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GU-Rich RNA: Expanding CUGBP1 Function, Broadening mRNA Turnover

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Abstract

In this issue of *Molecular Cell*, Vlasova et al. (2008) identify the GU-rich element (GRE) as a novel, widespread, degradation-promoting sequence through which the RNA-binding protein CUGBP1 elicits mRNA decay.

Gene expression is vitally regulated through posttranscriptional processes (Keene, 2007). Among them, altered mRNA stability profoundly affects the availability of template transcripts for protein translation. First described by Shaw and Kamen (1986), the AU-rich element (ARE) has been the quintessential mRNA decay sequence. AREs were originally defined by the presence of AUUUA or UUAUUUAUU canonical sequences, and later expanded to include RNA elements lacking the AUUUA pentamer (Chen and Shyu, 1995). AREs are particularly interesting because they appear in the 3′ untranslated regions (UTRs) of many labile mRNAs encoding proteins that regulate processes including tumorigenesis, the immune reaction, differentiation, the cell division cycle, and the stress response. ARE-regulated mRNA turnover is governed through the relative association/dissociation of ARE-binding proteins (ARE-BPs) that either enhance or reduce mRNA half-life, including AU-rich binding factor-1 (AUF1), KH-type splicing regulatory protein (KSRP), tristetraprolin (TTP), Hu proteins, poly(C)-binding protein (αCP), and butyrate response factor-1 (BRF1). The study of ARE-ARE-BP complexes has been extremely helpful in advancing our understanding of the process of mRNA turnover (Wilusz et al., 2001).

Despite the hegemony of AREs as decay elements, an increasing number of examples of 3′UTR decay-promoting sequences lacking AREs have been emerging. For example, labile mRNAs bearing CU-rich, U-rich, poly(C), GC-rich, and CA-rich regions are rendered stable through the action of RBPs including αCP, HuR, HuD, and hnRNP L (e.g., Yang et al., 2003). In this issue of *Molecular Cell*, Bohjanen and coworkers (Vlasova et al., 2008) build on their earlier en masse transcript analysis showing that most labile mRNAs in activated T cells lacked AREs (Raghavan et al., 2004). To test the hypothesis that other decay-signaling sequence(s) existed among these transcripts, they identify computationally a conserved GU-rich element (termed the GRE) in the 3′UTRs of the short-lived mRNA collection. Using heterologous reporter assays, the authors characterize GREs functionally and show that they effect the turnover of labile mRNAs, as the half-life of a stable β-globin transcript

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was dramatically diminished by the insertion of wild-type (but not mutant) GRE-containing sequences from mRNAs encoding c-*jun*, jun B, and the TNF receptor 1B. Through RNA-binding assays, the authors identify the RBP CUG-binding protein 1 (CUGBP1) as the major protein interacting with the GRE. Subsequent examination of the GRE-CUGBP1 interactions by RNA interference revealed that CUGBP1 contributed to GRE-dependent mRNA decay (Vlasova et al., 2008). These discoveries have far-reaching implications in two important areas of ribonucleoprotein (RNP) biology.

First, the functional characterization of the GRE-CUGBP1 complex highlights a novel role for CUGBP1, a ubiquitous RBP that was previously implicated in modulating pre-mRNA splicing, enhancing translation, and triggering mRNA deadenylation (Barreau et al., 2006). In its newly identified capacity as a decay-promoting RBP, CUGBP1 resembles its *Xenopus laevis* homolog, EDEN-BP/CELF, previously shown to promote mRNA degradation. Nonetheless, it remains to be formally studied whether the CUGBP1-triggered mRNA degradation is separable from the CUGBP1-elicited mRNA deadenylation. It will also be important to investigate directly how the various CUGBP1 functions are regulated. Are they influenced by the interaction of CUGBP1 with other RBPs? Are they dictated by the location, e.g., coding region or UTR, of the target mRNA sequence? By its nucleotide composition? Is it modulated through the action of microRNAs? These questions are particularly pressing as CUGBP1 is implicated in myotonic dystrophy 1 (DM1), a disease characterized by muscle degeneration, myotonia, and cardiac conduction abnormalities. Linking CUGBP1 function and DM1 is the observation that expanding CUG triplets in the 3′UTR of DM protein kinase (DMPK) upregulates CUGBP1 protein stability, at least partly through PKC-mediated phosphorylation (Kuyumcu-Martinez et al., 2007). In turn, increased CUGBP1 causes muscle pathology by triggering the aberrant splicing of three pre-mRNAs, i.e., those encoding muscle-specific chloride channel (ClC-1), insulin receptor (IR), and cardiac troponin T (cTNT), and by increasing MEF2A and p21 translation (Timchenko et al., 2004). In light of CUGBP1's decay-promoting role, further analysis of the influence of CUGBP1 on the stability of GRE-bearing mRNAs encoding muscle proteins is warranted.

