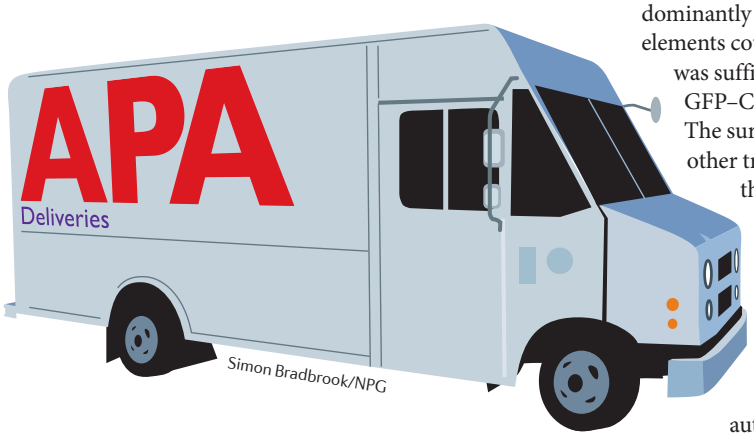
Nature Reviews Molecular Cell Biology | AOP, published online 8 May 2015; doi:10.1038/nrm3996

RNA

3′ UTR alternatives to protein localization

> “the long 3′ UTR isoform was found to promote cell-surface localization of proteins”



Alternative polyadenylation (APA) generates mRNA isoforms with 3′ untranslated regions (UTRs) of different lengths; longer 3′ UTRs contain regulatory elements that affect mRNA localization and mRNA and protein abundance. Berkovits and Mayr now show that APA can also regulate protein localization, independent of mRNA localization.

The authors examined the cellular localization of the cell-surface protein CD47 in human cell lines, the mRNA of which has two 3′ UTR isoforms. Depletion of the long 3′ UTR isoform reduced CD47 protein levels specifically at the cell surface. Indeed, the long 3′ UTR isoform was found to promote cell-surface localization of proteins, as a GFP–CD47 fusion protein encoded by the long 3′ UTR (with a mutated proximal polyadenylation signal; *gfp–CD47*–LU) was predominantly localized to the plasma membrane, whereas a fusion protein encoded by the short 3′ UTR (*gfp–CD47*–SU) was localized mostly at the endoplasmic reticulum (ER), even though the two mRNA isoforms had a similar cellular localization. The authors termed this phenomenon 3′ UTR-dependent protein localization (UDPL).

The long 3′ UTR contains many putative binding elements for the RNA-binding protein (RBP) HUR (also known as ELAV1). HUR depletion did not alter CD47 mRNA isoform and protein abundance, but it did reduce the cell-surface expression of CD47. Furthermore, an artificial 3′ UTR composed predominantly of putative HUR-binding elements could bind to HUR and was sufficient to mediate some GFP–CD47 surface localization. The surface localization of four other transmembrane proteins, the mRNAs of which can be bound by HUR, was also found to decrease following HUR depletion; total protein levels remained constant. Three of these proteins undergo APA, and the authors showed that their longer 3′ UTRs increased protein surface localization.

To elucidate the mechanism of HUR-mediated UDPL, the authors examined the HUR-interacting protein SET and the GTPase RAC1, which targets SET to the cell membrane. Depletion of SET or RAC1 reduced surface levels of CD47. Importantly, SET associated with the *gfp–CD47*–LU mRNA in a HUR-dependent manner, and tethering HUR or SET to the *gfp–CD47*–SU transcripts redirected the protein from the ER to the plasma membrane. This indicates that long 3′ UTRs function as scaffolds that recruit SET to the site of translation to mediate UDPL. Indeed, endogenous SET interacted with the *gfp–CD47*–LU-encoded protein, but not with that encoded by *gfp–CD47*–SU, and blocking binding of SET to the cytoplasmic domains of CD47 abolished cell-surface GFP expression. *gfp–CD47*–LU-encoded protein surface localization was also dependent on RAC1 activity.

In summary, 3′ UTRs can function as scaffolds that recruit HUR, which interacts with SET to enable it to bind to the cytoplasmic domains of several membrane proteins. As HUR binds to thousands of mRNAs, UDPL could be a widespread process that involves various types of protein (including other RBPs) and, together with APA, it could serve to diversify the functionality of the genome.

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ORIGINAL RESEARCH PAPER Berkovits, B.D. & Mayr, C. Alternative 3′ UTRs act as scaffolds to regulate membrane protein localization. *Nature* http://dx.doi.org/10.1038/nature14321 (2015)