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Review Article

Mitochondrial stress signaling in longevity: A new role for mitochondrial function in aging

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ABSTRACT

Mitochondria are principal regulators of cellular function and metabolism through production of ATP for energy homeostasis, maintenance of calcium homeostasis, regulation of apoptosis and fatty acid oxidation to provide acetyl CoA for fueling the electron transport chain. In addition, mitochondria play a key role in cell signaling through production of reactive oxygen species that modulate redox signaling. Recent findings support an additional mechanism for control of cellular and tissue function by mitochondria through complex mitochondrial–nuclear communication mechanisms and potentially through extracellular release of mitochondrial components that can act as signaling molecules. The activation of stress responses including mitophagy, mitochondrial number, fission and fusion events, and the mitochondrial unfolded protein response (UPR^{MT}) requires mitochondrial–nuclear communication for the transcriptional activation of nuclear genes involved in mitochondrial quality control and metabolism. The induction of these signaling pathways is a shared feature in long-lived organisms spanning from yeast to mice. As a result, the role of mitochondrial stress signaling in longevity has been expansively studied. Current and exciting studies provide evidence that mitochondria can also signal among tissues to up-regulate cytoprotective activities to promote healthy aging. Alternatively, mitochondria release signals to modulate innate immunity and systemic inflammatory responses and could consequently promote inflammation during aging. In this review, established and emerging models of mitochondrial stress response pathways and their potential role in modulating longevity are discussed.

Contents

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Introduction

The concept that mitochondrial function declines during aging has been a basic tenet of the biology of aging for many years. Paradoxically, it has been shown, first in yeast and later in mice, that perturbations of some mitochondrial electron transport chain (ETC) complexes increase lifespan [1–3]. These results are counterintuitive, yet they have the potential to significantly shift the way we think about the role of mitochondrial function in general and especially in aging. Recent studies have provided evidence to support the hypothesis that up-regulation of mitochondrial stress responses contributes to enhanced longevity in the long-lived mitochondrial mutants [3–5]. These stress responses include mitochondrial turnover, fission and fusion events, regulation of mitochondrial number (induction of mitochondrial biogenesis), retrograde signaling, and the mitochondrial unfolded protein response UPR^{MT}. Compromised mitochondrial stress responses could contribute to age-related accumulation of damaged proteins, reduced oxidative phosphorylation, increased reactive oxygen species production, and induction of cellular apoptosis. As a result, maintenance of mitochondrial stress responses has gained recognition as a potential pro-longevity mechanism in the aging field. Understanding the molecular mechanisms by which mitochondrial stress responses might lead to longevity is key for the development of interventions to prevent age-associated diseases and improve healthspan. Here, we review recent studies that have shed light on the relationship between mitochondrial stress signaling and longevity.

Yeast retrograde response

Retrograde signaling in yeast is a mitochondrial-to-nuclear signal transduction pathway resulting in the induction of nuclear-encoded mitochondrial genes in response to mitochondrial stress (see Fig. 1). Ron Butow discovered the yeast retrograde response in 1987 [6]. Butow showed that yeast lacking mitochondrial DNA (*rho*° cells) modulate the transcript levels of nuclear-encoded mitochondrial genes [6]. A genome-wide analysis of *rho*° cells and yeast treated with mitochondrial electron transport chain (ETC) inhibitors demonstrated alterations in a wide-range of nuclear-encoded genes [7]. The majority of the genes up-regulated encode for proteins that facilitate a metabolic switch from aerobic to anaerobic respiration [8].

