Alternative Poly(A) Tails Meet miRNA Targeting in *Caenorhabditis elegans*

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In this commentary, Khraiwesh and Salehi-Ashtiani explore the findings of Blazie et al. (2017) published in this issue of GENETICS*, on the interrogation of tissue-specific, alternative polyadenylation and miRNA targeting in Caenorhabditis elegans somatic tissues.*

Although alternative polyadenylation (APA) of messenger RNA is a well-known phenomenon, the biological consequences of APA, especially with respect to tissue-specificity, is not fully understood. In 2010, Mangone *et al.* (2010) reported a genome-scale study mapping polyadenylation in adult and several larval stages of *C. elegans*. The study showed a surprisingly widespread occurrence of APA usage, but did not include cell- or tissue-specific information. To further dissect the intricacies of 3′UTR and APA usage, Blazie *et al.* (2015) developed the PAT-Seq method to study the integration of 3′-UTR usage dynamics with cell- or tissue-specific gene expression in *C. elegans*. PAT-Seq allows the capture of polyadenylated mRNAs, in conjunction with gene expression in specific targeted cells or tissues, and can, therefore, define precise tissue-specific UTR usage within the target cells.

In their present study, Blazie *et al.* (2017) applied the PAT-Seq approach to systematically isolate, sequence, and map 3′UTRs from five highly studied *C. elegans* somatic tissues: GABAergic and NMDA neurons, arcade and intestinal valve cells, seam cells, and hypodermal tissues. The integration of these datasets with previously profiled transcriptomes of the intestine, pharynx, and body muscle tissues (Blazie *et al.* 2015) allowed the investigators to define tissue-specific expression dynamics for 60% of all annotated *C. elegans* protein-coding genes, providing a valuable resource for the worm scientific community. Importantly, the mapping of 15,956 unique, high-quality tissue-specific poly(A) sites in all eight somatic tissues revealed a pervasive tissue-specific 3′UTR isoform switching through APA.

In addition to widespread occurrences of APA, the obtained information suggests that APA may be a significant regulatory mechanism to fine-tune tissue-specific gene expression through post-transcriptional regulatory mechanisms. Almost all ubiquitously transcribed genes interrogated displayed APA, and harbored miRNA targets in their 3′UTRs, which were frequently lost in a tissue-specific manner. The genes expressed with intestine or muscle-specific 3′UTRs were significantly enriched with predicted, and experimentally validated, miRNA targets. These data suggest a crosstalk between APA and miRNA-induced post-transcriptional gene regulation. This interaction may, in turn, play a role in either promoting or maintaining tissue identity. That is, genes commonly transcribed in multiple tissues may use APA to modulate the repression mediated by ubiquitously expressed miRNAs. In support of this hypothesis, Blazie *et al.* (2017) discovered that tissue-specific APA correlated with gain or loss of miRNA target elements, indicating a role for APA in tissue-specific, post-transcriptional gene regulation. Within the studied cases, the *C. elegans* orthologs of human disease-related genes, *rack-1* and *tct-1*, were found to use APA to

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switch to shorter 3′UTR isoforms to evade miRNA regulation in the body muscle tissue, resulting in the appropriate expression level for the muscle function. Altogether, these results highlight a major regulatory role for APA, allowing genes to counteract miRNA regulation (Hobert 2008; Khraiwesh *et al.* 2010) in a tissue-specific manner. Last, an interesting hypothesis proposed by the authors suggests that the 3′end formation is linked to mRNA splicing, such that CDS isoforms expressed through alternative splicing are also expressed with specific 3′UTR isoforms due to APA.

The future application of PAT-Seq to other cell types or tissues of the worm, in conjunction with temporal cellular development, is likely to provide additional insight on the alternative poly(A) usage and its interplay with miRNA regulation. Importantly, similar studies in other organisms can provide additional and comparative information. Transgenic animals, plants, and eukaryotic microbes can be analyzed in a similar manner to capture poly(A) dynamics. Additionally, a parallel *in vitro* PAT-Seq method, developed by Harrison *et al.* (2015), can be used for cases where molecular genetic tools are not available or cannot be used, *e.g.*, for nonmodel organisms of interest. For instance, identification of polyadenylation and APA in biopsied tissues may lead to the identification of disease biomarkers that may be used as diagnostic and therapeutic tools in the future (Curinha *et al.* 2014). Altogether, with future expanded application of PAT-Seq, the dynamics of alternative poly(A) usage, which have been elusive in most cases, will likely become a well-characterized biological process, and its interplay with other cellular processes, or even disorders, far better understood.

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