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Paradigms and pitfalls of yeast longevity research

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Abstract

Over the past 10 years, considerable progress has been made in the yeast aging field. Multiple lines of evidence indicate that a cause of yeast aging stems from the inherent instability of repeated ribosomal DNA (rDNA). Over 16 yeast longevity genes have now been identified and the majority of these have been found to affect rDNA silencing or stability. Environmental conditions such as calorie restriction have been shown to modulate this mode of aging via Sir2, an NAD-dependent histone deacetylase (HDAC) that binds at the rDNA locus. Although this mechanism of aging appears to be yeast-specific, the longevity function of Sir2 is conserved in at least one multicellular organism, *Caenorhabditis elegans* (*C. elegans*). These findings are consistent with the idea that aging is a by-product of natural selection but longevity regulation is a highly adaptive trait. Characterizing this and other mechanisms of yeast aging should help identify additional components of longevity pathways in higher organisms.

Keywords: Aging; Yeast; Heterochromatin; *SIR2*; *Caenorhabditis elegans*; Caloric restriction

1. Introduction

In 1959, Mortimer and Johnson proposed that the budding yeast *Saccharomyces cerevisiae* might serve as a model for aging (Mortimer and Johnston, 1959). Their proposal met with some skepticism—and for seemingly good reasons. Although yeast has proven to be a valuable model for basic cellular processes, such as DNA repair and the cell cycle, it has been difficult to accept that a simple unicellular organism could provide information about human aging, which involves complex organs and systems (Gershon and Gershon, 2000). Nevertheless, over the past decade there has been considerable progress in the yeast aging field. A major cause of yeast aging has been elucidated, more than 16 longevity genes[1] have been identified, and the homologs of at least two yeast genes have been shown to extend life span in the nematode worm, *Caenorhabditis elegans* (Guarente and Kenyon, 2000; Sinclair, 2002). Budding yeast has now emerged as a highly informative and respected model for the study of metazoan longevity.

In this perspective I propose that many key questions in the yeast aging field can be better

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[1] Longevity genes increase average life span when mutated or overexpressed. Genes whose variants reduce life span do not fall within this definition.

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addressed by making a clear distinction between the terms *aging* and *longevity*. I then give a historical overview of yeast aging research and discuss the two ways by which yeast life span can be measured. Finally, I present models that attempt to explain the most recent findings showing the relevance of yeast longevity to metazoans and discuss their potential relevance to human longevity.

2. Is yeast a better model for longevity regulation than for aging?

Recent findings showing the relevance of yeast longevity to metazoans imply that some assumptions about aging in model organisms need reevaluation. I propose that some of the apparent contradictions and conflicts can be resolved by distinguishing between the terms *aging* and *longevity*. These two terms are often used interchangeably, however, they are fundamentally different. Aging is a stochastic process that primarily relates to the intrinsic processes leading to death (e.g. oxidative damage to DNA and proteins). In contrast, longevity is the length of time an individual remains alive in the absence of death from external causes; it is the pace at which aging occurs. The important difference between the two is that *aging is essentially a by-product of natural selection whereas longevity is evolutionarily adaptive* (Kirkwood, 1992).

The view of longevity as an adaptive trait was first formulated in the disposable soma theory (Kirkwood and Holliday, 1979), which is based on the premise that all biological activities come at a price and that once an organism devotes resources to one activity those resources are no longer available for other activities. Due to the competing priorities of reproduction an organism can not afford to allocate sufficient resources to somatic maintenance to ensure indefinite survival (reviewed in Kirkwood et al., 2000).

Similarly, an individual has a greater chance of producing more offspring if it can adjust the amount of energy it devotes to growth and reproduction in response to environmental changes that occur within that individual's lifetime. An extreme example is the state of diapause that many animals enter when conditions become unfavorable such as the reproductive diapause in *Drosophila* and the *C. elegans* dauer larval stage (Tatar and Yin, 2001). Longevity genes appear to have evolved to increase somatic maintenance in a harsh environment and to increase growth and reproduction when conditions are favorable (Kirkwood et al., 2000; Kenyon, 2001).

