eRNA's surprising function

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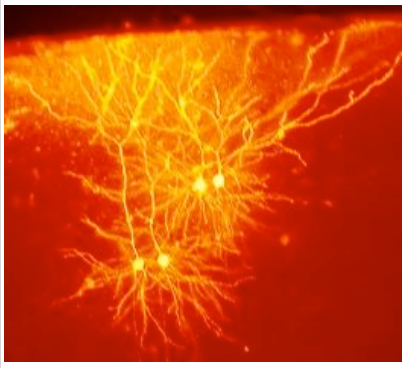
Long viewed as merely a genetic curiosity, eRNA plays a significant role in how neurons control genetic activity in response to external stimuli.

A team of researchers from Harvard Medical School (HMS) and Children's Hospital Boston have unraveled the mystery that surrounds the function of enhancer RNA (eRNA). Since 1980, scientists have known that certain sections of DNA enhance the transcription process by which messenger RNA (mRNA) forms a copy of the nucleotide code contained in DNA to create proteins. However, how and why eRNA accomplished the acceleration of mRNA remained a scientific curiosity. New research from the HMS and Children's Hospital Boston team has uncovered that eRNA plays a significant role in helping neurons transmit genetic signals in response to environmental stimuli.

When a neuron is excited by external stimuli, the brain releases neurotransmitters, chemicals that bind to a receptor on the surface of a neuron. These chemical reactions initiate the set of events that leads to the genetic activity that occurs in a cell. This process modifies the synaptic connections between neurons, helping the brain to grow and develop memory.

The team—led by Michael Greenberg, Nathan Marsh Pusey professor and chair of neurobiology at HMS, and Gabriel Kreiman, assistant professor of ophthalmology at Children's Hospital Boston—set out to determine what happens inside a cell after it is stimulated by a neurotransmitter. Using mouse neuronal cells in culture, researchers used RNA-Seq to identify the RNA sequences that were synthesized after a neuron was stimulated.



eRNA formed neuronal connections based on life experience in mice. Source: Wikipedia Commons

After identifying these sequences, the researchers were able to analyze the subsequent progression of intercellular signals that followed. Using ChIP-Seq—which combines chromatin immunoprecipitation (ChIP) and massively parallel DNA sequencing—the team identified, sequenced, and established the genetic location of the DNA binding sites for transcription factors that control gene expression in the brain in response to outside stimuli.

The researchers discovered that individual patches of DNA appeared to be responsible for amplifying the activity of genes in the brain, which thereby enhanced the action of mRNA. These enhancer regions targeted genes over large genomic distances, which the researchers believe is possible because these enhancer regions create their own RNA molecules—the eRNAs. This study showed that eRNA intensifies the enzymatic process that regulates the genetic control of protein production.

"We've found that there are thousands of these enhancers, that they're spread throughout the genome, and that they are essential to the process in which experience results in new synaptic connections," Greenberg said in a press release. "What's more, we suspect that they're active in many other mammalian cell types, not just neurons."

Scientists have long sought to understand how life experience affects genes that influence synaptic connections between neurons. According to Greenberg, understanding these signals could provide critical insight into cognition disorders, including autism spectrum disorders.

"It's incredibly important to know all about the brain's genetic regulatory mechanisms in order to think more deeply about how to develop therapies for treating these sorts of conditions," said Greenberg. "Biologists have known about enhancers since 1980, and there has even been a paper or two describing RNA produced at enhancer regions," said Greenberg. "But it was largely considered an isolated curiosity. What we've discovered here is how widespread this phenomenon is."

The current study did not establish exactly how eRNA improves the construction of synaptic connections, or what locations eRNA targets within a neuron. Though, Greenberg would like explore these questions.

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