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Yeast longevity and aging—the mitochondrial connection

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Abstract

Studies of the yeast *Saccharomyces cerevisiae* reveal four processes determining life span: metabolism, stress resistance, chromatin-dependent gene regulation, and genome stability. The retrograde response, which signals mitochondrial dysfunction resulting in changes in nuclear gene expression, extends yeast life span and is induced during normal aging. This response involves extensive metabolic adaptations. The retrograde response links metabolism and genome stability during yeast aging. A reduction in the availability of nutrients also extends yeast life span. This metabolic mechanism operates by pathways distinct from the retrograde response, although it shares with the latter some longevity effectors. Life extension by calorie restriction entails re-modeling of mitochondrial function. The retrograde response appears to compensate for age changes, while calorie restriction may be a preventive mechanism. The maintenance of age asymmetry between the mother and daughter yeast cells also depends on mitochondrial function. Loss of this age asymmetry occurs during normal yeast aging and may be a paradigm for stem cell aging. The importance of mitochondrial integrity in yeast longevity is emphasized by the role of prohibition function in attenuating oxidative damage. Our studies point to the central role of mitochondria in yeast aging. They highlight the importance of the maintenance of mitochondrial membrane potential, which drives the transport of biosynthetic precursors derived from the Krebs cycle. Common threads weave their way through the studies of aging in yeast and in other model organisms. This suggests conserved features of aging across phyla.

Keywords: Retrograde response; Calorie restriction; Genome stability; Stress resistance; Mitochondrial membrane potential; Reactive oxygen species

1. Introduction

The yeast *S. cerevisiae* has become an accepted model in aging research (Guarente and Kenyon, 2000; Jazwinski, 2003a). The limits to yeast longevity have been examined in two different experimental paradigms: chronological aging is measured by the loss of cell viability during storage in stationary culture. The metric of replicative aging is the number of daughters produced by individual yeast cells. The latter is the subject of this discussion, although there appears to be a relationship between the two (Ashrafi et al., 1999).

Each time a yeast cell divides the probability that it will divide again decreases (Mortimer and Johnston, 1959), and this decline is exponential (Pohley, 1987; Jazwinski et al., 1989). Interestingly, the mortality rate plateaus for the last 10% or so of an aging yeast cohort (Jazwinski et al., 1998), indicating that the demise of the remaining yeasts is due to stochastic extrinsic events. A finite life span does not in itself demonstrate a biological aging process at work. It is apparent, however, that yeasts do age. This is readily concluded from the observation of the many changes that occur during the replicative life span, some of which clearly represent functional decline (Jazwinski, 2003b).

One of the strengths of the yeast model is the facility with which genetic analysis can be applied. Over the past 15 years, some 40 genes have been implicated in yeast aging. These genes encode proteins, which are involved in a wide array of biochemical processes. However, it has been clear for some time that these processes fall into just four categories: metabolism, stress resistance, chromatin-dependent gene regulation, and genome stability (Jazwinski, 1996). Importantly, this categorization is applicable to longevity genes identified in other species (Jazwinski, 1996; Martin et al., 1996; Guarente and Kenyon, 2000), including

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human (Geesaman et al., 2003; Barzilai et al., 2003). This article emphasizes the metabolic aspects of life span determination in yeast. These aspects appear to play a primary role in longevity with the other three categories listed above having a derivative function, as will be evident from the discussion.

2. Retrograde response

The measure of the replicative life span is the number of daughters produced by a yeast mother cell. This production requires significant metabolic activity. Thus, metabolism is in reality a surrogate measure of longevity. This argues that metabolism is important in determining life span. However, nothing beats an experimental demonstration of this truism. Such a demonstration first came with our direct implication of the retrograde response in determining yeast longevity (Kirchman et al., 1999).

