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A universal code for mRNA stability?

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Abstract

Precise elimination of maternal mRNAs plays a critical role during maternal-to-zygotic transition (MZT) to promote developmental processing. Two new studies demonstrate that, in eukaryotes, codon-mediated decay is a conserved mechanism to shape maternal mRNA stability by affecting deadenylation rate through a translation-dependent manner. These two new studies add to a growing body of literature that suggest that translational elongation rates are a major determinant of mRNA stability.

Keywords

maternal-to-zygotic transition (MZT); codon optimality; mRNA decay; deadenylation; translation

Messenger RNA (mRNA) degradation plays a critical role in regulating transcript levels in the cell and is a major control point for modulating gene expression. A major pathway of mRNA degradation is initiated by removal of the 3' poly(A) tail (deadenylation), followed by cleavage of the 5' 7^mGpppN cap (decapping), and exonucleolytic degradation of the mRNA body in the 5'-3' direction. Despite being targeted by a common degradation pathway, turnover rates for individual mRNAs differ dramatically - with half-lives ranging from minutes to hours. RNA features that influence transcript stability have long been sought, and a number of sequence and/or structural elements localized often to 5' and 3' untranslated regions (UTRs) have been implicated in contributing to the turnover rate of a subset of individual mRNAs. These features, however, regulate mRNA stability predominantly in a transcript-specific manner (through binding of regulatory factors) and are unable to account for the wide variation in half-lives observed across the entire transcriptome. Additional mRNA features, therefore, must exist to modulate mRNA decay rates and contribute to the vast range of mRNA stabilities observed in cells.

During early development, differential mRNA stability plays a critical role in the regulation of gene expression. In the earliest stages of embryonic development, *de novo* transcription is silenced and the maternally-deposited mRNAs and proteins drive developmental processes post-transcriptionally - thus controlling transcript stability is paramount for regulated gene events. Dramatic remodeling of gene expression is conducted by activating the transcription

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of the zygotic genome and removing maternal transcripts; a phase characterized as the maternal-to-zygotic transition (MZT). The mechanism for selective destabilization of maternal mRNAs during the MZT is unclear.

Maternal mRNA decay can occur either dependent or independent of zygotic transcription during the MZT. Transcripts that decay independent of zygotic transcription are referred to as undergoing “maternal mode decay”, while mRNAs whose decay depends on the induction of zygotic transcription are referred to as subject to “zygotic mode decay” [1]. Both modes of decay are hallmarked by the selective use of 3'UTR nucleotide elements and corresponding binding partners that tether components of the mRNA degradation machinery. For instance, the zygotic mode of decay involves the recruitment of destabilizing micro-RNAs (miRNAs) or PUF-proteins to specific maternal transcripts bearing the appropriate 3'UTR element. Likewise, the maternal mode of decay involves recruitment of the destabilizing factors such as SMAUG or ARE-binding proteins to mRNA containing these binding sites within the 3'UTR [2, 3]. Despite the well-recognized role of *cis*-element regulation, a large proportion of maternal mRNAs are eliminated by unknown determinants. The question has remained, therefore, to determine if there are general properties of maternal mRNAs that control stability during the MZT?

It has long been appreciated that in dividing cells, mRNA turnover is tightly coupled to the translation status of the message. Specifically, mRNA that is efficiently translated is more stable than mRNA that is translated poorly. Until recently, a mechanistic understanding of this relationship was, however, lacking. Recent work in yeast discovered that the identity of codons within an mRNA open-reading frame (ORF) is a critical determinant of mRNA half-life [4]. The genetic code, which uses 61 triplet codons to encode 20 amino acids, is by-and-large universal across all species. The inherent degeneracy of the genetic code leads to the possibility that synonymous codons are recognized at distinct rates by the ribosome in response to differences in tRNA availability, decoding fidelity, and varying propensities for the local RNA to form secondary structure. Specific examples of codon composition inhibiting translation elongation rate and the efficiency of nascent peptide folding, stability and/or activity have been described. Codon optimality represents a scale of translational efficiency. Theoretically, optimal codons have a higher tRNA availability, so they can be decoded faster than non-optimal codons. Recent studies show that codon optimality connects translation elongation rate and mRNA degradation in yeast [4] and bacteria [5]. Transcripts of high codon optimality are more stable compared to those of lower codon optimality.