The difference between *aging* and *longevity* has two important implications for simple organisms in aging research. First, a 'universal mechanism' of *aging* is unlikely to exist because there is no selective pressure for such a mechanism. There has been strong selective pressure to conserve basic cellular processes, such as metabolism, the cell cycle and DNA repair, because these processes are required for the long-term viability of every species. However, this is not true for aging. Thus, it is not surprising that we find different intrinsic causes of death in distantly related species. Even within a genetically diverse species as *S. cerevisiae*, there will likely be particular genetic backgrounds that are predisposed to particular aging processes.

The second implication is pathways that regulate *longevity* will have evolved early and will have been maintained by natural selection because they are highly adaptive. These pathways are likely to be conserved between organisms that now bear little resemblance to one another.

Of course, there are limits to what can be learned about metazoan longevity by studying yeast, particularly in relation to systemic aging. Nevertheless, the pathways downstream of systemic signals that regulate longevity at the cellular level are certainly within the scope of unicellular organisms, as recent findings have shown. A recent report that the protozoan *Tetrahymena thermophilus* expresses a functional insulin-like receptor raises the possibility that cell-cell communication may also regulate aging in some unicellular organisms (Christensen, 2001).

3. Chronological yeast aging

Many researchers have proposed that aging in dividing or 'mitotic' tissues may be fundamentally

different from aging in tissues that remain in a post-mitotic state. Similarly, in *S. cerevisiae* a distinction is made between the aging of mitotic cells and those that are quiescent. Yeast 'replicative life span' is defined as the number of divisions an individual yeast cell undergoes before dying. The alternative measure, 'chronological life span', also referred to as 'post-diauxic survival', is the length of time a population of cells remains viable in a non-dividing state following nutrient deprivation reviewed in Sinclair et al., 1998.

Yeast cells grown in a nutrient rich medium multiply until all readily utilizable nutrients are exhausted. At this point, cells cease dividing and enter a post-diauxic, hypometabolic state, where they can remain viable for weeks. In synthetic medium, cells readily deplete the medium and cease dividing, yet they retain relatively high metabolism (Longo, 1999). Such cells have a greatly reduced life span relative to cells in rich medium and are thought to more closely resemble post-mitotic cells in multi-cellular organisms (Longo et al., 1996).

A number of lines of evidence indicate that aging in multicellular organisms is, at least in part, due to oxidative damage by reactive oxygen species (ROS). Antioxidants can promote longevity in *C. elegans* (Melov et al., 2000) and the expression of superoxide dismutase (an enzyme that detoxifies oxygen radicals) in *Drosophila* neurons extends life span (Parkes et al., 1998).

It is becoming increasingly apparent that yeast chronological aging is also due to damage by ROS. Yeast lacking superoxide dismutase have a greatly reduced chronological life span (Longo et al., 1999) and the expression in yeast of the human Bcl-2 gene, which in humans stimulates defenses against ROS, allows cells to survive longer in stationary phase (Longo et al., 1997). Fabrizio, Longo and colleagues screened for oxidative stress resistant mutants with extended chronological life span and identified two loss-of-function mutations in the *SCH9* and *CYR1* genes (Fabrizio et al., 2001). *SCH9* encodes a protein kinase with homology to *C. elegans* AKT-1 and AKT-2, which function downstream of the longevity-regulating IGF-1/DAF-2 insulin-like signaling pathway (Vanfleteren and Braeckman, 1999). *CYR1* encodes adenylate cyclase, which regenerates cyclic AMP in response to increased metabolism. Mutation of *CYR1* also extends yeast replicative life span (Lin et al., 2001), demonstrating that there is some overlap between the regulation of replicative and chronological aging. Conserved pathways of longevity regulation in *S. cerevisiae* and *C. elegans* are shown in Fig. 1.

