Global Regulator of mRNA Editing Found

Protein controls editing, expanding the information content of DNA

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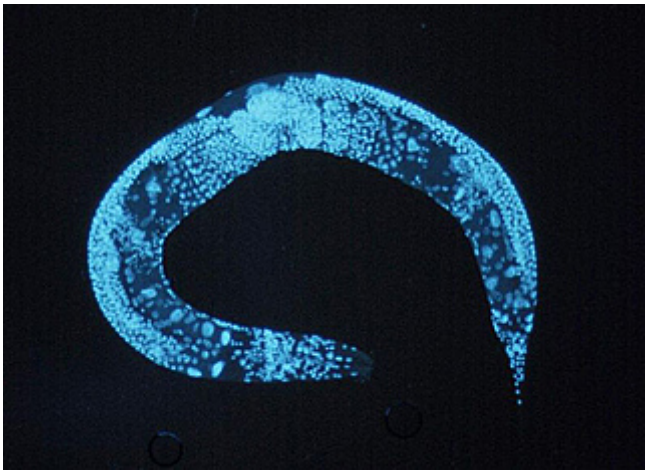
An international team of researchers, led by scientists from the University of California, San Diego School of Medicine and Indiana University, have identified a protein that broadly regulates how genetic information transcribed from DNA to messenger RNA (mRNA) is processed and ultimately translated into the myriad of proteins necessary for life.

The findings, published today in the journal *Cell Reports*, help explain how a relatively limited number of genes can provide versatile instructions for making thousands of different messenger RNAs and proteins used by cells in species ranging from sea anemones to humans. In clinical terms, the research might also help researchers parse the underlying genetic mechanisms of diverse diseases, perhaps revealing new therapeutic targets.



Model organism *Caenorhabditis elegans*.

"Problems with RNA editing show up in many human diseases, including those of neurodegeneration, cancer and blood disorders," said Gene Yeo, PhD, assistant professor in the Department of Cellular and Molecular Medicine at UC San Diego. "This is the first time that a single protein has been identified that broadly regulates RNA editing. There are probably hundreds more. Our approach provides a method to screen for them and opens up new ways to study human biology and disease."

"To be properly expressed, all genes must be carefully converted from DNA to messenger RNA, which can then be translated into working proteins," said Heather Hundley, PhD, assistant professor of biochemistry and molecular biology at Indiana University and co-senior author of the study. RNA editing alters nucleotides (the building blocks of DNA and RNA) within the mRNA to allow a single gene to create multiple mRNAs that are subject to different modes of regulation. How exactly this process can be modulated, however, has never been clear.

Using the nematode *Caenorhabditis elegans* as their model organism and a novel computational framework, Hundley, Yeo and colleagues identified more than 400 new mRNA editing sites – the majority regulated by a single protein called ADR-1, which does not directly edit mRNA but rather regulated how editing occurred by binding to the messenger RNAs subject to editing.

"Cells process their genetic code in a way analogous to how the programming language Java compiles modern software. Both systems use an intermediate representation that is modified depending on its environment" said co-first author Boyko Kakaradov, a bioinformatics PhD student in the Yeo lab. "We're now finding how and why the mRNA code is being changed en route to the place of execution."

The scientists noted that a protein similar to ADR-1 is expressed by humans, and that many of the same mRNA targets exist in people too. "So it is likely that a similar mechanism exists to regulate editing in humans," said Hundley, adding that she and colleagues will now turn to teasing out the specifics of how proteins like ADR-1 regulate editing and how they might be exploited "to modulate editing for the treatment of human diseases."

Co-authors include Michael C. Washburn and Emily Wheeler, Indiana University; Balaji Sundararaman, UCSD; and Shawn Hoon, A*STAR and Nanyang Technological University, Singapore.

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