Two independent studies recently showed that codon composition also plays a major role in destabilizing maternal mRNA during the MZT [6, 7]. To discriminate maternal mode and zygotic mode pathways, both groups performed RNA sequencing to determine mRNA half-lives during the MZT of zebrafish embryos after inhibition of zygotic transcription by the RNA polymerase II inhibitor (α -amanitin). Mishima and Tomari compared their mRNA half-life data with codon adaptation index (CAI), a measurement of synonymous codon bias present in highly expressed genes [8]. They found that unstable mRNAs degraded independently of zygotic transcription (i.e. maternal mode) are enriched in non-optimal codons (i.e. codons not represented in highly expressed genes). Bazzini *et al.* observed similar findings using a distinct metric, codon stabilization coefficient (CSC), which is

defined by calculating the Pearson correlation coefficient between mRNA half-life and codon occurrence [4]. They observed that, in both zebrafish and *Xenopus*, mRNAs enriched in optimal codons are more stable compared to those enriched with non-optimal codons (Figure 1A). Importantly, CSC is a metric that is determined by *in vivo* experimental data and authors show the positive correlation of CSC between zebrafish and *Xenopus* indicates the conservation role of codon-mediated decay between species. This is fully consistent with results from budding yeast demonstrating non-optimal codons are a major determinant of mRNA instability. Bazzini *et al.*, further show that tRNA concentrations of optimal codons are more abundant than those of non-optimal codons in zebrafish embryos (Figure 1B). This observation is consistent with the idea that codon optimality reflects the translational efficiency in terms of the balance between supply (tRNA levels) and the demand (codon usage) in cells [9]

Studies in yeast have shown that codon-mediated effects on mRNA decay are through the normal deadenylation-dependent decapping pathway [4]. Consistently, both groups in zebrafish show that maternal mRNAs with lower codon optimality have shorter poly(A) tails and the shortening of poly(A) tails is mediated by the activity of CCR4-NOT complex (Figure 1C).

These two recent reports from Mishima & Tomari and Bazzini *et al.* highlight an emerging theme in mRNA turnover, i.e. that an ancient and conserved mechanism for modulating mRNA stability exists in all organisms. Specifically, findings from *E. coli*, yeast, and now zebrafish clearly show that translational elongation rate is intimately connected to mRNA stability. In addition, Bazzini *et al.* also observed that codon optimality influences mRNA degradation in *Drosophila*, *Xenopus*, and Mice. Thus in diverse species, the rate at which the ribosome decodes is sensed and feeds into mRNA degradation pathways. These findings imply that the speed at which the ribosome decodes, and the stability of individual transcripts is a property of its primary gene sequence. Therefore, the usage of synonymous triplets over others is evolutionary selected for because it dictates mRNA and protein levels. These findings prompt new and interesting views on how the transcriptome might be regulated. For instance, the major driver of codon optimality is functional tRNA concentration. Modulation of tRNA function or concentration, therefore, could powerfully shape the expressed mRNA landscape through mRNA stability. In fact, a recent study demonstrates that tRNA levels in breast cancer lines are remarkably different with respect to non-tumorigenic cell line. During cancer metastasis, upregulation of a subset tRNAs stabilize transcripts enriched with their cognate codons [10]. Thus tRNA expression patterns could be an unappreciated modulator of gene expression in various cell types, cellular stages and diseases and perhaps dynamically controlled to achieve higher order gene expression.

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A

B

C

Figure 1. Proposed model for Codon-mediated maternal mode decay

1. (A) In maternal mode decay, transcripts with non-optimal codons (Red) decay faster than those with optimal codons (Green) during MZT. (B) In zebrafish embryos, optimal codons have higher concentrations of corresponding tRNAs than non-optimal codons. (C) In maternal mode decay, codon optimality impacts mRNA stability in a translation-dependent manner and promotes deadenylation of non-optimal mRNAs by CCR4-NOT complex.