Second, the discovery of mRNA decay resulting from GRE-CUGBP1 interactions is particularly exciting given the widespread existence of GREs among mammalian mRNAs. As with the ARE, it will be important to know whether the consensus UGUUUGUUUGU sequence is flexible, to find out which other RBPs associate with GREs, what their influence is on mRNA stability, and whether the net association of RBPs with GREs ultimately determines the half-life of the mRNA and/or its translation. Within the framework of the study, it will also be interesting to investigate whether T cell activation affects the interaction of CUGBP1 and GRE-containing mRNAs: do RNP complexes increase, decrease, or change subcellular location? Broader questions center on the elucidation of the degradation machineries responsible for the breakdown of GRE-containing mRNAs: Are the exosome, the proteasome, or processing bodies implicated or is there a specialized GRE-mRNA-degrading apparatus? Is CUGBP1-triggered deadenylation required for the decay of GRE-containing mRNAs?

As examples accumulate of both ARE-bearing stable mRNAs and labile mRNAs lacking AREs, the ARE dogma has incrementally given way to alternative bona fide instability

sequences. In this context, the novel GRE degradation motif identified by Vlasova et al. (2008) provides the fast-advancing field of accelerated mRNA decay with broader insight into the nature of turnover determinants. With an increasing understanding of mRNA regulatory elements and the mRNA-binding factors (RBPs, microRNAs) that interact with them, the 3′UTR emerges as an ever richer platform from which to govern gene expression.

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REFERENCES

Barreau C, Paillard L, Méreau A, and Osborne HB (2006). Biochimie 88, 515–525. [PubMed: 16480813]

Chen C-Y, and Shyu A-B (1995). Trends Biochem. Sci 20, 465–470. [PubMed: 8578590]

Keene JD (2007). Nat. Rev. Genet 8, 533–543. [PubMed: 17572691]

Kuyumcu-Martinez NM, Wang GS, and Cooper TA (2007). Mol. Cell 28, 68–78. [PubMed: 17936705]

Raghavan A, Dhalla M, Bakheet T, Ogilvie RL, Vlasova IA, Khabar KS, Williams BR, and Bohjanen PR (2004). Genomics 84, 1002–1013. [PubMed: 15533717]

Shaw G, and Kamen R (1986). Cell 46, 659–667. [PubMed: 3488815]

Timchenko NA, Patel R, Iakova P, Cai ZJ, Quan L, and Timchenko LT (2004). J. Biol. Chem 279, 13129–13139. [PubMed: 14722059]

Vlasova IA, Tahoe NM, Fan D, Larsson O, Rattenbacher B, SternJohn JR, Vasdewani J, Karypis G, Reilly CS, Bitterman PB, and Bohjanen PR (2008). Mol. Cell 29, this issue, 263–270. [PubMed: 18243120]

Wilusz CJ, Wormington M, and Peltz SW (2001). Nat. Rev. Mol. Cell Biol 2, 237–246. [PubMed: 11283721]

Yang E, van Nimwegen E, Zavolan M, Rajewsky N, Schroeder M, Magnasco M, and Darnell JE Jr. (2003). Genome Res. 13, 1863–1872. [PubMed: 12902380]