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

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Overview

Motivation

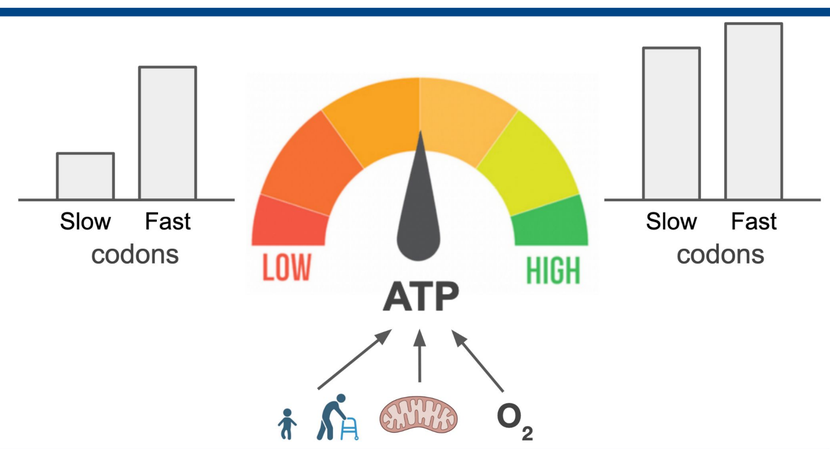
- Codon usage is a major determinant of mRNA translation and degradation rates[1,2,3]
- Effects of codon usage are tissue-specific[4,5,6], but their mechanisms, scale and regulatory impact remain poorly understood

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

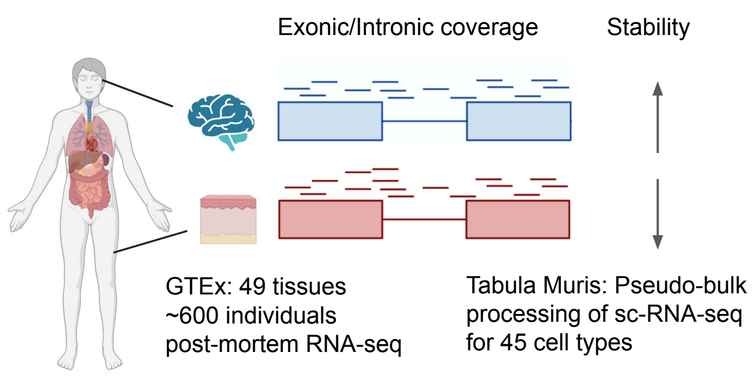
Implications

- 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-seq[6]
- The GTEx[7] and Tabula Muris[8] datasets allow us to estimate mRNA half-life in multiple tissues (human and mouse) and individuals (human)

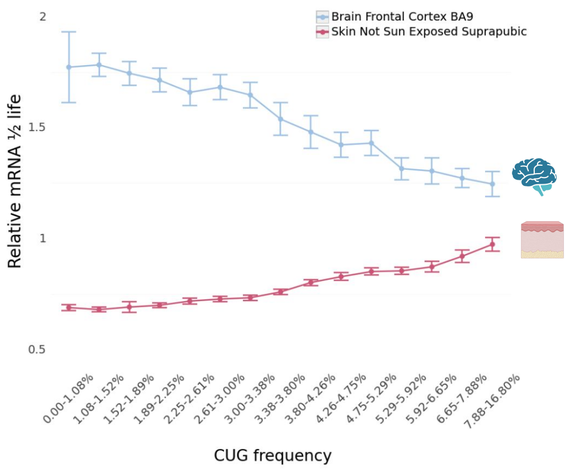


GTEx: 49 tissues
~600 individuals
post-mortem RNA-seq

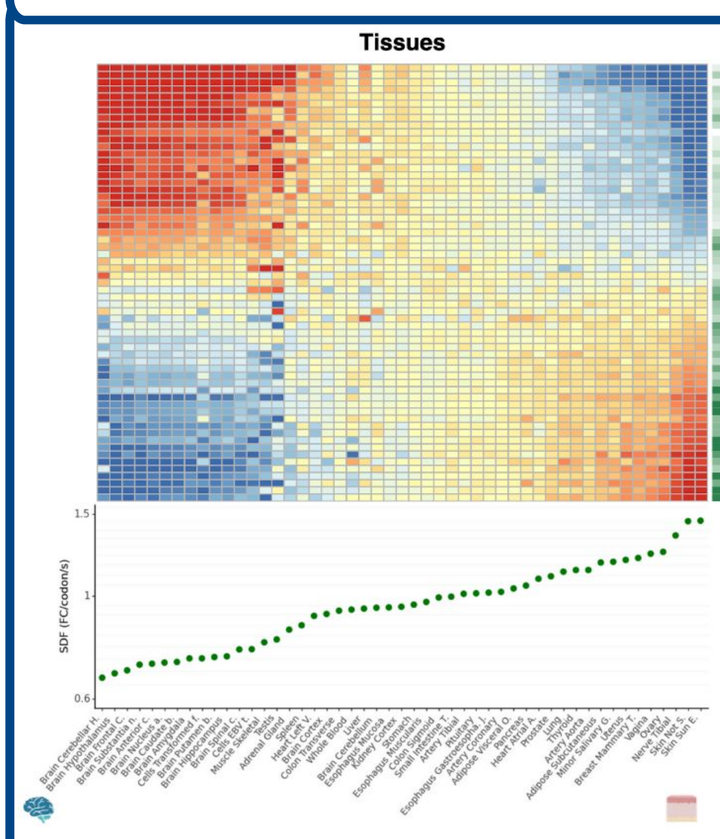
Tabula Muris: Pseudo-bulk processing of sc-RNA-seq for 45 cell types