4. Replicative yeast aging.

In *S. cerevisiae*, cell division is asymmetric: a newly formed 'daughter' cell is almost always smaller than the 'mother' cell that gave rise to it. In 1950 Andrew Barton took advantage of this property to follow the fate of individual cells by micro-manipulation and discovered that mother cells are mortal (Barton, 1950). On average mother cells divide about 20 times before dying, depending on the strain. For the next 40 years most yeast aging research remained descriptive. It was noted that as yeast cells grow older they accumulate bud scars, divide more slowly and finally become sterile (reviewed in Sinclair et al., 1998). In the 1990s, two key observations were made. The first was that daughter cells arising from old mothers inherit characteristics of old age and have a shorter life span (Johnson, 1966; Kennedy et al., 1994). This effect was not the result of mutation because the premature aging phenotype could be diluted through successive generations, eventually restoring a normal life span in descendants. Based on these observations, Jazwinski and Egilmez proposed that yeast aging might be due to the stochastic appearance of a senescence factor that accumulates exponentially until it kills cells (Egilmez and Jazwinski, 1989). Such a factor was proposed to diffuse from old mothers into daughters, thus explaining how old age could be inherited and then diluted through successive generations.

The second important observation came from a genetic screen for long-lived yeast mutants. Kennedy, Guarente and colleagues first identified starvation resistant mutants, having noted that in many other organisms there is a strong correla-

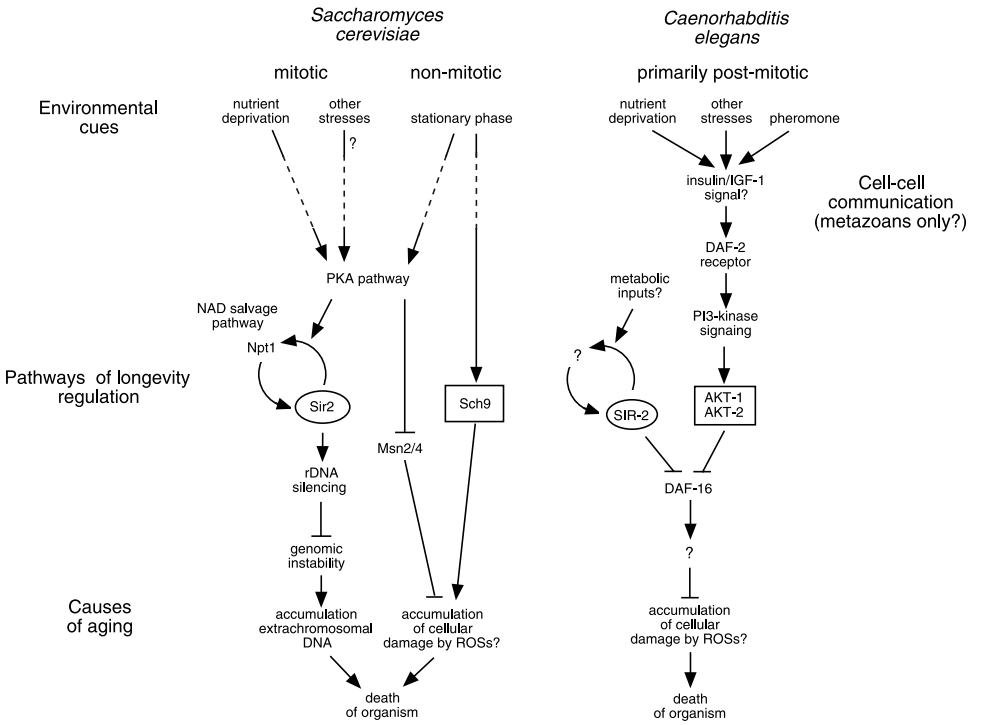

Fig. 1. Conserved longevity regulatory pathways in *S. cerevisiae* and *C. elegans*. There are two ways to measure longevity in *S. cerevisiae*: replicative (mitotic) life span and chronological (quiescent) life span. Recent work has identified genes with functional homologs in the conserved insulin-like signaling pathway that regulates longevity in *C. elegans*, *Drosophila* and possibly mice (Kenyon, 2001). These findings are consistent with the idea that *longevity* regulation is highly adaptive and components of a primordial longevity pathway will have been conserved in a diverse range of species. In contrast, *aging* is a by-product of natural selection and no 'universal mechanism' of aging is likely to exist.