The retrograde response is a pathway of interorganellar communication (Butow, 2002). This signaling pathway is triggered by mitochondrial dysfunction. It is most readily observed in petite yeast cells. These are cells that have dysfunctional mitochondria, because of mutations in or complete lack of mitochondrial DNA (Parikh et al., 1987) or because of mutations in nuclear genes that encode certain mitochondrial proteins (Kirchman et al., 1999). The key signaling proteins in the retrograde response are Rtg2p and the transcription factor Rtg1p–Rtg3p, which is activated by Rtg2p. However, this is an elaborate pathway, which cross talks with other pathways that sense cellular status (Jazwinski, 2003a). The retrograde response is potentiated by Ras2p (Kirchman et al., 1999). The net effect of activation of the retrograde pathway is the translocation of the Rtg1p–Rtg3p from the cytoplasm to the nucleus (Sekito et al., 2000), and the resulting induction of numerous nuclear genes (Epstein et al., 2001). These induced genes code for metabolic enzymes and stress proteins.

The retrograde response portends a remarkable metabolic adaptation to the metabolic duress resulting from mitochondrial dysfunction. Notably, there is an induction of glyoxylate cycle genes. It appears that the cell can utilize fatty acids and acetate, in general, as a carbon source. This is a more economical source of biosynthetic precursors than the Krebs cycle, because the two carbon atoms of acetate are conserved by the glyoxylate cycle, while the Krebs cycle releases them as carbon dioxide. This and other anaplerotic reactions bolster the flagging activity of the Krebs cycle in petite yeast cells. The retrograde response is induced in direct proportion to the extent of mitochondrial dysfunction (Kirchman et al., 1999). Furthermore, the extent of life extension is directly proportional to the activity of the retrograde response (Jazwinski, 2000). Thus, the retrograde response is not a simple on–off switch, but rather it responds in a continuous manner to the changing metabolic needs of the cell. The life extension observed in petites might be considered a curiosity that has nothing to do with normal aging. However, we have shown that mitochondrial dysfunction accumulates with age in yeast (Lai et al., 2002), as much as it does in human cells (Shigenaga et al., 1994). The dysfunction is likely linked to the increased production of oxidants by mitochondria in old cells (Laun et al., 2001). Significantly, this accumulating dysfunction coincides with an increasing induction of the retrograde response (Borghouts et al., 2004). Thus, the retrograde response has a role to play during the course of normal yeast aging. Perhaps its induction is the reason yeasts live as long as they do.

Evidence has been available that the glyoxylate cycle is active in long-lived *Caenorhabditis elegans* (Vanfleteren and De Vreese, 1995). This activity is part of a pattern of gene expression changes, similar to the retrograde response, which is characteristic of the long-lived dauer larval state in this nematode (Holt and Riddle, 2003). Interestingly, long-lived nematodes result from the attenuation of the expression of genes encoding mitochondrial proteins (Lee et al., 2003; Dillin et al., 2002). This finding was the result of a long-lived mutant hunt in one case (Lee et al., 2003). It is worth noting that mitochondrial encephalopathies take several years to develop pronounced symptoms. This may be partially due to metabolic adaptations, much like the retrograde response that compensate for the primary mitochondrial defect.

The activation of the retrograde response has a puzzling consequence in yeast. It results in a higher than usual steady state level of extrachromosomal ribosomal DNA circles (Conrad-Webb and Butow, 1995). These circles can cause cellular demise (Sinclair and Guarente, 1997). It is now known that the retrograde response can counteract the detrimental effects of these circles and at the same time potentiate life extension independently (Borghouts et al., 2004). The Rtg2p plays a critical role in the relationship between the production of these circles and the induction of the retrograde response. It suppresses the production of circles. However, it cannot do this when it is transmitting the retrograde signal (Borghouts et al., 2004). Rtg2p may function in several protein complexes in the cell, and its quantities appear to be limited, so that it cannot protect the cell from the circles and perform in other capacities at the same time. This protein is part of the SLIK histone acetyltransferase complex, which is a transcriptional co-activator (Pray-Grant et al., 2002). It is also involved in suppression of the events associated with trinucleotide repeat expansion by recombination (Bhattacharyya et al., 2002).

Nutrient limitation can also extend yeast longevity (Jiang et al., 2000; Lin et al., 2000), and in many ways it resembles the calorie restriction paradigm described in rodents (Masoro, 1995). This mode of life extension operates in a pathway clearly separate from the retrograde response (Jiang et al., 2000). However, some of the downstream longevity effectors may be common to both, as indicated by the genetic analysis. Combining nutrient limitation with mutations in histone deacetylase genes has delimited the range of gene expression changes associated with life extension by calorie restriction in