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Genome-wide identification of conserved longevity genes in yeast and worms

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Abstract

Technological advancements in invertebrate model organisms have recently made it possible to survey many or all of the genes in the genome for phenotypes of interest. In both *C. elegans* and *S. cerevisiae*, genome-wide searches for hypomorphic mutations that extend life span have been performed. The results from these screens are starting to provide a more complete view of the range of life span determinants in eukaryotes. In addition, it is becoming possible to test the premise that conserved aging genes and pathways regulate aging in disparate eukaryotic species. Here we compare and contrast the results from genome-wide aging screens and assess the likelihood that there are ''public'' aging mechanisms.
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1. Introduction

Many different model organisms have been used to study the biology of aging, including the budding yeast, *S. cerevisiae*, the nematode, *C. elegans*, the fly, *D. melanogaster*, and the mouse, *M. musculus*. Major advances in our understanding of the molecular basis of aging have been made, with dozens of interventions demonstrated to modulate life span in one or more of these organisms. Genetic analysis of various mutants has led to the identification of several important genes involved in aging, such as those in the insulin/IGF-1 signaling pathway (Kenyon et al., 1993; Duhon et al., 1996), genes important for stress resistance (Lithgow and Walker, 2002; Longo and Fabrizio, 2002) and genomic maintenance (Lombard et al., 2005), and the sirtuin family of protein deacetylases (Kaeberlein et al., 1999; Tissenbaum and Guarente, 2001; Rogina and Helfand, 2004). These and many other studies have demonstrated clearly that there is a genetic component to the aging process, reviewed in Kenyon (2005).

Environmental cues, as well as genetic factors, can also play a major role in longevity determination. The best characterized environmental determinant of longevity is calorie restriction (CR). CR has been shown to extend life span in nearly every organism in which it has been tested (Walford et al., 1987, Masoro, 2005). Although several models have been put forth to explain how CR slows aging, no commonly accepted mechanism for CR has been described in any organism, and there is much interest in determining whether the mechanism underlying CR is conserved in different organisms.

Several years ago George Martin described the idea that the aging process is likely to be a combination of ''public'' and ''private'' features. Public features of aging are evolutionarily conserved among disparate organisms; whereas, private features of aging are specific to a given organism or closely related group of organisms. One example of a private feature of aging is the role of extrachromosomal rDNA circles (ERCs) in mother cell senescence of *S. cerevisiae* (Sinclair and Guarente, 1997); although ERCs are one cause of replicative aging in yeast, there is no evidence that ERCs accumulate or cause aging in any organism other than yeast. Public features of aging include the ability of CR to increase longevity in many different organisms and the observation that decreased signaling through the insulin/IGF-1 pathways can increase life span in worms, flies, and mammals. It remains to be determined, however, to what degree the aging process has been evolutionarily conserved and whether public determinants of longevity are the exception or the norm.

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As part of a consortium of researchers located at the University of Washington and funded by the Ellison Medical Foundation, we are taking a multi-organism approach to identify conserved longevity genes. The underlying rational for this approach is that if a particular gene family regulates longevity in yeast, worms, and mice, then there is a good chance this gene family will play a similar role in humans. Here we summarize the results form genome-wide longevity screens in yeast and worms, to date, and we discuss how these data are facilitating the search for conserved longevity genes.

2. Genomic approaches to the identification of aging genes

The rapid increase in whole genome sequencing has dramatically changed the way scientists do research in genetics, molecular biology and biochemistry, and biogerontology is no exception. The complete sequence of the yeast genome was published in 1996 (Goffeau et al., 1996), followed by the worm genome in 1998 (Consortium, 1998), the fly in 2000 (Adams et al., 2000), and the mouse in 2002 (Waterston et al., 2002). In the years since these genomes were published, a plethora of genomic tools have been developed, including databases such as Saccharomyces Genome Database (SGD; Hong EL et al., 2006), Wormbase (2006), Flybase (Grumbling and Strelets, 2006), Biobase Biological Databases (2006), and even a database devoted to cataloging aging genes and interventions (Kaeberlein et al., 2002). The impact of these databases, combined with technologies, such as microarrays and other genomic tools, on progress in the biology of aging is unquestionable (reviewed in Kaeberlein, 2004).