tion between stress resistance and longevity (Kennedy et al., 1995). Rescreening of the stress resistant mutants for increased longevity led to the isolation of four so-called 'youth mutants', *uth1–4*. Interestingly, three of these have been found to affect the same cellular process, the formation of silent heterochromatin.

In yeast, transcriptional silencing occurs at telomeres, the two silent mating-type loci (*HML* and *HMR*) and at the ribosomal DNA (rDNA) locus, *RDN1* (Loo and Rine, 1995; Moazed, 2001). The establishment of heterochromatin at telomeres and mating-type loci requires the yeast Sir2/3/4 protein complex. Sir2, but not Sir3 or Sir4, also mediates silencing at the rDNA (Bryk et al., 1997; Smith and Boeke, 1997). In many strains, the overexpression of Sir2 increases the extent of silencing at both telomeres and rDNA, implying that Sir2 is a limiting component of the silencing apparatus (Smith et al., 1998; Kaeberlein et al., 1999).

The most informative allele isolated in the screen for longevity mutants was *SIR4–42*, which extends yeast life span by 45% (Kennedy et al., 1995). This semi-dominant mutation truncates the Sir4 protein, causing the Sir complex to relocalize to the nucleolus (Kennedy et al., 1997) and increase rDNA silencing (Sinclair, 2002). The *UTH1* gene encodes a SUN domain protein whose expression is greatly induced by oxidative stress and whose deletion results in a global increase in silencing and life span extension (Austriaco and Guarente 1997). *UTH4*, which encodes a *Drosophila* Pumilio homolog (Edwards et al., 2000), influences the distribution of the Sir complex within the nucleus (Gotta et al., 1997;

Kennedy et al., 1997). Deletion of *UTH4* reduces life span and decreases rDNA silencing, whereas overexpression of Uth4 has the opposite effect (Kennedy et al., 1997). Although the biochemical function of Uth1 and Uth4 remain to be determined, a clear trend has emerged from these studies: increased silencing at the rDNA locus in yeast correlates with increased longevity.

5. The ERC mechanism of yeast replicative aging

The increase in yeast life span associated with the localization of Sir4–42 to the nucleolus led to the idea that a defect at the rDNA might be one cause of yeast aging (Kennedy et al., 1997). The rDNA locus in yeast and other organisms is inherently unstable due to its highly repetitive nature (Linskens and Huberman, 1988; Gangloff et al., 1996) and unidirectional mode of DNA replication (Kobayashi et al., 1992; Wiesendanger et al., 1994 Lopez-Estrano et al., 1999).

Bernard Strehler, a pioneer of aging research to whom this issue is dedicated, was the first to appreciate that one of the most difficult functions for a cell is to maintain the integrity of highly repeated DNA (Johnson and Strehler, 1972). In the early 1970s, Strehler and his colleagues published a series of thought provoking papers showing that the quantity of rDNA in post-mitotic organs such as heart, skeletal muscle and brain declines with age in humans and dogs (Johnson and Strehler, 1972; Johnson et al., 1975; Strehler and Chang, 1979; Strehler, 1986). To Dr Strehler's disappointment, his research in this area was never followed up in a rigorous manner and to this day his theory remains largely ignored. One consolation is that Dr. Strehler's ideas about the difficulty of maintaining rDNA and how rDNA deletion may be achieved through 'episome' formation (Strehler and Chang, 1979) were both prophetic and influential in the elucidation of a major cause of yeast aging.

