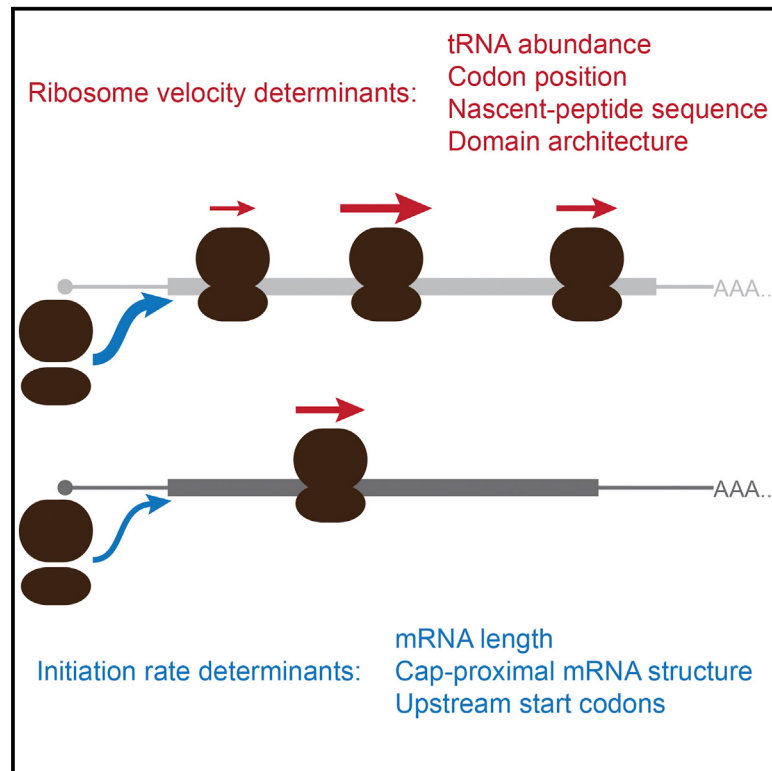


Cell Reports

Improved Ribosome-Footprint and mRNA Measurements Provide Insights into Dynamics and Regulation of Yeast Translation

Graphical Abstract



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In Brief

Ribosome-footprint profiling provides genome-wide snapshots of translation, but technical challenges can confound its analysis. Here, Weinberg et al. use improved methods to obtain ribosome-footprint profiles and mRNA abundances that together reveal key features of translational control in yeast.

Highlights

- Ribosome dwell times are typically longer at codons for less abundant tRNAs
- The first 200 codons tend to be translated more slowly, regardless of codon choice
- Accurate yeast mRNA abundances reveal a narrow range of translational efficiencies
- A statistical model explains much of the variation in initiation efficiencies

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Improved Ribosome-Footprint and mRNA Measurements Provide Insights into Dynamics and Regulation of Yeast Translation

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SUMMARY

Ribosome-footprint profiling provides genome-wide snapshots of translation, but technical challenges can confound its analysis. Here, we use improved methods to obtain ribosome-footprint profiles and mRNA abundances that more faithfully reflect gene expression in *Saccharomyces cerevisiae*. Our results support proposals that both the beginning of coding regions and codons matching rare tRNAs are more slowly translated. They also indicate that emergent polypeptides with as few as three basic residues within a ten-residue window tend to slow translation. With the improved mRNA measurements, the variation attributable to translational control in exponentially growing yeast was less than previously reported, and most of this variation could be predicted with a simple model that considered mRNA abundance, upstream open reading frames, cap-proximal structure and nucleotide composition, and lengths of the coding and 5' UTRs. Collectively, our results provide a framework for executing and interpreting ribosome-profiling studies and reveal key features of translational control in yeast.

INTRODUCTION

Although most cellular mRNAs use the same translation machinery, the dynamics of translation can vary between mRNAs and within mRNAs, often with functional consequences. For example, strong secondary structure within the 5' UTR of an mRNA can impede the scanning ribosome, thereby reducing the rate of protein synthesis (Kozak, 1986; Andersson and Kur-

land, 1990; Bulmer, 1991; Kudla et al., 2009; Tuller et al., 2010, 2011; Plotkin and Kudla, 2011; Ding et al., 2012; Bentele et al., 2013). The accessibility of the 5' cap (Godefroy-Colburn et al., 1985; Richter and Sonenberg, 2005) and the presence of small open reading frames (ORFs) within 5' UTRs referred to as upstream ORFs (uORFs) (Kozak, 1986; Ingolia et al., 2009; Brar et al., 2012; Zur and Tuller, 2013) can also modulate the rate of translation initiation (Sonenberg and Hinnebusch, 2009). Likewise, codon choice, mRNA structure, and the identity of the nascent polypeptide can influence elongation rates (Varenne et al., 1984; Brandman et al., 2012). In addition, differences in elongation rates can influence co-translational protein folding, localization of the mRNA or protein, and in extreme cases the rate of protein production (Kimchi-Sarfaty et al., 2007; Xu et al., 2013; Zhou et al., 2013). Finally, stop-codon readthrough can introduce alternative C-terminal regions that affect protein stability, localization, or activity (Dunn et al., 2013). Despite known examples of regulation at each of these stages of translation, translation is largely controlled at initiation, which is rate limiting for most mRNAs (Andersson and Kurland, 1990; Bulmer, 1991; Chu and von der Haar, 2012; Shah et al., 2013).

Variation in protein abundances observed in yeast cells largely reflects variation in mRNA abundances, indicating that much of gene regulation occurs at the level of mRNA synthesis and decay (Greenbaum et al., 2003; Csárdi et al., 2015). However, differences in translation rates also contribute. Studies using microarrays for global polysome profiling indicate that ribosome densities for different mRNAs vary over a 100-fold range (from 0.03 to 3.3 ribosomes per 100 nucleotides), indicating extensive translation control in *Saccharomyces cerevisiae* (Arava et al., 2003). More recently, the use of ribosome-footprint profiling has enabled transcriptome-wide analyses of translation using high-throughput sequencing, which again suggested a nearly 100-fold range of translational efficiencies (TEs) in log-phase yeast (Ingolia et al., 2009).

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