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

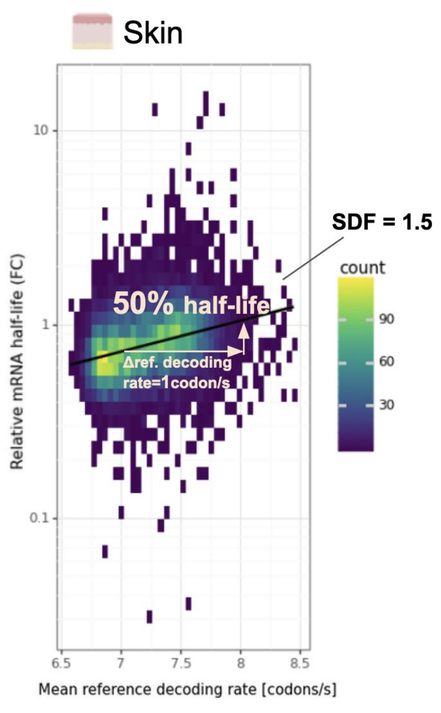
- The fold change between tissue specific exonic/intronic expression and the global mean (relative mRNA half-life) reveals tissue-dependent mRNA half-life[9]
- We observe that codon frequencies are correlated with tissue-specific mRNA half-life changes



3. Stability to decoding rate dependency factor (SDF)

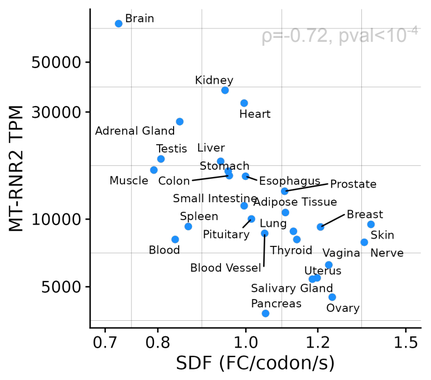


- Stability to decoding rate dependency factor (SDF) allows investigating the relationship between the decoding of an mRNA and its tissue-specific relative half-life

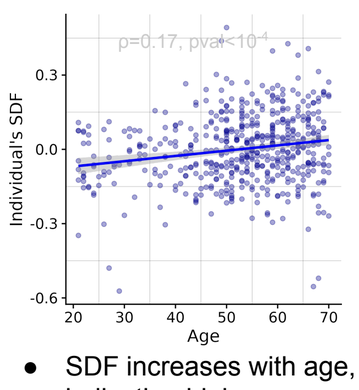


- SDF is computed per tissue by estimating the slope between relative mRNA half-life and the average reference decoding rate of the mRNA in the HEK293 cell line[10]
- In Skin SDF indicates that an increase of 1 codon/s in the average reference decoding rate of an mRNA is predicted to change its half-life by 50% when compared to the average tissue, and by 2.2 times when compared to Brain.

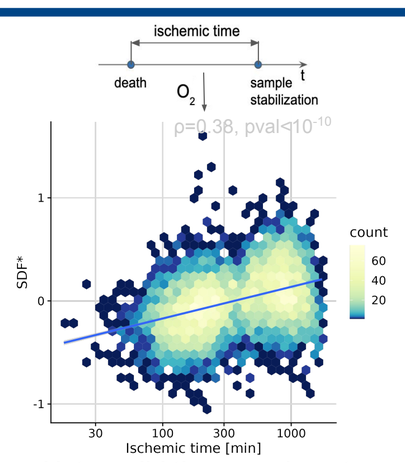
4. Mitochondrial pathways, age and ischemic time associate with SDF



- 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

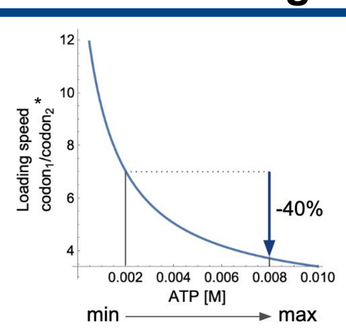


- *Nature did the experiment:* Longer Ischemic times, which reduce the flow of O_2 to cells, positively associate with SDF

