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Researchers identify regulation process of protein linked to bipolar disorder

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Researchers from Tufts have gained new insight into a protein associated with bipolar disorder. The study, published in the June 3 issue of *Science Signaling*, reveals that calcium channels in resting neurons activate the breakdown of Sp4, which belongs to a class of proteins called transcription factors that regulate gene expression.

This study, led by Grace Gill, identifies a molecular mechanism regulating Sp4 activity. Her previous research had determined that reduced levels of Sp4 in the brain are associated with bipolar disorder. Her work overall suggests that misregulation of Sp4 may contribute to the development of bipolar disorder.

"Understanding how transcription factors like Sp4 are regulated may provide us with ways to change neuronal gene expression to treat symptoms of mental illness, including bipolar disorder," said Gill, Ph.D., an associate professor in the department of developmental, molecular & chemical biology at Tufts University School of Medicine and member of the neuroscience; genetics; and cell, molecular and developmental biology program faculties at the Sackler School of Graduate Biomedical Sciences at Tufts.

The main goal of the study was to determine whether a specific type of calcium channel—store-operated calcium channels—drive the breakdown of Sp4 protein. Along the way, however, the research team also discovered that signaling by these calcium channels is most active in the so-called "off" or "resting" phase.

"The calcium-signaling regulation of Sp4 during the resting phase was unexpected and suggests two things: resting neurons are more active than we had thought and calcium signaling influences gene expression in both active and resting neurons," Gill said.

"We tend to think about cells being "on" or "off," but the reality of the biology is far more complex. Cells are always busy," she continued.

In neurons – cells that can be stimulated by electrical signals – transcription factors are regulated by calcium entry that is initiated when the cell depolarizes. Depolarization occurs when the overall voltage of the cell is increased. This is the "on" or "active" state for the cell. In contrast, when the cell's voltage is decreased, hyperpolarization occurs. This is called the "off" or "resting" phase for the cell.

Store-operated calcium channels (SOCC) are a type of calcium channel found in all cells. These channels are activated when stores of calcium inside the cell are reduced. A calcium sensor called stromal interaction molecule 1 (STIM1) is responsible for calcium entry into the cell through SOCCs.

To determine whether STIM1 controlled Sp4 breakdown, the researchers reduced STIM1 levels in cells and measured Sp4 levels. A control group of cells contained normal levels of STIM1, while a comparison group contained reduced STIM1 levels. Both cell groups were placed in a solution for 60 minutes to place them into their "resting" state.

The cells in the control group displayed significantly less Sp4 when at rest while, in contrast, cells in the comparison group – those with reduced STIM1 levels – had higher Sp4 levels.

"These findings provide evidence that STIM1 is required for the breakdown of Sp4 when the cell hyperpolarizes, which tell us the

presence of STIM1 directly influences Sp4 levels in neurons," said first author, Jasmin Lalonde, Ph.D., a former postdoctoral fellow in Gill's lab and now a research fellow at the Center for Human Genetic Research and the department of neurology at the Massachusetts General Hospital.

This is ongoing work by Gill to understand the role of Sp4 in bipolar disorder. Some of Gill's previous research, performed in collaboration with researchers from Spain, found that Sp4 levels were lower in two areas of the brain in postmortem samples from patients with bipolar disorder. In a study published in May of this year in the Journal of Neurochemistry, she and her team determined that one mechanism of Sp4 regulation is a glutamate receptor called the NMDA receptor.

More information: Lalonde J, Saia G, and Gill G (2014). Store-Operated Calcium Entry Promotes the Degradation of the Transcription Factor Sp4 in Resting Neurons. *Science Signaling* 7(328) ra51, June 3, 2014. DOI: 10.1126/scisignal.2005242

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