Aging mechanisms revealed by large-scale genetic profiling of yeast lifespan

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The aging process is modulated by **conserved genes and cellular pathways**

Guevara-Aguirre et al.  
*Sci Transl Med* 2011
Which are the genes and genetic pathways that influence the rate at which organisms age?

How are different genetic aging factors integrated with one another and with the environment?

Our approach:
Large-scale genetic analysis of lifespan phenotypes in the budding yeast *Saccharomyces cerevisiae*
The **budding yeast** is one of the most important model organisms used in aging research.

**Replicative lifespan (RLS):**
Number of mitotic divisions

\[ n = \text{Replicative lifespan} \]

**Chronological lifespan (CLS):**
Number of days viable in stationary phase

\[ t = \text{Chronological lifespan} \]
We developed a **competition-based strategy** to characterize the chronological lifespan of yeast.
We integrated an **automated cell-assay** station to scale-up genetic analyses of yeast chronological lifespan.

- **Liquid handling**
- Detection (OD & fluor)
- 96w-plate incubation ~3,000 cultures
A single-knockout screen shows that a substantial fraction of the genome influences yeast lifespan.
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Long-lived mutants typically **proliferate slower**

**Lifespan phenotype**

**Long-lived knockouts**
Our screen reveals **cellular processes** that are relevant for lifespan

Genetic interactions are defined as deviations from additive mutation effects.

Survival, $s$

$\Delta xy$

$\Delta x + \Delta y$

$\Delta xy$

$\Delta x$

$\Delta y$

wt

-0.5

-0.3

-0.2

0

Negative (synergistic)

Positive (antagonistic)

Pathway X

Pathway Y

Complex
We generated and characterized a collection of **double knockouts** of aging factors.

145 KOs (Mat-α) \[ \times \] 145 KOs (Mat-α) \[ \rightarrow \] SGA

>20,000 double-KOs

Lifespan epistasis

\[ \epsilon = s_{xy} - (s_x + s_y) \]

- observed
- expected

Wild type

Stationary phase
We generated and characterized a collection of **double knockouts** of aging factors.
We described the lifespan-genetic interactions of autophagy genes in a systematic manner.
A genetic interaction network describes **functional associations** within longevity pathways.

- **Core ATG**
- **CVT pathway**
- **PIP**
- **Signaling**

**Negative lifespan epistasis**

**Positive lifespan epistasis**
The novel longevity factor \textbf{Arv1} extends lifespan together with the autophagy machinery.

\textit{arv1}Δ,\textit{atgX}Δ double knockouts

\textbf{Antagonistic lifespan epistasis}

\textbf{Reduced autophagy activity in arv1Δ}

\textbf{Expected lifespan, }s_{arv1} + s_x \text{ (additive effects)}

\textbf{Observed lifespan, }s_{arv1,x} \text{ (double knockout)}

\textbf{Nitrogen-starved cells}

\textbf{WT}

\textbf{Arv1}

\textbf{atg1Δ}

\textbf{arv1Δ}

<table>
<thead>
<tr>
<th>GFP-Atg8</th>
<th>FM4-64</th>
<th>DIC</th>
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<tbody>
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<td>WT</td>
<td>0 2 5 7</td>
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<tr>
<td>atg1Δ</td>
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</tr>
<tr>
<td>arv1Δ</td>
<td>0 2 5 7</td>
<td>0 2 5 7</td>
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\textbf{Pgk1-GFP}

\textbf{GFP}
We systematically described the way in which lifespan phenotypes are affected by dietary restriction.
Highlights

• We have introduce a platform for high-resolution genome-wide screens, gene-gene, and gene-environment interaction analyses of yeast lifespan

• Arv1 is a modulator of bulk autophagy, needed to maintain WT lifespan

• A large-scale genetic analysis uncovers cellular mechanisms of lifespan extension by dietary restriction
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