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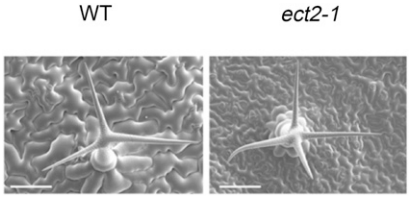
IN BRIEF

A Tale of Three Studies: Uncovering the Crucial Roles of m^{6}A Readers [OPEN]

The story behind m^{6}A (methylation of the *N6* position of adenosine), the most common internal mRNA modification in eukaryotes, has long been a source of intrigue. This epitranscriptomic mark is deposited at specific mRNA sequences by m^{6}A writers and removed by m^{6}A erasers. The m^{6}A marks recruit and anchor m^{6}A binding proteins (readers) that function in processes such as pre-mRNA splicing, mRNA degradation, and translation, thus regulating gene expression. The best-characterized m^{6}A readers, YTH domain proteins, contain a highly conserved aromatic cage that recognizes m^{6}A. YTH proteins function in fundamental processes ranging from stem cell fate regulation in vertebrates to sex determination in fruit fly (*Drosophila melanogaster*), but whether these or similar proteins act as m^{6}A readers in plants has been a mystery.

Arabidopsis thaliana contains 13 YTH proteins with highly conserved C termini, including EVOLUTIONARILY CONSERVED C-TERMINAL REGION1 (ECT1) to ECT11. The observation that *ECT2* is highly expressed in Arabidopsis, especially in rapidly growing tissues, prompted **Wei et al. (2018)** to focus on ECT2 as a possible m^{6}A reader. Cryo-scanning electron microscopy showed that *ect2* mutants have increased trichome branching compared with the wild type (see figure). ECT2 binds strongly to m^{6}A residues in mRNA, whereas ECT2 lacking the YTH domain does not. Complementation experiments confirmed the role of ECT2 as an m^{6}A reader that functions in trichome development. Transcriptome-wide analysis to identify ECT2-RNA interaction sites using a new formaldehyde cross-linking/immunoprecipitation method uncovered a plant-specific m^{6}A motif in the 3′ untranslated regions of target genes that is recognized by ECT2, which was confirmed to be methylated in vitro. While the human m^{6}A reader, YTHDF2, promotes mRNA degradation,



Cryo-scanning electron microscopy of trichome morphology in wild-type (WT) and *ect2* plants. Trichomes are from the third and fourth leaves of 3-week-old Arabidopsis plants. Bars = 100 μm. (*Reprinted from Wei et al. [2018], Figure 2A.*)

ECT2 appears to support m^{6}A-mediated mRNA stability in the cytoplasm. Indeed, ECT2 bound to three trichome morphogenesis-related transcripts with m^{6}A modifications, and disrupting *ECT2* accelerated their degradation and altered trichome branching.

Scutenaire et al. (2018) took the long view before honing in on ECT2. Evolutionary analysis of YTH domain proteins suggested that all Viridiplantae YTH domains display a canonical aromatic cage and thus carry bona fide m^{6}A binding pockets. However, unlike their animal counterparts, it appears that the functions of plant YTH proteins are not fully redundant, as YTH domains from different clades are predicted to have different m^{6}A binding affinities, a feature conserved across evolution. Epifluorescence imaging suggested that the trichome branching defect in *ect2* mutants is related to an excessive number of endoreduplication cycles, a phenotype also observed in hypomethylated plants. Like many mRNA binding proteins, ECT2 relocates from the cytoplasm to stress granules upon exposure to heat stress. The authors demonstrated that ECT2 bind to m^{6}A-RNA in vivo; this property requires a functional aromatic cage.

Since ECT3 is also highly expressed in Arabidopsis and belongs to the same phylogenetic subclade as ECT2, **Arribas-Hernández et al. (2018)** focused their analysis on both proteins. They showed that in addition to ECT2, ECT3 is necessary for trichome branching and that ECT2 and ECT3 are only expressed during early stages of trichome development. In addition, the *ect2 ect3* double mutants displayed a compelling new phenotype: delayed first true leaf emergence. The mutation of *ECT4*, a close homolog of *ECT2*, enhanced this phenotype, suggesting that ECT2, ECT3, and ECT4 control the timing of postembryonic leaf formation. These proteins, and the m^{6}A binding sites in ECT2 and ECT3, are also required for proper leaf morphology.

The story of m^{6}A readers in plants is nowhere near complete. Additional studies will no doubt leave their mark on plant biology.

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