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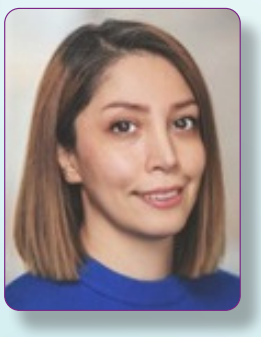

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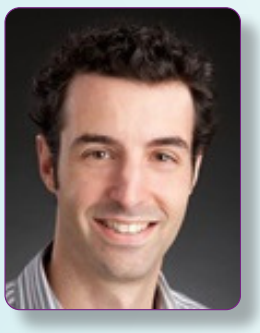

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Cell Reports

High-resolution mapping of CCR4-NOT recruitment elements reveals transcriptome-wide drivers of mRNA decay

Zijun Luo, Aldo Hernandez-Corchado, William R. Brothers, Zahra Aryanpour, Zia Z. Zhao, Justin Zhao, Lindsay Clarke, Connor CampbellSmith, Gene W. Yeo, Hamed S. Najafabadi, and Marc R. Fabian.

Cells tightly control gene expression not only by making mRNA but also by regulating how mRNAs are translated and how quickly they are destroyed. Much of this control happens in the 3' UTR, a region of mRNA that contains short sequences recognized by microRNAs and RNA-binding proteins (RBPs) such as Pumilio, TTP, and Roquin. These factors often trigger mRNA decay by recruiting a major degradation machine called the CCR4-NOT complex.

The CCR4-NOT complex is a central regulator of gene expression, orchestrating mRNA turnover through interactions with RNA-binding proteins (RBPs) and the microRNA (miRNA)-induced silencing complex. However, identifying which RBP- and miRNA-associated RNA elements recruit CCR4-NOT remains challenging, due in part to the multiple modes by which the complex can be recruited.

To address this, we developed TRACER (targeted RNA association with CCR4-NOT and element recovery), a high-throughput method for transcriptome-wide identification of RNA elements that recruit the CCR4-NOT to target RNAs. TRACER analysis in human epithelial cells uncovers thousands of CCR4-NOT-associated elements, including many that map to known and/or predicted RBP and miRNA target sites.

TRACER acts like a multiplexed, high-resolution version of CLIP-seq: It captures interactions from all CCR4-NOT-associated RBPs at once; It uses reversible crosslinking, making library prep simpler; It highlights functional decay-driving elements, not just binding events. The method can help identify regulatory elements involved in disease, guide therapeutic strategies (e.g., antisense oligos that stabilize mRNAs), and map decay programs across different cell types or conditions.

In conclusion, we show that TRACER-identified elements drive mRNA repression and decay, and disrupting elements via gene editing or antisense oligonucleotides can relieve repression, boosting target gene expression. This positions TRACER as a powerful discovery platform for identifying regulatory RNA elements that can be targeted to control gene expression.

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