The yeast rDNA locus is comprised of 100–200 tandem copies of a 9 kb rDNA unit on chromosome XII (reviewed in Linskens and Huberman, 1988). Each repeat contains three adjacent autonomously replicating sequences (*ARS*s) that can support the replication of recombinant plasmids (Larionov et al., 1984). The following model for yeast aging was proposed to explain the phenomenon of yeast replicative aging (Sinclair and Guarente, 1997). At a stochastically-determined point in a yeast cell's life span, an extrachromosomal rDNA circle (ERC) is excised from the rDNA array by homologous recombination. ERCs have replicative potential and they tend not to be passed to daughter cells. These two properties cause the number of ERCs in the nucleus of the mother cell to multiply with each cell division. After about 15 divisions, the number of ERCs reaches more than 1000 copies, which is more DNA than is contained in the entire the yeast genome. The observation that occasionally daughters from old mothers inherit characteristics of old age could occur if ERCs were to 'leak' from old mothers into daughters. The abundance of ERCs may cause death by titrating essential transcription and replication factors. Southern blotting has confirmed that the vast majority of young cells do not contain any ERCs whereas old yeast cells typically contain over 1000 (Sinclair and Guarente, 1997).

6. Is there support for the ERC model?

Since we proposed the ERC model in 1997 it has been subjected to considerable scrutiny by numerous laboratories. There are now several lines of experimental evidence that support a causal role for ERCs in the yeast aging process (Fig. 2). First, mutations that increase the rate of ERC formation (e.g. a *sir2* mutation) accelerate the aging process and reduce life span (Kaeberlein et al., 1999). Second, with the exception of *cdc6* (described below), every mutation, overexpressed protein, or environmental condition that extends yeast life span correlates with increased rDNA stability and/or silencing when examined (Defossez et al., 1999; Kaeberlein et al., 1999; Kim et al., 1999 Park et al., 1999; Lin et al., 2000; Roy and Runge, 2000; Defossez et al., 2001). Third, the ERC levels in long-lived strains (e.g. *fob1*, *2xSIR2* and *cdc25–10*) are decreased and this decrease is proportional to the life span extension (Defossez

et al., 1999; Lin et al., 2000). Fourth, the ectopic release of an ERC into a 'virgin' daughter cell results in premature aging and a two-fold reduction in life span (Sinclair and Guarente, 1997). Together, these results demonstrate that ERCs are both necessary and sufficient for aging in wild-type cells. Pedigree analyses of individual yeast cells has shown that ERCs are kept within mother cells but they can transfer from very old mother cells to their daughters, a pattern of inheritance that is fully consistent with the ERC model.

