Gene expression profiles in *Saccharomyces cerevisiae* strongly reflect energetic costs of gene products

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Energy expenditures in protein synthesis in yeast have substantial fitness costs (1) and vary by >10^5-fold over the proteome. Gene expression profiles should thus reflect the heterogeneity not only of functional advantages but also of energetic costs of synthesizing each gene's product.

Here we examine (a) how protein abundances in log phase (LP) and mRNA change-folds in the shift from LP to late stationary phase (SP) relate to the energetic costs of maintaining each protein's steady state level; and (b) what basic strategies have evolved that minimize these costs.

LP and SP represent two extremes of cell physiology. In LP, cells have abundant resources available, rely mostly on glycolysis for energy production, gear gene expression towards maximum growth, and let growth-related dilution contribute substantially to the turnover of many proteins. In SP resources are too scarce for growth, cells rely mostly on respiration for energy production and gear gene expression towards maximum survival. Selective pressures on energy expenditure should be even stronger than in LP.

The ATP-equivalents expenditures in maintaining the level of each of 3009 proteins (~45% of the yeast proteome) were computed as

$$E = \sum_{i=1}^{20} f_i (c_i + 4)(D + V)P \qquad \text{Eq. 1}$$

with P the protein's concentration (from ref. 2), D the degradation rate constant (from ref. 3), V growth-related dilution (7.7×10^{-3}/min for LP, 0 for SP), f_i the frequency of aminoacid i in the protein's primary sequence (from the Comprehensive Yeast Genome Database), c_i the biosynthetic cost of aminoacid i (from ref. 1), and 4 the polymerization cost. We used the c_i values for fermentative or respiratory metabolism for LP or SP, respectively. (Results are robust with respect to this choice.) Eq. 1 is well approximated by

$$E = n(a + 4)(D + V)P$$

with n and a the protein's primary sequence length and mean aminoacid biosynthetic cost.

We found that in LP protein abundances decrease very significantly with estimated per-

molecule energetic cost ($e \propto E/P$). Turnover numbers ($D+V$), n, and a are significantly lower for abundant vs. rare proteins, but only the former two factors contribute substantially for variance in e. For very abundant (>10000/cell) proteins cells rely mainly in a slow turnover to limit e.

In the LP→SP shift, transcripts for proteins in the top E tercile (per Eq. 1, and were protein concentrations to remain as in LP) are significantly more down-regulated (from ref. 4) than those for proteins in the bottom E tercile. A similar significant transcriptomic trend holds for P and for n (despite n correlating negatively with P in LP), but not for a. In contrast, transcripts for proteins in the top D tercile are significantly less down-regulated than those for the upper tercile, in apparent contradiction to energy-cost minimization. However, the latter trend may reflect both the negative correlation of D with P in LP and a transcriptome-level compensation for growth-related dilution. The latter possibility is consistent with the observation that the transcriptomic trend is reverted at the proteome level when the fact that V=0 in SP is accounted for in estimating the protein change-folds.

Altogether, these results suggest that the energetic costs of protein synthesis are an important factor in shaping gene expression at a genome-wide scale. In LP cells afford energy by preferentially limiting the abundance of expensive proteins, and the turnover and size of proteins that must be abundant. Shifted to a resource-depleted environment, cells respond by preferentially down-regulating expensive, abundant and large proteins.

Acknowledgements
This work was financed in part through CRUP's Portuguese-Spanish integrated action E-6/07 and grant BFU2005-0234 from Spanish Ministerio de Educacion y Ciencia.

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