A Massively Parallel Reporter Assay of 3' UTR Sequences Identifies InăVivo Rules for mRNA Degradation

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The stability of mRNAs is regulated by signals within their sequences, but a systematic and predictive understanding of the underlying sequence rules remains elusive. Here we introduce UTR-seq, a combination of massively parallel reporter assays and regression models, to survey the dynamics of tens of thousands of 3' UTR sequences during early zebrafish embryogenesis. UTR-seq revealed two temporal degradation programs: a maternally encoded early-onset program and a late-onset program that accelerated degradation after zygotic genome activation. Three signals regulated early-onset rates: stabilizing poly-U and UUAG sequences and destabilizing GC-rich signals. Three signals explained late-onset degradation: miR-430 seeds, AU-rich sequences, and Pumilio recognition sites. Sequence-based regression models translated 3' UTRs into their unique decay patterns and predicted the inăvivo effect of sequence signals on mRNA stability. Their application led to the successful design of artificial 3' UTRs that conferred specific mRNA dynamics. UTR-seq provides a general strategy to uncover the rules of RNA cis regulation.

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