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Non-coding RNA Controls the Epigenetics of Memory

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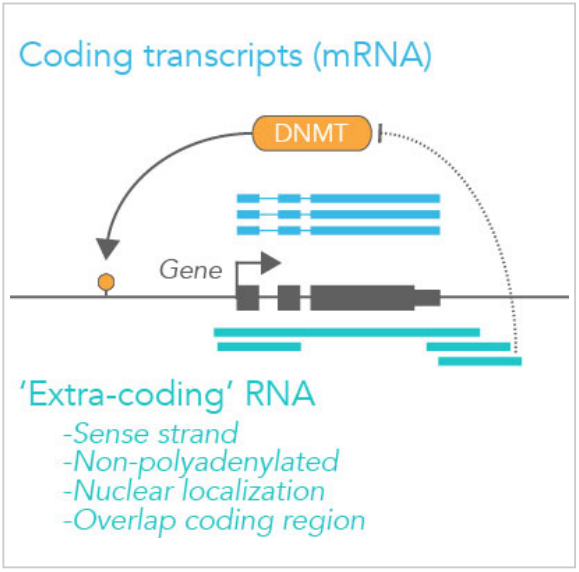
A newly identified class of RNAs is needed for the formation of long-term memories. Read more...

In 2013, scientists discovered “extracoding” RNA (ecRNAs) (1). These RNAs don’t code for protein, but their sequences overlap with those of a protein-coding region. Another member of a growing cast of gene regulators, ecRNAs bind to and block the enzymes that silence genes—probably the very ones they overlap.



For Jeremy Day of the University of Alabama at Birmingham and his collaborators studying the role of DNA methylation in cognition and brain disorders, that discovery provided a clue to a mystery: How does the brain control methylation when DNA methyltransferases—the family of enzymes that add the methyl tag to silence genes—are present throughout the cell’s nucleus?

Day’s group targeted an ecRNA from Fos, a well-known gene encoding a protein that marks cells that have recently been active in the brain. Rodents lacking Fos have memory deficits. And, according to their new results in Nature Communication, so do rats missing the Fos ecRNA (2).

“The surprising part is that we can target in the brain a single ecRNA and find this robust behavioral phenotype,” Day said. “This is one of the first times a long noncoding RNA in the brain has been shown to have this effect on animal behavior.”

Behind the new study was a substantial amount of work needed just to identify the Fos ecRNA because the noncoding regions of the genome are not as well annotated as coding regions are, especially in rat.

But the subsequent steps of experimentally interfering with the function of a specific noncoding RNA are straightforward, and other ecRNAs crucial in brain health and disease could be probed using these methods, Day said. Indeed, the study found, more broadly, that ecRNAs are present throughout the genomes of neurons and are derived from protein-coding counterparts that respond to neuronal activity and that are already tied to disorders.

How does the Fos ecRNA work? “To [block] methylation at only that gene, it would have to stick around somehow,” Day said. That’s one thing his group is exploring now using several complementary approaches, including single-molecule fluorescence in situ hybridization (FISH). They can also artificially target the ecRNA to a specific spot on the gene using CRISPR-Display to study its function.

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Day is not only interested in studying the mechanism of the Fos ecRNA—he also wants to know how ecRNAs are made in general. Many protein-coding genes are made by RNA Polymerase II, but not ecRNAs. Also, the researchers want to know how and whether the shape of an ecRNA molecule, which contains stem-loop structures, relates to its function.

References

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