Connection between faulty neural activation and schizophrenia revealed

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(Medical Xpress)—By studying what happens in the normal brain when neurons fire, Australian scientists have been able to identify a finely and dynamically regulated process. They also describe how dysfunction of this process is associated with schizophrenia.

The process involves a specific class of genes known as 'long non-coding RNAs'. For DNA to act, it must first be 'transcribed' into RNA, nucleic acids that form a variety of long and short molecules. Some RNA molecules are literally 'translated' or encoded into chains of amino acids – proteins that carry out tasks in cells. Others are not, and appear to have important regulatory roles.

This is the first study to show that long non-coding RNAs are regulated by basic neuronal activity. The findings are published online today in the top ranking international journal *Molecular Psychiatry*.

Dr Guy Barry from the Institute for Molecular Bioscience at the University of Queensland and Professor John Mattick from Sydney's Garvan Institute of Medical Research showed that levels of the long non-coding RNA called 'Gomafu' drop dramatically when a neuron is activated in the normal brain, causing a chain of other regulatory events to occur inside the cell.

By investigating Gomafu and its 'binding partners' further, Barry and Mattick saw that certain proteins associated with schizophrenia bound strongly to Gomafu. Later in the study, they were not surprised to find

that levels of Gomafu are abnormally low in the post-mortem brains of people with schizophrenia.

Until this century, long non-coding RNAs such as Gomafu were unknown and unsuspected. Two decades ago, when most scientists considered 95% of the genome as junk, Professor Mattick predicted that the non-protein-coding stretches would be functional and produce regulatory RNAs that would provide the key to our developmental and cognitive complexity.

It is now accepted that non-protein-coding RNAs perform multiple processes critical to cellular differentiation and development, by regulating the organization of the genome, the expression of other genes and how they are 'spliced', or re-formed to perform different functions.

In this study, the team used 'induced pluripotent stem cells' derived from human cells (IPS cells), which differentiate into cortical-type neurons. They stimulated these neurons with potassium chloride, well known to mimic neuronal activity, and perceived the dramatic drop in Gomafu levels after stimulation.

Adopting a protein microarray approach in collaboration with Dr Seth Blackshaw at Johns Hopkins University in Maryland, they were able to scan all known proteins against Gomafu to see which bound.

One binding partner, a particular 'splicing factor', was already known to be associated with schizophrenia. This was the first major piece of the puzzle that led the group to investigate potential links between Gomafu and schizophrenia.

"Taking this approach, investigating the normal, and then letting it lead us down the path towards what might be involved in the disorder, was very productive," said Dr Guy Barry.

"We found a very finely tuned mechanism in cells – with Gomafu restored to previous levels within hours of its degradation after neuronal stimulation."

"What we are predicting right now, along with other groups, is that long non-coding RNAs help to bring together different components in the cell – RNA, DNA or protein – by forming a kind of modular functional scaffold."

"In this case, when Gomafu gets degraded by a signal, it releases all these different kinds of components into the cell and they go and perform a particular function. After a few hours, when the levels of Gomafu are restored again, it soaks the components up once more. At that point, it waits for another activation signal".

"You can imagine that if the schizophrenic brain is firing differently – and Gomafu levels are consistently lower – it would cause havoc within the cell, with all sorts of genes, splicing factors and proteins free floating and available to act, where in a normal brain they would be tethered to Gomafu."

Professor Mattick said that "this study is gratifying as it demonstrates very elegantly that these non-coding RNAs are all likely to be involved in something – most likely the finer regulation of cellular patterns and networks.

"It's impossible to treat a disease when you don't fully understand the mechanisms that underpin it. Knowing now that long non-coding RNAs are regulated by neuronal activity and associated with schizophrenia gives us some hope that its treatment might be tackled differently and more successfully in the future."

More information: www.nature.com/mp/journal/vaop …

t/abs/mp201345a.html

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