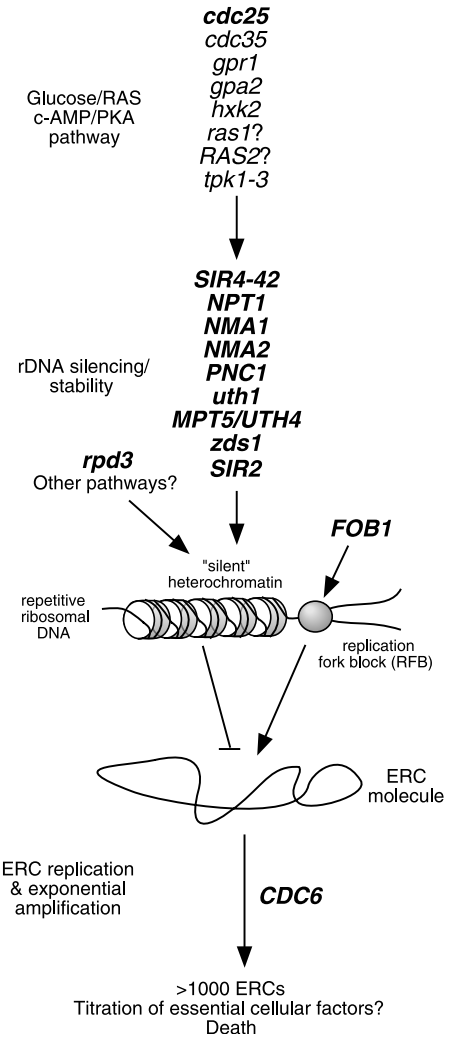

Fig. 2. The regulation of rDNA stability by caloric restriction. A cause of yeast aging is the stochastic release of an ERC which amplifies exponentially as cells replicate. Longevity genes that are known to affect rDNA silencing, rDNA stability or ERC amplification are shown in bold. Life span extensions by *fob1*, *cdc25-10* and overexpression of *SIR2* have been shown to correlate with ERC levels in old cells. *FOB1* does not affect rDNA silencing, arguing against the hypothesis that dysregulation of heterochromatin is a primary cause of yeast aging (adapted from Defossez et al., 2001).

For exemplary purposes I will discuss three yeast longevity genes that prevent ERC accumulation via three very different mechanisms. The first is the *CDC6* gene, which is involved in the establishment of pre-replication complexes at origins. Cells with the *cdc6-1* temperature-sensitive mutation have severe defects in origin firing and replicate ERCs inefficiently. Consistent with the ERC model, we observed that *cdc6* strains live about 15% longer than wild type cells (Sinclair and Guarente, 1997).

Yeast life span can also be extended by inhibiting ERC formation. This can be achieved at least two ways. The first is to prevent the formation of inherently unstable replication fork blocks (RFB) at the rDNA. The replication of the rDNA in yeast and other species occurs in a unidirectional manner due to formation of RFBs (Brewer and Fangman, 1988; Kim and Wang, 1989; Kobayashi et al., 1998). The formation of RFBs requires the nucleolar protein Fob1 (Kobayashi et al., 1998) and *fob1* mutants have ten-fold greater rDNA stability during mitosis. In 1998, Defossez and colleagues showed that *fob1Δ* cells live over twice as long as wild type, in fact they are the longest-lived yeast strains ever recorded[2] (Defossez et al., 1999). Further consistent with the ERC model, the various life spans of the *fob1* alleles that were tested correlated with a reduction in ERC levels in age-matched old cells.

Another way to inhibit ERC formation is to increase the level of heterochromatin at the rDNA locus. In a landmark paper, Kaeberlein and colleagues showed that an additional copy of the *SIR2* gene increases rDNA silencing and extends life span by 30% (Kaeberlein et al., 1999). Deletion of *SIR2* has the opposite effect. Importantly, the abundance of ERCs in age-matched old cells correlated with the life spans of the strains.

[2] Jiang et al. (2000) reported a 123% increase in life span, however, the life span of the parental strain was relatively short.

A number of mutations that correlate rDNA stability with replicative life span, including *fob1* and a variety of mutations that disable DNA repair, do not display increased rDNA silencing (Park et al., 1999; Kaeberlein, personal communication). These findings argue against the hypothesis that a primary cause of yeast aging is the result of altered heterochromatin or rRNA transcription in old cells (Jazwinski, 2000).

The ERC model has recently been challenged in two reports. First, Jazwinski et al. have reported that ERC levels are not increased in *sir2* mutants (Kim et al., 1999). However, the authors examined ERCs levels in a logarithmically growing culture of yeast cells, which contain almost exclusively young cells. A second report found that short-lived *sgs1* strains do not accumulate ERCs faster than wild type (Heo et al., 1999), which has been cited as evidence against the ERC model (Gershon and Gershon, 2000). However, *sgs1* cells have additional defects that are unrelated to the aging process, most likely defects in DNA replication (McVey et al., 2001).