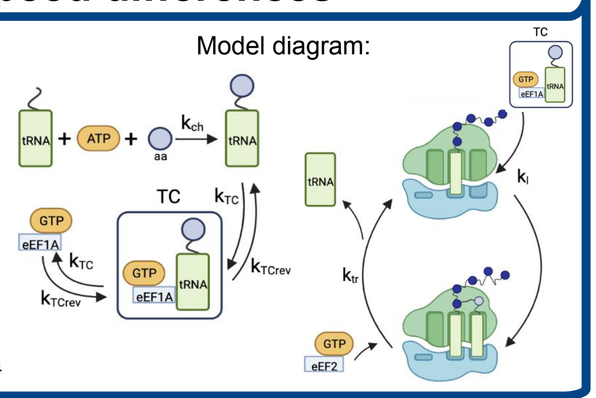
5. Biochemical model predicts higher ATP&GTP attenuates loading speed differences

- Not only tRNAs but also ATP and GTP concentrations determine decoding rates

Translation is one of the most energy demanding process in the cell

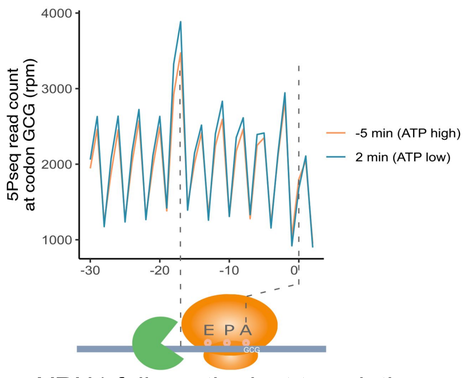


* codon 1 (fast) - ratio of tRNA:ribosome = 4:1
codon 2 (slow) - ratio of tRNA:ribosome = 1:4

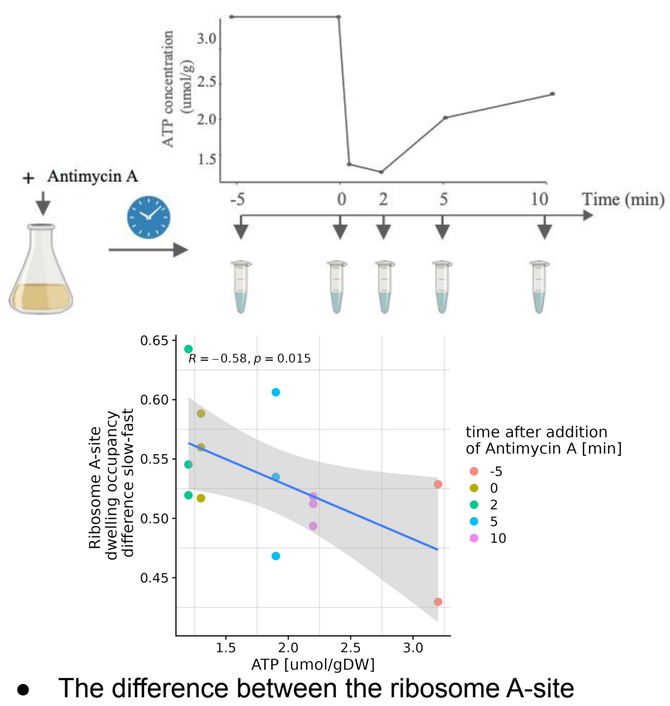


6. Differences in decoding of fast and slow codons depend on intracellular ATP concentration

- To investigate the effect of cellular energy metabolism on codon decoding we performed 5P-seq[11] on trehalose-grown yeast before and after the addition of the respiration inhibiting drug antimycin A [12]



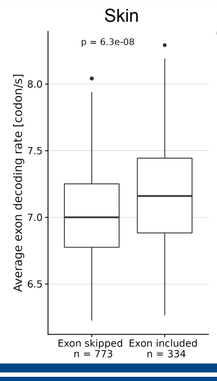
- XRN1 follows the last translating ribosome, generating a footprint of its position, obtained by sequencing the ends of 5'P mRNA fragments (5P-seq)
- 5P-Seq allows for the modelling of codon-specific ribosome A-site dwelling occupancies



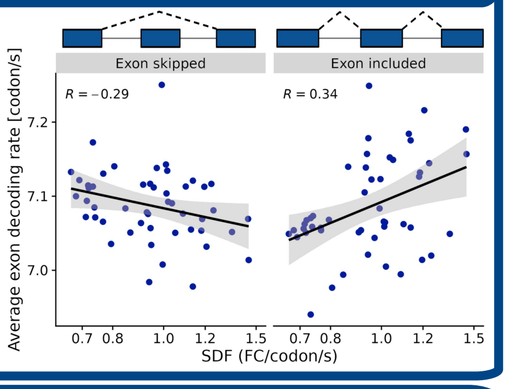
- The difference between the ribosome A-site dwelling occupancy of faster and slower codons is decreased for higher ATP concentration

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.



7. References

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