A Network of Multiple Regulatory Layers Shapes Gene Expression in Fission Yeast http://www.sanger.ac.uk/PostGenomics/S_pombe Jürg Bähler Wellcome Trust Sanger Institute /Cancer Research UK

Regulation of Gene Expression at Multiple Levels



Global data on different layers of gene expression control



Microarray-based approaches to measure control at multiple levels

Translational Profiling:

Determine ribosome numbers associated with transcripts





Example profiles: Control genes peak in expected fractions



Global translational properties of mRNAs



Ribosome number shows little increase relative to length



Genes ranked by ORF length

Short mRNAs are more efficiently translated



Similar effect described in S. cerevisiae: Arava et al., PNAS 2003

Are short proteins more abundant?

Inverse correlation between protein level and ORF length

ORFeome data: 2.5_T **Ribosome density** Matsuyama et al., *r* = 0.31; *P* < 2.2e-16 Nat. Biotech. 2006 2.0 Ribosome density (rb/kb) ORF length (kb) .5 3 1.0 **ORF** length r = -0.26; P <2.2e-16 0.5-0 0 10'00 2000 30'00 Genes ranked by protein level

Addition of poly(A) tails to mRNA 3'-end has been implicated in translational control

5' mRNA 3'AAAAAAAAAAA

Is polyadenylation reflected in translational efficiency on a global scale?

Determination of global mRNA polyA tail lengths (Collaboration with Preiss lab, Sydney)

1. Fractionation of mRNAs 2. Hybridize fractions to by poly(A) tail length microarray 25 30 35 45 60 MA poly(U) sepharose 10 70 2°C 25°C 30°C 35°C 45°C 45' -60 -50 -40 OR -30 -20 thermal elution 25°C 30°C 35°C 45°C 50°C OR

-10

mRNAs with long poly(A) tails are more efficiently translated



Shorter mRNAs tend to have longer poly(A) tails

mRNAs with long poly(A) tails tend to be more abundant



Abundant mRNAs are associated with more ribosomes



Coordination of mRNA levels with global translational efficiency?!

Abundant mRNAs are more efficiently translated



Translation and polyadenylation aligned on a global scale with both the lengths and levels of mRNAs:

Efficiently translated mRNAs tend to have longer poly(A) tails and tend to be shorter and more abundant (more efficiently transcribed and more stable)

Lackner et al., 2007, Mol Cell, in press

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These relationships seem to be conserved (unpublished data Preiss lab)

Conclusions

Substantial coordination between different regulatory layers to streamline protein production

Multiple genome-wide data-sets from standardized condition in simple model organism: framework for systems-level understanding of multi-layered gene expression programs

Global data on different layers of gene expression control



Microarray-based approaches to measure control at multiple levels

- Integrate data from different levels of regulation
- Dynamic changes in regulation, genetic and environmental perturbations







Daniel Lackner Samuel Marguerat Falk Schubert Stephen Watt Juan Mata Chris Penkett Val Wood Sofia Aligianni Tannia Gracia Luis López-Maury Brian Wilhelm

Victor Chang Cardiac Research Institute, Sydney, Australia

Thomas Preiss Traude Beilharz

Apologies for lack of equations!



Schizosaccharomyces pombe (Fission Yeast)



- unicellular eukaryote (fungus)
- genome: ~5,000 genes
- easy to handle / genetics
- evolutionary distant to S. cerevisiae
- simple model system
- no beauty but what a beast!

Effects of mRNA length on ribosome number





Use <u>**ribosome density</u>** rather than absolute ribosome number as measure for translational efficiency</u>

Determination of global mRNA half-lives



Samuel Marguerat



Stable mRNAs are more efficiently translated

+



Genome-wide estimates of transcriptional efficiency: ChIP-chip with RNA polymerase II



ChIP-chip with RNA polymerase II



Transcriptional efficiency and mRNA stability are not correlated









Long half-lives

Highly transcribed mRNAs are more efficiently translated



Transcription and mRNA stability independently contribute to the alignment of mRNA abundance with translational efficiency

Transcription is not directly linked to poly(A) tail length



Transient population of long tailed mRNAs upon induction of transcription

The sequence context around the start codon and translational efficiency





Stable mRNAs tend to be associated with more ribosomes



Polysome fractions

ORF length as main determinant of translational efficiency: Genes encoding ribosomal proteins