7. Calorie restriction extends replicative life span by inhibiting ERCs

The disposable soma theory of aging predicts that organisms will allocate more of their resources to somatic maintenance during times of stress. Many organisms including rodents, *C. elegans* and *Drosophila* live longer and are generally healthier when calories are restricted (reviewed in Masoro, 2000). This correlation between calorie intake and longevity has also been demonstrated for *S. cerevisiae*. Yeast cells that are deprived of either glucose or non-essential amino acids have a significantly longer replicative life span (Lin et al., 2000). The molecular mechanism by which glucose availability regulates life span has recently been established. Lin and colleagues showed that yeast cells grown on 0.5% glucose live about one-third longer than cells grown on 2.0% glucose (Lin et al., 2000). Interestingly, a variety of mutations that interfere with glucose metabolism (*hxk1*) or cAMP production (*tpk1Δ* and *cdc25–10*) can mimic this effect. Consistent with the ERC model, cells grown on 0.5% glucose or carrying a *cdc25–10* mutation have high levels of rDNA silencing and old *cdc25–10* cells have fewer ERCs than age-matched old wild type cells (Lin et al., 2000).

Do these observations fit with the disposable soma theory of aging? The theory predicts that ERC suppression should come at a cost that subtracts from growth and reproduction. In 1999, two groups led by Leonard Guarente and Rolf Sternglanz published that Sir2 is a histone deacetylase (HDAC) that consumes nicotinamide adenine dinucleotide (NAD) (Imai et al., 2000; Landry et al., 2000). Recent data from our laboratory indicates that the maintenance of silent heterochromatin requires NAD—even in non-cycling cells (K.B. Bitterman and Sinclair, unpublished). These findings indicate that ERC suppression requires energy that could otherwise be utilized for cell growth and reproduction.

The fact that Sir2 requires NAD for its deacetylase activity suggests that the increased rDNA silencing in calorically restricted cells might be due to increased NAD levels (Campisi, 2000). Consistent with this, old yeast cells have higher NAD levels and deletion of the *NPT1* gene reduces the steady-state level of NAD by two-fold (Smith et al., 2000) and abrogates the life span extension provided by calorie restriction (Lin et al., 2000). However, the pathways of NAD metabolism are complex and the idea of NAD steady-state levels regulating life span may be too simplistic. The Sir2 deacetylation reaction cleaves one molecule of NAD to generate nicotinamide and a previously unknown metabolite, *O*-acetyl-ADP-ribose (Tanner et al., 2000; Tanny and Moazed, 2001). Nicotinamide is thought to be recycled back to NAD in four steps via the NAD salvage pathway (Smith et al., 2000). The important implication is that Sir2 catalyzes a key step in the NAD salvage pathway (Fig. 3). Given that the salvage pathway is cyclical, any NAD that becomes freely available will likely be consumed and any that is consumed will likely be regenerated. Under conditions of calorie restriction or stress, we may find that there is no significant increase in NAD steady-state levels but that flux through the NAD salvage pathway is increased.

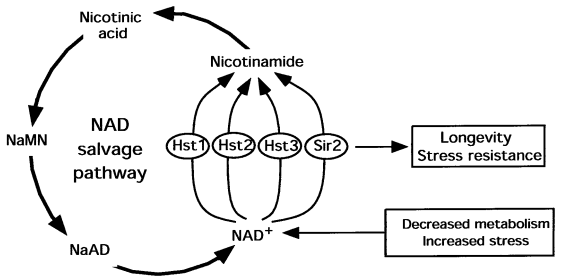

Fig. 3. Model for life span extension via increased flux through the NAD salvage pathway. Type III deacetylases, such as Sir2 and Hst1-4, catalyze a key step in the NAD salvage pathway by converting NAD to nicotinamide. Increased flux through the salvage pathway occurs following increased stress or calorie restriction, which stimulates Sir2 activity and extends life span without increasing steady-state NAD levels. NaMN, nicotinic acid mononucleotide; NaAD, desamino NAD^+.

