

The *RAS* genes: a homeostatic device in *Saccharomyces cerevisiae* longevity[☆]

S. Michal Jazwinski*

Department of Biochemistry and Molecular Biology, Louisiana State University Medical Center, New Orleans, LA 70112, USA

Received 3 August 1999; received in revised form 8 September 1999; accepted 17 September 1999

Abstract

The genetic analysis of the yeast replicative life span has revealed the importance of metabolic control and resistance to stress. It has also illuminated the pivotal role in determining longevity that the *RAS* genes play by the maintenance of homeostasis. This role appears to be performed by the coordination of a variety of cellular processes. Metabolic control seems to occupy a central position among these cellular processes that include stress resistance. Some of the features of metabolic control in yeast resemble the effects of the *daf* pathway for adult longevity in *Caenorhabditis elegans* and the metabolic consequences of selection for extended longevity in *Drosophila melanogaster*, as well as some of the features of caloric restriction in mammals. The distinction between dividing and nondividing cells is proposed to be less important for the aging process than generally believed because these cell types are part of a metabolic continuum in which the total metabolic capacity determines life span. As a consequence, the study of yeast aging may be helpful in understanding processes occurring in the aging brain. © 1999 Elsevier Science Inc. All rights reserved.

Keywords: Aging; Longevity; Metabolic control; Stress resistance; Mitotic cells; Post-mitotic cells; *Saccharomyces cerevisiae*; *RAS1*; *RAS2*

1. Introduction

The metric of the yeast life span is the number of divisions (generations) that an individual cell completes or, in other words, the number of daughter cells produced [30,33]. We call this the replicative life span. More recently, aging has also been studied as the length of time yeast cells remain viable in stationary phase [25]. These two rather distinct ways of looking at longevity and aging in this organism may not be as disparate as it would seem. (This statement will be subjected to a critical evaluation later in this article.) Unless stated otherwise, life span will refer here to the replicative life span.

Yeasts undergo many morphological and physiological changes as they progress through their replicative life span [15]. Among the most universal age changes are the increase in generation time (the time between consecutive buddings) [8], increase in size [7], and progressive decline

in mating ability [32,44]. It is difficult to use these changes as biomarkers of aging. The increase in generation time can be uncoupled from life span, resulting in an early appearance of this senescent phenotype [21]. This uncoupling has also been found for size increase [4]. The decline, with age, in the ability to respond to the mating pheromone α -factor has been used to define premature or accelerated senescence in yeast [42,44]. Mutations that give rise to such premature aging cause a redistribution of Sir-transcriptional silencing complexes [35,42] to either extrachromosomal ribosomal DNA [41] or double-stranded DNA breaks [29]. This redistribution results in a loss of transcriptional silencing at the silent mating-type loci that is the direct cause of the loss of response to the mating pheromone. Thus, it is difficult to use loss of response to the pheromone as a measure of the global aging process. Perhaps, the loss of mating ability in yeast is the equivalent of a unimodal progeroid syndrome [27].

This discussion regarding phenotypic changes points to the difficulty of defining biomarkers of aging in yeast, which mirrors the problem with biomarkers of aging in other species. The best predictor of mortality remains replicative age itself. Indeed, the mortality rate of yeast, defined as the probability that an individual yeast will fail to divide, rises exponentially as a function of age, which is the number

[☆] The work in the author's laboratory was supported by grants from the National Institute on Aging of the National Institutes of Health.

* Corresponding author. Tel.: +1-504-568-4725; fax: +1-504-568-4725.

E-mail address: sjazwi@lsu.edu (S.M. Jazwinski)

of divisions already completed [16,37]. Thus, replicative life span is the tool most commonly used in yeast aging studies. Interestingly, the mortality rate plateaus late in the life span. A mathematical model based solely on change as the cause of aging predicts, counterintuitively, that such a plateau must occur, suggesting that the leveling of mortality rate at later ages may be an expression of age changes in individual yeast [17].

