining health and function during human aging incurs energetic costs. This compensation plays out differently in males and females, and variation in nuclear genes whose products affect mitochondrial function influences the outcome. Thus, the theme of mitochondria-nucleus communication as an adaptive response during aging appears very widespread.

1. Introduction

Mitochondria are the only organelles in animal and fungal cells, in addition to the nucleus, that possess their own genomes. These ancient endosymbionts (Dyall et al., 2004) have established an intimate relationship with their host cells by successively exporting their own genes to the nucleus. In yeast, this process has resulted in only eight of the mitochondrial proteins remaining encoded by mitochondrial DNA (mtDNA) out of the approximate 1000 present in this organelle, with the remainder being nuclear DNA encoded (Sickmann et al., 2003). This arrangement requires a two-way line of communication between the mitochondrion and the nucleus to accommodate changing cellular and environmental conditions. An obvious example of this in the yeast *Saccharomyces cerevisiae*, is the diauxic shift which occurs in the transition from fermentation to aerobic respiration and involves a spectacular induction of genes encoding mitochondrial proteins and resulting in mitochondrial biogenesis (DeRisi et al., 1997).

The nucleus and the mitochondria share a structural relationship. The outer nuclear envelope is contiguous with the endoplasmic reticulum membrane system, a fact which has been long established. More recently, the tethering of mitochondria to the endoplasmic reticulum through an endoplasmic reticulum-mitochondria encounter structure (ERMES) has been shown (reviewed in (Lang et al., 2015)). This structure appears to play a regulatory role in several aspects of mitochondrial and cellular physiology, including calcium signaling, protein import, mitochondrial fission, and mitophagy (Lang et al., 2015). Replication and partition of mtDNA is also affected by the ERMES (Lang et al., 2015).

The products of mitochondrial metabolism, such as nicotinamide adenine dinucleotide (NAD^+) not only function in metabolism but also play a signaling role by being the cofactor for the NAD^+-dependent histone deacetylase Sir and the sirtuins, its relatives in higher organisms (North and Verdin, 2004). In addition to this mode of communication, there are several signaling pathways from the mitochondrion to the nucleus that are more akin to intercellular signal transduction pathways. These will be reviewed here, with a focus on those that affect

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lifespan and whose distal effectors are known. The emphasis will be on baker's yeast, *Saccharomyces cerevisiae*, with some corresponding pathways in other organisms mentioned to support generalizations.

2. Retrograde response

The retrograde response is the quintessential interorganelle signaling pathway (reviewed in (Jazwinski, 2014)). It communicates the status of the mitochondria to the nucleus (Liu and Butow, 2006). It was first described as an unusual accumulation of cytoplasmic RNA in yeast cells lacking mtDNA (rho^0). Other mitochondrial defects also result in the induction of this pathway. For example, the accumulation of dysfunctional mitochondria during the replicative lifespan (RLS), evidenced by a reduction in mitochondrial membrane potential, results in progressive activation of the retrograde response (Borghouts et al., 2004) allowing the cells to live longer (Kirchman et al., 1999). In addition, retrograde signaling is important in chronological lifespan (CLS) extension (Barros et al., 2004).

The signal proximal to the mitochondrion that activates the retrograde response is the drop in mitochondrial membrane potential (Miceli et al., 2011). However, it is possible that a decrease in ATP levels may modulate this effect (Zhang et al., 2013). The first component of the signal transduction pathway is the protein Rtg2, which binds ATP (Liu and Butow, 2006). Rtg2 sequesters a negative regulator of the retrograde response Mks1, which in turn allows Rtg3 to be partially dephosporylated. Rtg3 is part of a heterodimer with Rtg1, which then translocates from the cytoplasm to the nucleus (Liu and Butow, 2006). Both of these proteins are basic, helix-loop-helix, leucine zipper transcription factors that bind to the sequence GTCAC, known as the R box. This activates the expression of some 400 genes throughout the yeast genome (Epstein et al., 2001). The net effect is a substantial metabolic re-modeling, as revealed by metabolomics profiling (Hashim et al., 2014). These effects resemble those that occur during calorie restriction (Wang et al., 2010). Retrograde signaling also regulates stress resistance (Torelli et al., 2015) and resistance to toxic compounds such as long-chain sphingoid bases (Panwar and Moye-Rowley, 2006).

The retrograde response pathway, sketched out above, intersects with several other signaling pathways (reviewed in (Jazwinski, 2014)). These include the target of rapamycin complex 1 (TORC1) pathway and its substrate Sch9. TORC1 contains Lst8, another negative regulator of Rtg2, and it responds to the presence of glutamate inside the cell. Furthermore, glutamate in the medium is sensed by the plasma membrane SPS amino acid sensor, which may also negatively regulate retrograde signaling. Osmotic stress transiently blocks phosphorylation of Sch9 by TORC1 and recruits Rtg1-Rtg3. In fact, the Hog1 hyperosmolarity-activated protein kinase is required for the translocation of Rtg1-Rtg3 to the nucleus, its binding to chromatin, and transcriptional activation. The retrograde pathway also interacts with Ras2 signaling.

