Newly discovered RNA steers brain development

By *NLN*
Created *04/16/2010 - 21:36*

How does the brain work? This question is one of the greatest scientific mysteries, and neurobiologists have only recently begun to piece together the molecular building blocks that enable human beings to be "thinking" animals.

One fundamental property of the mammalian brain is that it continues to develop after birth, and one of the biggest drivers of the formation of new links between neurons is experience. Every time a baby sticks her finger on a pin or laughs in response to an adult's embellished gestures, a cascade of genetic activity is triggered in her brain that results in new, and perhaps even lifelong, synaptic connections.

New research from the lab of Michael Greenberg, Nathan Marsh Pusey professor and chair of neurobiology at HMS, in collaboration with bioinformatics specialist and neuroscientist Gabriel Kreiman, assistant professor of ophthalmology at Children's Hospital, Boston, has found that a particular set of RNA molecules widely considered to be no more than a genomic oddity are actually major players in brain development—and are essential for regulating the process by which neurons absorb the outside world into their genetic machinery.

"This discovery may inform disorders of cognition such as autism spectrum disorders," says Greenberg. "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."

This research will be published online April 15 in the journal *Nature*.

For over 25 years, Greenberg and his lab have been unraveling the mechanisms that enable the outside world to have a profound and lasting effect on neuronal genes. Broadly speaking, when a neuron is stimulated by an external excitation (the pin, the gesture), it releases chemicals called neurotransmitters (the most common one is glutamate). This neurotransmitter binds to a receptor on the neuron surface and then sets in motion a chain of events that affects the genetic activity of the cell. This in turn helps to modify the synaptic connections between neurons, which are the basis of learning and memory.

But what exactly happens inside of a cell after it is activated by neurotransmitter release?

To get closer to the cellular action, Tae-Kyung Kim and Jesse Gray of the Greenberg lab, in collaboration with Martin Hemberg from the Kreiman lab at Children's, used two kinds of high-throughput, next-generation sequencing technologies, RNA-Seq and CHIP-Seq.

Working with mouse brain cells in culture, the researchers used RNA-Seq to identify, with great sensitivity, the RNA sequences that are newly synthesized when a neuron is stimulated in a manner that mimics the effect of a neurotransmitter, and which in turn touches off a domino-like cascade of intracellular signals. The researchers were then able to identify, sequence and—using CHIP-Seq—establish the genomic "address" and the regulatory factors that control the expression of all the genes switched on in these brain cells by the stimulus.

They discovered that there were individual and disparate stretches of DNA that appeared to be amplifying the genes' activity, escalating the process of messenger RNA and protein production. These bits of DNA, called "enhancer regions," were more often than not targeting their genes over vast genomic distances, like a computer dictating orders to a global digital network via satellite.

Most important, however, was the discovery that these enhancer regions accomplished this phenomenon by producing their own RNA molecules, and that these enhancer RNAs, or eRNAs, were intensifying the enzymatic processes that are essential for a gene's ability to create protein.

"Biologists have known about enhancers since 1980, and there has even been a paper or two describing RNA produced at enhancer regions, but it was largely considered an isolated curiosity," says Greenberg. "What we've discovered here is how widespread this phenomenon is. 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. What's more, we suspect that they're active in many other mammalian cell types, not just neurons."

It isn't clear yet precisely how these eRNAs accomplish their synaptic-building tasks, or even where they travel to within the neuron once they are produced. These are questions for further study. Still, the researchers believe there is a likelihood that these finding may eventually prove relevant to, and cast light on, our understanding of certain neurological and psychiatric disorders in which the regulation of gene activity plays a critical role.

Source [1]

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[1] http://hms.harvard.edu/