The genetics of aging in yeast is a well-developed discipline, with some 14 genes that influence longevity identified [15]. The first genes implicated in yeast longevity were *RAS1* and *RAS2*, the homologues of mammalian H-RAS [4]. The divergent roles of these two genes in determining yeast life span was later demonstrated [45]. The pleiotropic effects of yeast *RAS* are well known [46,47]. The role of *RAS* in metabolic control and in resistance to stress was instrumental in proposing the importance of these physiological mechanisms for aging and in their perceived interrelatedness, particularly given the emerging outlines of similar responses in other organisms [12]. Today, this proposal appears even better grounded [13,15].

2. Molecular and physiological mechanisms of aging

Because with each division the yeast cell must carry out the biosynthetic processes required to produce a daughter cell, any extension of replicative life span must entail an increase in the total metabolic effort, called metabolic capacity [12], if other things remain equal. Over expression of *RAS2* extends the life span and postpones the increase in generation time observed during yeast aging [45]. Thus, the yeasts complete more cell divisions and divide rapidly for an extended period. By definition, therefore, they display an enhanced metabolic capacity. Because this gene is important in coordinating cell growth and cell division *RAS2* is crucial [46]. Metabolic capacity is not as easy to assess in organisms in which life span is measured chronologically, because it is not directly related to the metric of longevity. In organisms other than yeast, this raises the question whether life extension has entailed more active life or simply more time.

2.1. The retrograde response

A clear example of a molecular mechanism of yeast aging comes from the analysis of the role of mitochondria in longevity. A signaling pathway from the mitochondrion to the nucleus that affects the expression of nuclear genes encoding mitochondrial, cytoplasmic, and peroxisomal proteins [34] also regulates yeast longevity [23]. Typically, this pathway, called the retrograde response, is induced in yeast lacking part or all of their mitochondrial DNA (ρ^0), resulting in mitochondria that are not fully functional. The retrograde response has been shown to be induced by both genetic and environmental means, with a concomitant ex-

ension of life span in four different yeast strains. Although the details of the conditions that elicit the retrograde response differ among these strains, life span is always extended when the retrograde response is induced. Increased longevity requires the activity of *RTG2*, a downstream effector of the retrograde response. The nature of the physiological signal that the mitochondrion sends to the nucleus is not clear at present, nor is it known whether it can be elicited by means other than the disruption of mitochondrial function.

The retrograde response underscores the fundamental role that metabolic control plays in yeast longevity. Interestingly, this pathway and its effect on the yeast life span are modulated by *RAS2* [23]. The induction of the retrograde response postpones senescence, as defined by a prolonged period of rapid cell division, and it enhances metabolic capacity [23]. The effect of this intracellular signaling pathway on yeast life span can be likened to a rheostat, rather than a simple on-off switch, in that the greater its induction the larger the effect on life span.

The retrograde response results in the increase in activity of several metabolic enzymes [3,43,49]. The net effect is a shift from the Krebs cycle to the glyoxylate cycle, a switch from the use of glucose to the use of acetate, and an increase in gluconeogenic activity. This is to some extent reminiscent of the mobilization of fat stores. The metabolic and enzymatic changes that occur in *Caenorhabditis elegans* whose life has been extended by the manipulation of the *daf-2/daf-16* pathway suggest similar biochemical adjustments. There are also similarities to the metabolic changes that are found in *Drosophila* that have been selected for an extended life span, including the storage of fat. The activation of gluconeogenic enzymes is also found during caloric restriction (without malnutrition), which results in the extension of life span in mammals. Rather than simply a caloric reduction, the retrograde response represents a shift from an energy source of high caloric content (glucose) to one of lower caloric content (acetate). All of these facts support the crucial role of metabolic control in determining life span across several species. These connections are more thoroughly discussed in Jazwinski [13,15].

2.2. Stress resistance

The potential significance of stress resistance in yeast aging is inherent in the action of *RAS2* in determining life span [45] because this gene modulates a variety of stress responses [26]. However, the fact that the resistance of yeast to ultraviolet radiation (UV) changes with age provided further grounding for this proposal [19]. UV resistance increases with age through midlife and then plummets. This biphasic profile parallels the *RAS2* expression during the yeast life span. *RAS2* is required to protect yeast from UV [9].

The viability of *Saccharomyces cerevisiae* in the stationary phase or after lethal heat shock is enhanced when the

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات