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The retrograde response links metabolism with stress responses, chromatin-dependent gene activation, and genome stability in yeast aging

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Abstract

Yeast can be used as a model to understand the impact mitochondria have on aging in higher organisms. Mitochondrial dysfunction increases with replicative age in yeast, and this is associated with the induction of the retrograde response. This intracellular signaling pathway from the mitochondrion to the nucleus results in changes in the expression of metabolic and stress genes, which adapt the yeast cell to the loss of tricarboxylic acid cycle activity by providing alternate anaplerotic sources of biosynthetic precursors. The induction of the retrograde response increases longevity. Paradoxically, it also leads to the production of extrachromosomal ribosomal DNA circles, which cause yeast demise. The deleterious effects of these circles are mitigated by the retrograde response, which increases longevity in part due to this effect and partly due to other activities. Rtg2p is the retrograde signal transducer proximal to the mitochondrion, and it interacts with several proteins in relaying the retrograde signal to the transcription factor Rtg1p-Rtg3p. Rtg2p also suppresses ribosomal DNA circle production. When it is engaged in retrograde signaling, it cannot fulfill the latter role. The SAGA-like SLIK complex is one of the protein complexes in which Rtg2p has been found. This histone acetyltransferase, transcriptional co-activator complex contains Gcn5p, and it potentiates the activation of retrograde responsive genes. SLIK complex integrity, and in particular Gcn5p, are needed for retrograde response extension of life span. Thus, the retrograde response through SLIK links metabolism, stress responses, chromatin-dependent gene regulation, and genome stability in yeast aging. Gene regulatory phenomena akin to the retrograde response also operate in human cells, which display both common and cell-type specific changes in gene expression on loss of mitochondrial function.

Keywords: Metabolism; Mitochondria; Stress; Genome stability; Gene activation; Longevity

1. Introduction

The retrograde response is a remarkable intracellular signaling pathway discovered in the yeast *Saccharomyces cerevisiae* by Parikh et al. (1987). This pathway signals mitochondrial dysfunction, or more specifically electron transport chain disruption, to the nucleus causing wide-ranging adaptations to the resultant metabolic duress (Butow and Avadhani, 2004). The changes in nuclear gene expression include metabolic enzyme genes and stress response genes (Epstein et al., 2001), which appear to compensate for the mitochondrial dysfunction. Among them are increases in transcripts encoding acetyl-CoA synthetase and glyoxylate cycle enzymes, suggesting a shift to the utilization of acetate as a carbon source. The glyoxylate cycle is an economical consumer of acetate in comparison with the tricarboxylic acid cycle, because the two carbons of acetate are retained rather than being lost as carbon dioxide. One way of viewing the retrograde response is that it is a means of bolstering the role of the tricarboxylic acid cycle as a source of biosynthetic intermediates. The products of the nuclear genes induced in the retrograde response include

Abbreviations: SAGA, transcriptional co-activator complex; SLIK, SAGA-like complex; TOR, target of rapamycin; TFIID, RNA polymerase II promoter transcription initiation factor; mtDNA, mitochondrial DNA; $\Delta\Psi_m$, mitochondrial membrane potential.

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cytoplasmic, mitochondrial and peroxisomal proteins (Epstein et al., 2001). Thus, the retrograde response is a pathway of interorganellar communication.

Retrograde signaling involves at least three specific transduction proteins. They are the subunits of the heterodimeric transcription factor Rtg1p-Rtg3p, which binds to the retrograde response element in the promoter of retrograde responsive genes (Liu and Butow, 1999), and Rtg2p. The Rtg2p is a cytoplasmic protein, possessing features of a chaperone (Koonin, 1994), which binds Rtg3p and promotes the translocation of the retrograde transcription factor from the cytoplasm to the nucleus (Sekito et al., 2000). There is crosstalk between the retrograde response and other pathways that monitor the status of the cell, such as the target of rapamycin (TOR) pathway (Butow and Avadhani, 2004). Rtg2p interacts with at least two proteins, Rtg3p and Mks1p (Sekito et al., 2000; Liu et al., 2003). It has also been found to be a component of the transcriptional co-activator complex SLIK, which binds to the promoters of retrograde responsive genes (Pray-Grant et al., 2002). SLIK is a version of the SAGA complex, and like SAGA it contains the Gcn5 histone acetyltransferase. SAGA can work interchangeably with another transcriptional co-activator, TFIID, but it specializes in the activation of stress response genes, which are suppressed by co-repressor complexes containing Rpd3p or Hda1p (Huisinga and Pugh, 2004).

