Protein linked to Alzheimer's may also play a role in schizophrenia

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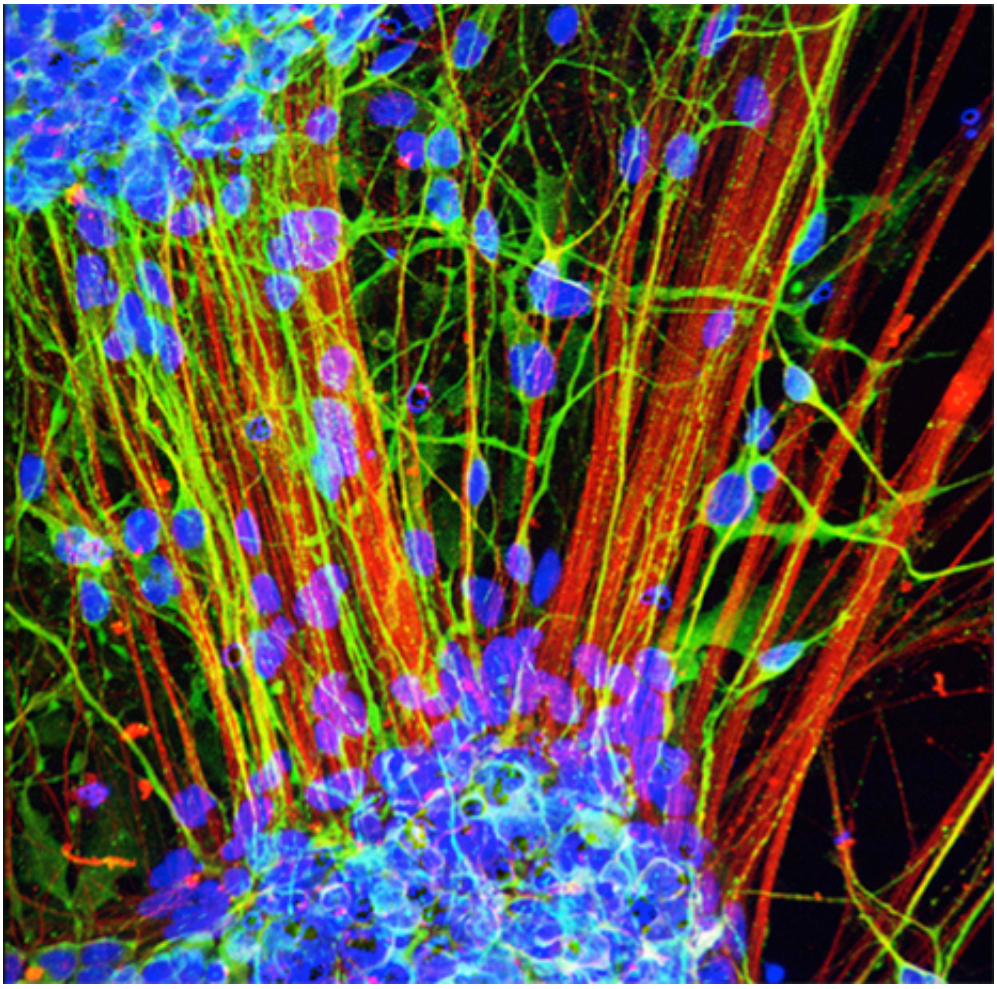

Neurons derived from skin cells of patients with schizophrenia express high levels of a protein linked to Alzheimer's, researchers have found. Credit: Icahn School of Medicine at Mt. Sinai

A specific protein implicated in the cognitive decline of Alzheimer's disease also appears to play a role in genetic predisposition to schizophrenia, meaning that a drug that targets that protein could treat a variety of neuropsychiatric disorders, according to a new study published October 18 in the journal *Molecular Psychiatry*.

Yale researchers have been studying the role that the STEP (STriatal-Enriched protein tyrosine Phosphatase) protein plays in healthy functioning of synapses—the connections between brain cells. Excessive amounts of STEP protein are found in the brains of humans and animal models of Alzheimer's disease, Parkinson's disease, fragile X syndrome, and schizophrenia. The increase in STEP leads to a disruption of synaptic function and contributes to the cognitive deficits present in these disorders.

The research was led by Yale's Paul Lombroso, the Elizabeth Mears and House Jameson Professor in the Child Study Center and professor of neurobiology and psychiatry, and Kristen Brennand at the Icahn School of Medicine at Mount Sinai.

In previous work, Lombroso and colleagues have shown that an experimental drug designed to inhibit the STEP protein restores cognitive deficits in a mouse model of Alzheimer's disease. In the new paper, Lombroso shows that genetically eliminating STEP or using the drug to inhibit STEP activity improves cognitive deficits in a mouse model that has behaviorial features related to symptoms of schizophrenia. A team led by Brennand also found increased levels of STEP in human stem cells derived from skin cells taken from two groups of schizophrenia patients. A STEP inhibitor applied to those human stem cells corrected some of the biochemical and electrophysiological deficits that characterized these abnormal cells.

While the drug used in the earlier Alzheimer's experiments has proven

difficult to develop for clinical use, Lombroso said he and colleagues at Yale (professors Eric Ellman in chemistry and Angus Nairn in psychiatry) are developing new STEP inhibitors and, if successful, these may have more practical therapeutic value.

"These findings suggest that a STEP inhibitor, when discovered, may be the basis of a new drug that can treat a number of neuropsychiatric disorders," Lombroso said.

More information: J Xu et al. Inhibition of STEP61 ameliorates deficits in mouse and hiPSC-based schizophrenia models, *Molecular Psychiatry* (2016). DOI: 10.1038/mp.2016.163

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