GENOME-WIDE TRANSLATIONAL CONTROL IN FISSION YEAST

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Declaration

I hereby declare that my dissertation contains material that has not been submitted for a degree or diploma or any other qualification at any other university. This thesis describes my own work and does not include the work that has been done in collaboration, except when specifically indicated in the text.

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Abstract

Studies on the regulation of gene expression most often focus on measuring steady-state mRNA levels, especially when using genome-wide approaches. Recently, however, it has become increasingly evident that the expression of genes is frequently also regulated at post-transcriptional levels. I therefore studied both global and mRNA-specific translational regulation and its coordination with other levels of gene expression control in the fission yeast *Schizosaccharomyces pombe*.

To obtain translational profiles for all mRNAs, polysome preparations were separated according to their size using a sucrose gradient, and the mRNAs in each fraction, or pools of fractions, were identified and quantified with DNA microarrays (translational profiling). Starting with exponentially growing cells, I analyzed 12 polysome fractions using DNA microarrays containing elements for all known and predicted genes of fission yeast. This approach provided data for the average number of associated ribosomes for most transcripts. These data were then integrated with other genome-wide data sets such as mRNA steady-state levels, polyadenylation profiles, start-codon sequence context, mRNA half-lives, and RNA polymerase II occupancy. Widespread and unexpected relationships between distinct levels of gene expression were uncovered. Translation and polyadenylation are aligned on a global scale with both the lengths and levels of mRNAs: short and abundant mRNAs have longer poly(A) tails and are more efficiently translated. Transcription and mRNA stability independently contribute to the alignment of mRNA abundance with translation.

Using these data sets a basis, I then used translational profiling to assess the extent of translational regulation in cells in respose to genetic and environmental perturbations. First, translational profiling was used in cells deleted for protein methyltransferase 3 (*rmt3*), and many mRNAs encoding proteins of the small ribosomal subunit were identified to be translationally up-regulated. Furthermore, translation profiling was used in cells exposed to various cellular stresses including heat shock and oxidative stress. Many genes that showed changes in total mRNA levels in these conditions were also regulated translationally. Furthermore, a few genes showed regulation only at the translational level and are good candidates for specific translational regulation. These data provide a comprehensive overview of translational control in fission yeast relative to other aspects of gene expression regulation.

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