Nature Reviews Molecular Cell Biology | Published online 28 Sep 2016; doi:10.1038/nrm.2016.136

RNA DECAY

Dhh1p condemns mRNAs with non-optimal codons to decay

> high density of slowly progressing (or stalled) ribosomes stimulates mRNA decay through Dhh1p

The stability of mRNAs is tightly linked to translation efficiency, but the mechanisms that link the two are poorly understood. The rate of translation elongation is affected by the availability of tRNA, and mRNAs that are enriched in optimal codons (triplets decoded by abundant tRNA species) are highly translated. Furthermore, it has been recently shown that stable mRNAs are enriched in optimal codons, whereas unstable mRNAs are enriched in non-optimal codons. Now, Coller, Green and colleagues tie these observations together by finding that, in budding yeast, the DEAD-box protein Dhh1p (also known as DDX6) binds to ribosomes and mediates the decay of inefficiently translated, low-codon optimality mRNAs.

GETTY

The authors created 11 gene constructs that encode an identical polypeptide but are composed of mixtures of synonymous codons that differ in codon optimality, and confirmed that the higher the number of non-optimal codons, the less stable the reporter transcripts are. They went on to investigate the role of the mRNA-decapping and translation inhibition factor Dhh1p in linking codon optimality with mRNA decay. The stability of two transcripts consisting of either only optimal codons (the OPT transcript) or synonymous non-optimal codons (NON-OPT) was examined. Whereas the NON-OPT mRNA was less stable than the OPT mRNA in wild-type cells, its stability was increased in *DHH1*-null cells (but not in cells lacking other mRNA decay genes), becoming as stable as the OPT mRNA. Moreover, analysis of the 11 constructs described above and globally of endogenous genes revealed that loss of *DHH1* increased the abundance of mostly low-codon optimality mRNAs.

Affinity pull-down experiments on the NON-OPT and OPT transcripts and analysis of published transcriptome-wide crosslinking immunoprecipitation data indicated that Dhh1p preferentially binds to low-codon optimality mRNAs. To test whether Dhh1p is associated with such mRNAs owing to a high density of slowly progressing ribosomes, a stretch of non-optimal codons, which is predicted to substantially slow ribosomes and increase their number on transcripts, was introduced into the highly optimal *PGK1* gene at increasing distances from the start codon. In wild-type, but not in *DHH1*-null, cells, the least stable *PGK1* mRNAs were those with the non-optimal stretch that was the farthest from the start site. These transcripts were predicted to accumulate the highest number of translating ribosomes, suggesting that the high density of slowly progressing (or stalled) ribosomes stimulates mRNA decay through Dhh1p.

Finally, Dhh1p was found to directly bind to ribosomes, and ribosome profiling revealed that overexpression of Dhh1p (but not of catalytically inactive Dhh1p) enriched the density of ribosomes on low-codon optimality mRNAs. Furthermore, tethering Dhh1p, but not catalytically inactive Dhh1p, to the OPT and NON-OPT mRNAs increased ribosome occupancy on the NON-OPT mRNA relative to the OPT mRNA. These results indicate that the observed differential ribosome occupancy between low- and high-codon optimality mRNAs depends not only on codon composition but also on the catalytic activity of Dhh1p.

Based on these results, the authors propose that Dhh1p is a sensor of ribosome progression and that its association with slowly translating ribosomes activates mRNA degradation.

Eytan Zlotorynski

ORIGINAL ARTICLE Radhakrishnan, A. *et al.* The DEAD-box protein Dhh1p couples mRNA decay and translation by monitoring codon optimality. *Cell* http://dx.doi.org/10.1016/j.cell.2016.08.053 (2016)

FURTHER READING Lykke-Andersen, S. & Jensen, T. H. Nonsense-mediated mRNA decay: an intricate machinery that shapes transcriptomes. *Nat. Rev. Mol. Cell Biol.* **16**, 665–677 (2015)