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RESEARCH HIGHLIGHT

Codon optimality and mRNA decay

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Recent evidence indicates that codon optimality is a broad determinant of mRNA stability. A study by Radhakrishnan *et al*. in *Cell* raises the possibility that the conserved DEAD-box protein Dhh1 underlies the phenomenon.

mRNA decay is a critical step in the gene expression process, and the decay rates of individual mRNAs can vary over two orders of magnitude. In eukaryotes, bulk mRNA decay is initiated by deadenylation [1], which allows decapping and 5′ to 3′ degradation but can also lead to 3′ to 5′ degradation [1].

Decay rates are inversely related to translation initiation rates, and perturbations that decrease translation initiation enhance both deadenylation and decapping rates. Moreover, specific sequence motifs that are recognized by *trans*-acting factors, such as microRNAs and RNA-binding proteins, often modulate mRNA stability by controlling translation initiation. This inverse relationship between translation initiation and degradation can be rationalized as the cap and poly(A) tail either being in a translationally competent mRNP or in an alternative nuclease accessible complex.

Studies in organisms from *E. coli* to zebrafish now demonstrate that the "optimality" of an mRNA's codons modulates its stability [2-5]. The general theme is that "optimal" codons, which are recognized by abundant tRNAs and efficiently translated, are correlated with mRNA stability, whereas "non-optimal" codons, which are recognized by less abundant tRNAs, are correlated with mRNA instability. These correlations show causality since substitutions of optimal codons in endogenous stable mRNAs with synonymous, non-optimal codons result in faster mRNA decay, whereas replacing non-optimal codons with optimal codons stabilizes unstable mRNAs [3, 5]. Since codon identity affects translation elongation speed, at least in part, via the process of cognate tRNA recognition [6], this argues that the speed of translation elongation somehow affects mRNA stability.

Several observations in *S. cerevisiae* are consistent with slower translation elongation rates decreasing translation initiation, which is coupled to increased mRNA degradation [7]. First, optimal and non-optimal versions of the *HIS3* mRNA show the same distribution on polysome gradients, which can be explained if slower elongation is coupled to reduced initiation rates [5]. Second, the amount of protein production per mRNA can be decreased up to 20-fold by converting optimal to non-optimal codons, which is more than the average difference in elongation rates between optimal and non-optimal codons (~2.5×) [8]. This difference could be explained by either an additional decrease in translation initiation, drop-off of elongating ribosomes, or changes in protein stability based on elongation rate. Third, when translation initiation is made inefficient, there is no difference in expression of mRNAs with optimal and non-optimal codons [9]. Finally, similar to decreased translation initiation, non-optimal codons increase the rate of both deadenylation and decapping.

One model to explain the coupling of elongation and degradation rates is that at any elongation step there is a competing event promoting mRNA degradation [7] (Figure 1A). However, pauses, albeit shorter, at optimal codons could also be recognized. Thus, this model predicts that, as mRNA length increases, mRNA half-life decreases even with all optimal codons. Although there are limited examples, mRNA half-life increases with length for engineered mRNAs made of optimal codons (Figure 1A, bottom) [5]. Thus, for this kinetic model to be viable, either the "decay" recognition events need to be somehow synergistic, or recognize a unique property of non-optimal codons, perhaps a non-cognate tRNA in the A-site.

An alternative model is that the timing of elongation is directly coupled to translation initiation rates. For example, as seen previously, efficient translation elongation at the 5′ end of the ORF can lead to increased initiation by faster clearance of ribosomes from the vicinity of the AUG (Figure 1B) [9]. Alternatively, efficient elongation could lead to faster translation initiation due to effects on mRNP organization (Figure 1C). In one example, since translation initiation is more efficient when the 5′ and 3′ ends of the mRNP interact, if a ribosome terminates before this interaction is lost, it may reinitiate translation efficiently (Figure 1C). If the 5′ and 3′ interaction is lost before the next initiation event, the next initiation event might either wait for reforming of the 5′ and 3′ interaction and/or be less efficient.