8. The relevance of yeast aging research to metazoans

The ERC model of yeast aging is now supported by considerable evidence and has led to the identification of ways to extend life span in both yeast and *C. elegans*. But are they relevant to metazoans? ERCs have been detected in a variety of metazoan cell lines and extrachromosomal inter-Alu DNAs have been shown to amplify in passaged fibroblasts (Lumpkin et al., 1985). However, the abundance of circular DNAs in tissue samples does not appear to correlate with aging (L. Guarente and B. Johnson, pers. commun.). This result should not raise concern about the validity of yeast as a model because specific mechanisms of aging are unlikely to be highly conserved between distantly related species. In contrast, longevity regulatory pathways appear to have arisen early in evolution and aspects of these primordial pathways appear to have been conserved (see Fig. 1).

Sir2 provides a case in point. The basic biochemical function of Sir2, NAD-dependent deacetylation, appears to be conserved both within yeast and between species (Shore, 2000 Perrod et al., 2001). In yeast there are four Sir2 homologs and in humans there are at least seven (Brachmann et al., 1995; Frye, 1999, 2000). Tissenbaum and Guarente have recently shown that a *C. elegans SIR2* homolog, *sir-2.1*, extends life span in that organism when overexpressed (Tissenbaum and Guarente, 2001). By epistasis analysis, *sir-2.1* has been placed within the insulin-like *daf-2*/*akt-1* dauer pathway. It appears that each species has evolved to utilize NAD-dependent deacetylases to regulate their own particular modes of aging. This is consistent with the recent finding that a mammalian Sir2 homolog, *SIR2α*/*SIRT1*, regulates the tumor suppressor p53 (Luo et al., 2001; Vaziri et al., 2001). Deacetylation of p53 by *SIR2α* inactivates an apoptotic pathway such that cells overexpressing SIR2α are more likely to survive DNA damage.

Another aspect of yeast replicative aging with potential relevance to metazoan aging is the effect of calorie restriction on life span. The ability of calorie restriction to extend life span in rodents has been known for many years but only recently has the phenomenon been modeled in yeast (Lin et al., 2000). A number of findings point to a critical role for the RAS/cyclic-AMP/protein kinase A (PKA) pathway in yeast calorie restriction. Loss-of-function mutations in the GTP-binding protein gene, *RAS1*, increase replicative life span by 40% and overexpression of Ras2 has a similar effect (Sun et al., 1994). Similarly, Lin et al. recently showed that two genes involved in cAMP metabolism, *TPK1* and *CYR1*, are involved in the life span extension provided by calorie restriction (Lin et al., 2000).

S. cerevisiae has also served as a model for diseases that resemble premature aging such as Werner syndrome (WS) and Rothmund–Thomson syndrome (RTS). The genes responsible for WS and RTS encode DNA helicases with homology to the Sgs1 helicase of *S. cerevisiae* (Gangloff et al., 1994; Watt et al., 1995; Oshima, 2000; Shen and Loeb, 2001). Cells derived from WS individuals undergo fewer divisions in culture than those from normal individuals (Goldstein et al., 1983) for reasons that are not clear. Recent work by our lab and others has shown that Sgs1 has a function in telomere maintenance (Cohen and Sinclair, 2001; Huang et al., 2001; Johnson et al., 2001). Yeast strains lacking both telomerase and Sgs1 undergo accelerated senescence and are defective in the process of recombination mediated telom-

ere rebuilding. The work supports the intriguing hypothesis is that premature aging in WS may be due in part to accelerated telomere erosion. The relevance of these findings to normal human aging is not yet known.

9. Conclusions

The usefulness of yeast as a model for longevity regulation is no longer in doubt and many of the questions in the field can be addressed by distinguishing between the terms *aging* and *longevity*. Longevity is evolutionarily adaptive, whereas aging is merely a by-product natural selection. It follows that the pathways that control longevity are likely to be conserved over a wide range of species whereas aging pathways are not. In yeast, the link between aging and the stability of rDNA has led to the identification of an aging mechanism. While this specific mechanism is unlikely to be conserved in metazoans, it has helped identify longevity regulatory pathways in both yeast and *C. elegans*. The exploration of other aging mechanisms in yeast should uncover more conserved components of eukaryotic longevity pathways.

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