A number of studies have defined the molecular pathways involved in the retrograde response [9–11]. Defective mitochondria release a retrograde signal to activate the nuclear-localization of the Rtg1/3 complex that consists of two basic helix–loop–helix leucine zipper transcription factors [11]. This complex regulates the expression of genes encoding for enzymes in mitochondrial metabolism, peroxisomal biogenesis and stress response pathways [8,12]. The activation of the Rtg1/3 complex is dependent on the phosphorylation of Rtg3 [11]. A cytoplasmic protein, Rtg2 promotes the partial dephosphorylation of Rtg3 through an interaction with Mks-1, a negative regulator of the retrograde response [11,13]. ATP competitively binds to Mks-1 releasing Rtg2 and allowing Mks-1 to bind to the 14-3-3 protein Bmh1/2, which inhibits the translocation of the Rtg1/3 complex [10,14]. Therefore, low levels of ATP promote the interaction between Rtg2 and Mks-1 and activation of the retrograde response. The exact mechanism of Rtg3 dephosphorylation is currently not known.

Regulation of the retrograde response

More recent work has investigated the mitochondrial signal that triggers the retrograde response. One potential signal is mitochondrial membrane potential. Loss of membrane potential was shown to trigger the retrograde response in *rho*° and *cox4* null

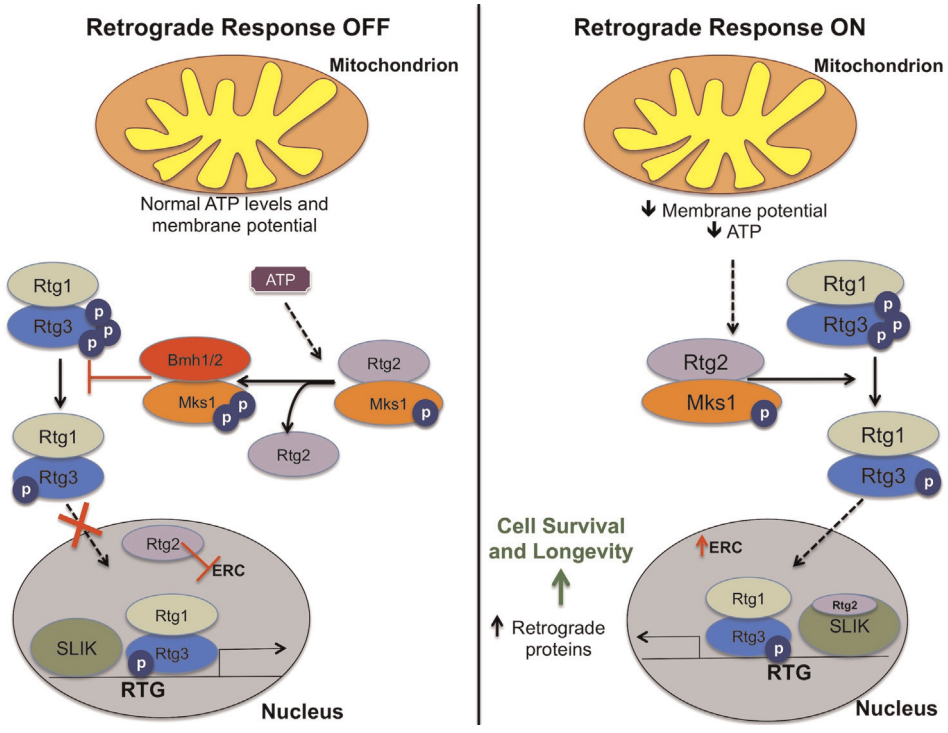

Fig. 1. Yeast retrograde response. Under normal conditions, ATP competitively binds to Mks1, a negative regulator of the retrograde response (RTG), releasing Rtg2 and allowing Mks-1 to bind to the 14-3-3 protein Bmh1/2, another negative regulator of the RTG. Consequently, this inhibits the nuclear translocation of the Rtg1/3 complex. Rtg2 has also been shown to suppress the formation of extrachromosomal rDNA circles (ERCs). Under conditions of reduced mitochondrial membrane potential or mitochondrial stress, Rtg2 is stabilized by Mks1. Stabilized Rtg2 promotes the dephosphorylation of Rtg3. Subsequently, Rtg1/3 complex translocates to the nucleus where is turns on the transcription of retrograde genes. Rtg2 can also modulate the retrograde response by interacting with the transcriptional co-activator SAGA-like (SLIK) complex. As a result, cell survival is promoted.