Cellular energy metabolism regulates mRNA translation and degradation in a codon-specific manner

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Overview

Motivation
- Codon usage is a major determinant of mRNA translation and degradation rates⁵,²,³
- Effects of codon usage are tissue-specific⁴,⁵,⁶, but their mechanisms, scale and regulatory impact remain poorly understood

Results
- mRNA stability depends less on codon usage in high energy metabolism tissues, but more under oxygen deprivation and with age
- Biochemical modelling predicts higher cellular ATP & GTP pool attenuates codon decoding rate differences
- This model is experimentally validated in yeast by blocking ATP synthesis

Implications
- We show a codon-dependent regulatory mechanism independent of tRNA regulation, which modulates the gap between slow and fast codons
- Our work uncovers a fundamental mechanistic link between cellular energy metabolism and eukaryotic gene expression which can contribute to shaping cell-type-specific phenotypes

1. Exonic and Intronic RNA coverage allows estimation of mRNA half-life

- mRNA half-life can be approximated by the ratio between exonic and intronic expression obtained from RNA-seq⁷
- The GTEx⁸ and Tabula Muris⁹ datasets allow us to estimate mRNA half-life in multiple tissues (human and mouse) and individuals (human)

2. Relationship between codon usage and mRNA half-life is tissue-specific

- The fold change between tissue specific exonic/intronic expression and the global mean (relative mRNA half-life) reveals tissue-dependent mRNA half-life⁴
- We observe that codon frequencies are correlated with tissue-specific mRNA half-life changes

3. Stability to decoding rate dependency factor (SDF)

- SDF is computed per tissue by estimating the slope between relative mRNA half-life and the average reference decoding rate of the mRNA in the HEK293T cell line¹⁰
- In Skin SDF indicates that an increase of 1 codon in the average reference decoding rate of an mRNA is predicted to change its half-life by 50% when compared to the average tissue, and by 2.2 times when compared to Brain.

4. Mitochondrial pathways, age and ischemic time estimate with SDF

- Expression of respiratory pathways strongly associate with differences in SDF across tissues both in human and mouse (GSEA)
- SDF increases with age, indicating higher differences between the effects of slow and fast codons on mRNA half-life as individuals get older
- Nature did the experiment: Longer ischemic times, which reduce the flow of O₂ to cells, positively associate with SDF

5. Biochemical model predicts higher ATP&GTP attenuates loading speed differences

- Not only mRNAs but also ATP and GTP concentrations determine decoding rates
- Translation is one of the most energy demanding process in the cell

6. Differences in decoding of fast and slow codons depend on intracellular ATP concentration

- To investigate the effect of cellular energy metabolism on codon decoding we performed SP-seq on 5P-seq for slow and fast codons on mRNA half-life with differences in SDF across tissues both in human and mouse (GSEA)
- XRNR1 follows the last translating ribosome, generating a footprint of its position, obtained by sequencing the ends of 5P mRNA fragments (SP-seq)
- SP-Seq allows for the monitoring of codon-specific ribosome A-site dwelling occupations
- The difference between the ribosome A-site dwelling occupancy of faster and slower codons is decreased for higher ATP concentration

7. Codon usage of cassette exons relates to its predicted tissue-specific impact

- In some tissues, the usage of faster codons in cassette exons is preferred
- Exons using slower codons are generally included in tissues with higher energy metabolism, while excluded in lower energy metabolism, where slow codons are postulated to be more expensive to use.

References

⁵Buschauer et al (2020). The Ccr4-Not complex monitors the translating ribosome for codon optimality.
¹⁰Tabula Muris: Pseudo-bulk processing of sc-RNA-seq for 45 cell types