Importantly, a new study by Radhakrishnan *et al*. provides evidence suggesting the RNA-dependent ATPase Dhh1 links slow ribosome movement and mRNA instability in *S. cerevisiae* [7]. First, in a *dhh1Δ* strain, synonymous

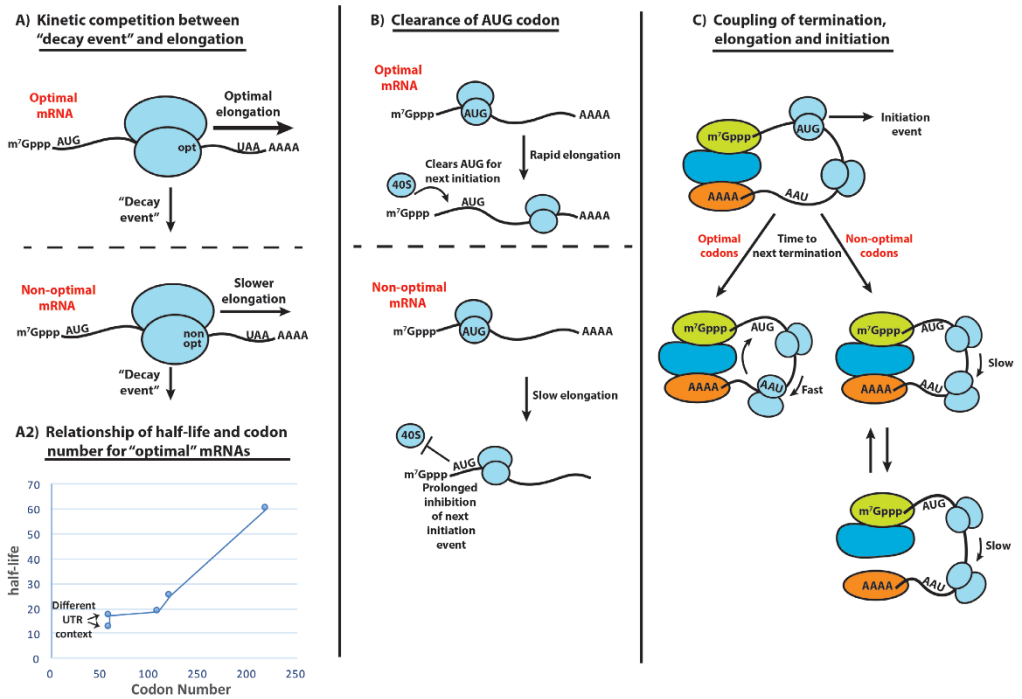

Figure 1 Possible models for elongation speed affecting mRNA function. **(A)** Kinetic competition between translation elongation and mRNA decay may underlie the codon-mediated decay. Half-lives of engineered transcripts are plotted against the number of optimal codons (Bottom). **(B)** Non-optimal codons may interfere with translation initiation, which may lead to mRNA instability. **(C)** Coupling of translation termination, elongation, and initiation may affect the mRNP structure and thereby mRNA stability.

reporter transcripts with high and low content of optimal codons decay in similar kinetics whereas, in a wild-type strain, the non-optimal transcript decays substantially faster than the optimal transcript. Second, Dhh1 is co-pulled down more efficiently with a non-optimal reporter transcript than with a synonymous, optimal counterpart.

Reporter-based analyses imply that Dhh1 may function to slow down ribosome movement; a yeast transcript with synonymous substitutions to non-optimal codons is associated with a greater number of ribosomes when tethered to Dhh1 than when tethered to a catalytically inactive Dhh1, which is interpreted that Dhh1 slows translation elongation on non-optimal codons depending on its catalytic activity. Consistent with this view, overexpression of Dhh1 leads to an increase of ribosome footprints on non-optimal mRNAs and a corresponding decrease on mRNAs with optimal codons.

Future goals will require understanding the molecular links between non-optimal codons and mRNA degradation, including determining Dhh1 function using *in vitro* translation systems. This is an important issue since Dhh1 and it orthologs are involved in mRNA decapping, miRNA-mediated translation repression and mRNA degradation, and storage of mRNAs in embryos and neurons. Moreover, while Dhh1 and its orthologs repress translation *in vitro*, they appeared to affect initiation, perhaps by interacting with the ribosome, which could also alter elongation in other contexts [7]. Alternatively, in yeast, non-optimal codons could be sensed by the ribosome-binding protein, Stm1, which is known to stall elongation and enhance Dhh1 function [10], and then Stm1 could recruit Dhh1 to repress initiation, although no clear Stm1 orthologs are known in other species. Thus an understanding of these molecular mechanisms may reveal new aspects of how cells coordinate mRNA function to elongation rates, which, fittingly, time will tell.

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