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Schizophrenia-linked gene controls the birth of new neurons

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A gene that is arguably the most studied "schizophrenia gene" plays an unanticipated role in the brain: It controls the birth of new neurons in addition to their integration into existing brain circuitry, according to a report in the March 20th issue of the journal *Cell,* a Cell Press publication. The finding suggests that loss of the gene, as occurs in some cases of schizophrenia as well as bipolar disorder and major depression, may "tip the balance" in the brain, leading to an increased risk of compromised cognition and behavioral abnormalities, the researchers said.

What's more, the protein encoded by the gene aptly known as Disrupted in Schizophrenia 1 (DISC1) exerts its influence through a well-studied molecular pathway. Specifically, it interacts directly with and blocks the activity of GSK3b, a protein that is the target of the lithium treatments that doctors have used for decades in the treatment of bipolar disorder.

"Lithium is still the most reliable [medication] for bipolar disorder," said Li-Huei Tsai of the Howard Hughes Medical Institute and the Massachusetts Institute of Technology. "This shows that DISC1 is almost like an endogenous lithium."

The findings are part of a larger picture of the genetic and developmental causes of psychiatric disorders that has recently begun to emerge and may point the way to new approaches for therapeutic intervention, Tsai said. Although people diagnosed with schizophrenia are typically resistant to treatment with lithium, she added, their

observations should encourage scientists to "think creatively" about new and more powerful strategies for targeting GSK3b.

Schizophrenia is a severe brain illness that affects 0.5% of the world population, the researchers said. While its causes are poorly understood, accumulating evidence suggests that neurodevelopmental defects are involved and recent studies have identified many risk genes associated with schizophrenia, DISC1 among them. Studies of a very large Scottish family with a high incidence of schizophrenia, bipolar disorder and major depression over several generations also found that those family members who develop psychiatric disorders carry a mutation in DISC1.

Biochemical evidence later showed that DISC1 interacts with a growing number of binding partners, Tsai said, and functional studies have revealed a role for the gene in the growth and migration of neurons and in the integration of neurons into the brain. Mice with the abnormal version of the gene also develop behaviors that are reminiscent of human psychiatric disorders, including schizophrenia and depression.

Now, Tsai's team has begun to connect the genetic and biochemical evidence with the behavior in studies of mice.

In addition to the known role of DISC1 in the function of existing neurons, the gene is also highly expressed in neural progenitor cells and is required for their proliferation, they report. This function of DISC1 involves regulation of the so-called b-catenin/GSK3b pathway.

In the adult mouse brain, loss of DISC1 function in the dentate gyrus, a portion of the brain that is important to the formation of new memories, led to reduced neural progenitor proliferation and elicited hyperactive and depressive behaviors in mice. Importantly, they found, those behavioral abnormalities were reversed when the DISC1-deficient animals were treated with a chemical that blocked GSK3b.

"These findings provide compelling evidence that DISC1 is a central player in the GSK3b/b-catenin signaling pathway that impinges on neural progenitor proliferation," the researchers concluded. Together with earlier findings, the new results suggest that behavioral abnormalities resulting from DISC1 loss of function in the dentate gyrus likely involve a combination of reduced numbers of newly born neurons and their aberrant integration into the existing circuitry, as well as effects on mature neurons.

"In the end, the human lesions may result in subtle functional changes that have an effect on the eventual size of the brain and the progenitor pool," Tsai said. While those changes might not be sufficient to cause psychiatric disorders on their own, she added, they may leave individuals more vulnerable to getting "pushed over the edge."

Source: Cell Press (news : web)