Some 400 genes are induced when the retrograde response is activated, as mentioned earlier. The challenge was to identify the target gene or genes that are responsible for the extension of RLS in the retrograde response from among them. The involvement of the Spt-Ada-Gcn5-Acetyl transferase complex (SAGA) and SAGA-like (SLIK) complexes in activation of retrograde response target genes and RLS extension was instrumental in whittling down the number of candidate genes. This number was further reduced by taking into account origin-recognition complex/open reading frame (ORC-ORF) binding sites (Jiang et al., 2016). In the process, a requirement for Sir2 in the retrograde response was uncovered. Out of the four genes whose expression involves the retrograde signaling pathway, SAGA/SLIK, and proximity of ORC-ORF, only *PHO84* is both necessary and sufficient for RLS extension (Jiang et al., 2016).

Pho84 is a high-affinity phosphate transporter in the plasma membrane. It is highly pleiotropic in its function. Overexpression of this gene activates the endoplasmic reticulum unfolded protein response, whose activation has been found to extend RLS (reviewed in (Jiang et al., 2016)). The engagement of this stress response in extending yeast longevity would be an attractive mechanism. However, this remains to be experimentally determined as the response to mitochondrial dysfunction that is involved.

Signaling from the mitochondrion to the nucleus that results in extension of lifespan has been demonstrated in several other systems (reviewed in (Jazwinski, 2014)). In the round worm *Caenorhabditis elegans*, there appear to be three such pathways. One of them is activated by reactive oxygen species (ROS) through the hypoxia-activated transcription factor HIF-1. Another involves the mitochondrial unfolded protein response and the transcription factors UBL-5 and DVE-3. The third is mediated by the transcription factor CEH-23. Mitochondrial dysfunction in the worm displays a variety of phenotypes, and it can include bile acid-like substances acting as hormones. Similarly, defects in assembly of respiratory chain components or coenzyme Q biosynthesis result in extension of lifespan in *Drosophila*. Recently, it has been found that CEH-23 functions together with CEP-1 (p53) downstream of AAK-2 (AMPK) and CRTC-1 to enhance both stress resistance and lifespan in the worm (Chang et al., 2017).

Mouse lifespan is extended by disruption of mitochondrial function (reviewed in (Jazwinski, 2014)). Lowering coenzyme Q levels by reduction of the activity of the *MLCK1* gene is one way that this occurs. Defective cytochrome oxidase assembly by conditional knockout of *SURF1* has a similar effect. Feeding mice dinitrophenol to induce mild mitochondrial uncoupling also extends lifespan. This effect can also be achieved in normal, human diploid fibroblasts in tissue culture. Restriction of methionine in the diet induces stress resistance and extends lifespan in yeast, mouse, and human cells in culture, while activating the retrograde response (Johnson and Johnson, 2014).

The retrograde response in yeast is a single pathway composed of the signal transducer Rtg2 and the effector Rtg1-Rtg3. It has numerous outputs, and it crosstalks with several other signaling pathways. In *C. elegans*, this unitary pathway appears to be split into three, perhaps to better accommodate the need for different outputs. It has been proposed that this division of function of the retrograde response pathway is a common feature of its evolution in various phyla (Jazwinski and Kriete, 2012). However, a master regulator in the form of NFκB has appeared to coordinate these related pathways of response to mitochondrial status (Jazwinski and Kriete, 2012). NFκB is known to mediate the retrograde response to loss of mtDNA in vertebrate cells in tissue culture, and NFκB is also involved in activation of the retrograde response on methionine restriction (Johnson and Johnson, 2014).

3. Signaling by defects in mitochondrial ribosomes

Inhibition of mitochondrial protein synthesis by erythromycin extends RLS in yeast (Holbrook and Menninger, 2002). The mechanisms involved are not known; however, two potentially related pathways may be involved. One has been termed mitochondrial back-signaling (Heeren et al., 2009). This pathway is activated when the *AFO1/MRLP5* gene which encodes a protein of the large, mitochondrial ribosome subunit is deleted. The downstream effector is the transcription factor Sfp1, and the RLS extension requires active TORC1. This mechanism appears distinct from the retrograde response because it was demonstrated in a yeast strain grown on glucose in which the retrograde response is repressed by this carbon source. However, independence from Rtg1-Rtg3 was not tested.

Disruption of protein synthesis in mitochondria by deletion of nuclear genes encoding components of the mitochondrial translation control complex, such as *SOV1*, also extends RLS (Caballero et al., 2011). This lifespan extension requires cAMP-dependent protein kinase A signaling and the Msn2-Msn4 transcription factor, which increases expression of Pnc1. This may function together with the requirement for Sir2, because Pnc1 scavenges the Sir2 product nicotinamide, a potent Sir2 inhibitor. As with back-signaling, any interaction between this mechanism and the retrograde response has not been critically