File S1

Supporting Material and Methods

Numerical implementation and parameter estimation.

Numerical simulations and parameter estimation were performed using Matlab (R2012a version). To estimate the values of the parameters β and L_0 in equation 2, we fitted equation 2 to experimental data of (Teixeira *et al.* 2004) (Fig. S1*A*) using the fitting toolbox of Matlab. The parameter p for the elongation length was estimated from the empirical cumulative distribution of the elongation length (Teixeira *et al.* 2004), which we fitted with the cumulative distribution function of parameter p (Fig. S1*B*). The probability function of the increasing length b was plotted in figure S1*C*.

To approximate the probability $P(L)$ of elongation of a telomere of length L, we used the following function

$$P(L)=\frac{1}{1+\beta(L-L_0)}, \quad (*)$$

where β and L_0 are fitting constant parameters. This expression was inferred from the biochemical process in which telomerase and Rap1/Rif1/Rif2 compete for the same substrate, namely the telomere (Fig. 1*A*).

To obtain the equation (*), we shall now derive from the analysis of chemical reactions regulating telomere length expression. There are two opposite reactions:

First, when telomerase is recruited, the telomere elongates:

$$Telomere + Telomerase \xrightarrow{k_2} Elongated\ Telomere \qquad (3)$$

where k_2 is the rate constant of the reaction.

Conversely, a shortening event occurs if the amount of Rap1/Rif1/Rif2 in *cis* is enough to inhibit telomerase recruitment:

$$Telomere + Rap1/Rif1/Rif2 \xrightarrow{k_1(L_n-L_0)} Shortened\ Telomere \qquad (4)$$

where $k_1(L_n-L_0)$ is the rate constant of the reaction.

We consider that the number of telomere-bound Rap1/Rif1/Rif2 protein complexes is proportional to the telomere length (Marcand *et al.* 1997) and thus the rate constant in equation 4 is proportional to the telomere length L_n-L_0. Combining equations 3 and 4, we obtain the steady-state probability distribution $P(L_n)=\frac{1}{1+\beta(L_n-L_0)}$ used in equation 2, where $\beta=\frac{k_1}{k_2}$. We fitted this expression to experimental data, and we found $\beta=0.045$ and $L_0=90$ bp (Fig. S1*A* and Table 1).

In the present model, we consider that the correspondence between the amount of Rap1/Rif1/Rif2 protein complexes and the constant rate of equation 4 is linear over the entire range of telomere lengths used for our simulations. Indeed, this assumption is verified *a posteriori* since expression (*) was a good fit to the data on the entire length interval.

Statistical analysis.

All statistical analyses were performed using the statistical toolbox of Matlab. The means of senescence indices measured by the spot assay were tested for statistical difference by unpaired two-sample Student's *t*-test, with "the means of senescence indices are equal for the two considered sets" being the null hypothesis. The ratio of the number of tetrads with differential senescence between two *tlc1Δ* spores to the total number of tetrads was compared to theoretical ratios using Pearson's χ^2 goodness-of-fit test, which is commonly used to assess whether an observed distribution differs from a theoretical one, with "the observed ratio is equal to the theoretical one" being the null hypothesis. We also used Pearson's χ^2 goodness-of-fit test to compare simulated distributions to the experimental one (Fig. 1*F*), with "the frequency distribution of telomere lengths in the same in the simulation and the experiment" as the null hypothesis. For both statistical tests, we used the *p*-value to evaluate the probability of obtaining the test statistic assuming the null hypothesis. 0.05 was chosen as a threshold for the *p*-value, below which we rejected the null hypothesis.

Oligonucleotide probe design.

The probes used for single-telomere Southern blot were designed using the sequence of the S288C strain from Saccharomyces Genome Database (SGD) version R64-1-1 and information about W303 strain telomeres from Ed Louis's group's website (http://www.nottingham.ac.uk/biology/people/louis/telomere-data-sets.aspx). All analyses were performed using Geneious Pro 5.5.2. To design specific probes, we tested divergent regions among telomeres within 1.5 kb of the telomeric repeats. Each candidate was blasted against the whole genome using the blastn algorithm and selected for its specificity, although cross-reactivity with nonterminal restriction region was allowed. To confirm specificity, we used each probe as a primer to amplify the corresponding telomeric region by PCR, with another specifically designed primer located at the junction of the telomeric repeats and the specific subtelomeric region. We only used probes for which PCR amplified a unique band. The PCR product was then sequenced (Eurofins MWG Operon), and the sequence was compared to the S288C genome. With the exception of the XIV-R telomere (Table S1), which failed to be sequenced, all sequences either were completely identical to S288C sequences or displayed some point mutations (only for the XI-L telomere), which was expected since the yT337 background is different from S288C. As IX-L and X-L subtelomeres were identical, the oT457 probe was not specific to a unique telomere (Table S1).

Quantitative senescence assay.

The quantitative senescence assay used in this study was based on the semi-quantitative senescence assay described in (Abdallah *et al.* 2009). In most experiments, yT337 tetrads were dissected and spores were grown for 2 days at 30°C on a YPD plate. A third of each colony was resuspended in 5 µl water, boiled at 95°C for 5 min, and used as a substrate in PCR for genotyping *TLC1* locus. Colonies grown from single spores were resuspended in water in microtiter plates, and their concentrations were normalized at 800,000 cells per ml after OD (optical density) at 600 nm using an Epoch spectrophotometer (Biotek). For each cell suspension, eight replicates of 10-fold serial dilution spots were grown on a YPD plate, so as to assess the intraclonal variation that could arise and to statistically compare cell growth from different spores. The spots were grown for 2 days at 30°C. For each replicate, the most concentrated spot was then resuspended, normalized at 800,000 cells per ml, and re-spotted with serial dilutions. The same procedure was repeated for the next passage as well. Compared to the quantification procedure in (Abdallah *et al.* 2009), a new senescence index was used in this study. After 2 days of growth, spot plates were scanned at 1200 dpi using an Epson Perfection V750 Pro scanner. Images were processed with ImageJ. After background subtraction, all the spot intensities were measured and plotted against the logarithm of the 10-fold dilutions. The senescence index corresponded to the logarithm of the 10-fold dilution needed to grow the cells up to a set standard intensity value, which corresponded to the median intensity reached by wild-type telomerase-positive cells in 2 days of growth. For example, an index value of 1.3 for a given spore at passage 2 meant that, at passage 2, these cells would have needed to be diluted to $10^{-1.3}$ (starting with 800,000 cells per ml concentration) in order to reach, after 2 days, the set standard intensity value.