In yeast, several genomic deletion collections are now commercially available (Winzeler et al., 1999). In these collections, yeast strains are genetically identical, except for a single gene deletion in each strain. Of note, there are genetic anomalies, including aneuploidy (Hughes et al., 2000) and suppressor mutations, in a small portion of the strains in the collection. Deletion collections are available in both haploid mating types, a and α, as well as homozygous and heterozygous diploids. In total, more than 20,000 unique single-ORF deletion strains have been created (Winzeler et al., 1999). Thus, researchers have the ability to screen for a phenotype of interest across the entire yeast genome in a gene-by-gene manner.

In *C. elegans*, a deletion collection similar to those available in yeast has not been developed; however, there are two independently derived RNAi libraries that are commercially available. The first is a genomic library generated by the Ahringer lab and contains over 16,000 unique bacterial strains expressing double-stranded RNA corresponding to individual genes (Kamath et al., 2003). The second library, generated by the Vidal lab, utilizes a similar expression vector and the same bacterial strain, but contains inserts derived from the ORFeome cloning project and does not include introns (Reboul et al., 2003; Rual et al., 2004). Both RNAi libraries are arrayed so that high-throughput screening is possible, where worms are fed individual clones to specifically down-regulate expression of individual genes and a phenotype of interest can been assayed.

2.1. Genome-wide longevity screens in yeast

We have taken a genomic approach to identify conserved determinants of longevity. Two different models of aging are commonly studied in yeast: replicative and chronological (Kaeberlein, 2006b). Replicative life span (RLS) is defined as the number of daughter cells that an individual mother cell can produce, and has been suggested as a model for the aging of mitotically active cells or stem cells. Chronological life span (CLS) is defined as the length of time that a yeast cell can survive in a non-dividing state (typically stationary phase), and has been suggested as a model for aging of post-mitotic cells. Together, both aging models make yeast a powerful system in which to study the genetics of aging, because RLS and CLS can be measured independently, allowing direct comparisons to be made between the genes regulating life span in dividing versus non-dividing cells.

2.1.1. Yeast replicative life span

The first longevity screen of the yeast deletion collection to be described was our characterization of the replicative aging properties of 564 single-gene deletion mutants from the *MAT* α ORF deletion collection (Kaeberlein et al., 2005). Due to the labor-intensive nature of the RLS assay, which involves microdissection of daughter cells away from the mother cells, an iterative method was developed for classifying mutants as likely to be long-lived or not, based on RLS measurements of five-cell sets (Kaeberlein and Kennedy, 2005). From this analysis, 13 single-gene deletion mutants were found to have a significantly increased RLS relative to control cells (discussed below), while approximately 20% of the single-gene deletion mutants analyzed were significantly short-lived. The genome-wide RLS screen is currently ongoing, with RLS data having been obtained thus far for more than 2500 single-gene deletion mutants.

Among the 13 verified long-lived mutants identified from the yeast RLS deletion set screen, both known and novel aging genes were identified. For example, deletion of the replication fork block gene, *FOB1*, was previously shown to increase RLS through regulation of ERC formation (Defossez et al., 1999), and *fob1*Δ was identified from our RLS screen as long-lived (Kaeberlein et al., 2005). Deletion of the gene coding for the nutrient responsive kinase Tori also increased RLS. Although *tor1*Δ cells had not been previously found to have long RLS in yeast, decreased TOR activity had been shown to increase life span in both worms and flies (Kapahi et al., 2004; Vellai et al., 2003).

In addition to *tor1*Δ, several strains lacking other components of the TOR signaling pathway were also found to be replicatively long-lived in our screen. These included two gene deletion strains lacking protein components of the large ribosomal subunit, *rpl31a*Δ and *rpl6b*Δ. TOR promotes ribosome biogenesis by regulating transcription of ribosomal proteins in yeast, and decreased TOR activity is known to result in down-regulation of many ribosomal proteins (Martin et al., 2004). In follow-up studies, we have observed long RLS in additional ribosomal protein mutants, leading us to speculate

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