Typically, the retrograde response is induced in yeast cells by partial or complete deletion of the mitochondrial DNA (mtDNA). Several studies have been carried out in which gene expression changes were analyzed in animal cell lines devoid of mtDNA (Butow and Avadhani, 2004). These studies showed reproducible gene expression changes within a given study, but there were no obvious similarities among them or with the retrograde response in yeast. Loss of function of the electron transport chain by deletion of mtDNA in yeast does not result in up-regulated expression of nuclear encoded subunits of the electron transport complexes (Epstein et al., 2001). On the other hand, such an apparent attempt at restoration of respiratory function occurs in animal cells under the same conditions (Heddi et al., 1999), suggesting less optimal coordination of synthesis of mitochondrial and nuclear encoded subunits of mitochondrial protein complexes.

Studies of aging in yeast encompass both the chronological life span and the replicative life span (Jazwinski, 2004). The former measures the time that cells survive in stationary phase, while the latter measures the number of progeny that individual cells produce. There is an age asymmetry between the yeast cell and the daughter it produces in that the daughter is in principle born young irrespective of the age of the mother cell. This age asymmetry begins to break down as the replicative age of the mother cell increases (Egilmez and Jazwinski, 1989; Kennedy et al., 1994), a phenomenon that can be traced at least in part to the segregation of less than a full complement of active mitochondria to daughter cells by older mother cells (Lai et al., 2002) and their lack of retention of oxidatively damaged proteins (Aguilaniu et al., 2003). This breakdown of age asymmetry may have implications for the aging of stem cells. Genetic analysis has shed light on the processes underlying the aging of the mother cell. It was pointed out that these processes belong to four categories: metabolism, stress resistance, chromatin-dependent gene regulation, and genome stability, not only in yeast but in other organisms as well (Jazwinski, 1996).

2. The retrograde response determines yeast replicative life span

It has been shown that certain yeast strains have an extended replicative live span when they lack mtDNA (Kirchman et al., 1999). This increased life span is associated with the induction of *CIT2*, the diagnostic gene for the retrograde response. Most importantly, deletion of *RTG2* (Kirchman et al., 1999) or *RTG3* (Borghouts et al., 2004) abrogates the life extension. This indicates that the extended life span is caused by the retrograde response. The life extension on deletion of mtDNA described here is not observed in all yeast strains. However, it becomes a general phenomenon when cells are grown on raffinose rather than the repressive carbon source glucose (Kirchman et al., 1999). The induction of the retrograde response and the resulting life extension are related to the loss of the respiratory chain, because they are elicited upon deletion of the nuclear gene *COX4*, which encodes a subunit of mitochondrial cytochrome oxidase (Kirchman et al., 1999). The retrograde response and the extension of life span in cells lacking mtDNA are potentiated by *RAS2* (Kirchman et al., 1999). The *MKS1* gene plays an inhibitory role in the retrograde response (Liu et al., 2003). This gene was originally identified as a negative regulator of *RAS2* activity (Matsuura and Anraku, 1993). The potentiation of the retrograde response is at least one mechanism by which *RAS2* extends the replicative life span (Sun et al., 1994; Shama et al., 1998a,b).

The retrograde response is not simply an on–off switch. Instead, it seems to function as a continuous dial. It has been shown that the greater the loss of mitochondrial function the higher is the induction of the retrograde response, and the greater the extension of life span (Jazwinski, 2000). What is the significance of this? During the replicative life span, mitochondria become more and more dysfunctional, as determined by the loss of mitochondrial membrane potential ($\Delta\Psi_m$) (Lai et al., 2002). Concomitantly, there is a progressive induction of the retrograde response to ever-higher levels (Borghouts et al., 2004). Thus, the retrograde response titrates the accumulating mitochondrial dysfunction. Perhaps, this is why yeast cells can live as long as they do. In any case, the extension of life span by the retrograde response constitutes a mechanism of normal aging, rather than simply a curiosity generated by mutation. The pathology generated