Potential target for treating schizophrenia found

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(Medical Xpress) -- Scientists at the University of Glasgow have identified a potential target for the treatment of schizophrenia.

Schizophrenia is a mental condition in which individuals experience a range of symptoms, including auditory hallucinations, paranoid delusions and muddled thought or speech.

It is one of the most common mental health conditions, affecting 2-4 people per 1,000 in the UK.

It is widely believed that a special protein called DISC1, which plays a key role in the development of the brain cortex, may be a susceptibility factor for schizophrenia, as well as mood disorders and autism.

The cortex is a part of the brain that plays a key role in memory, attention, awareness, thought, language and consciousness. While it is well-known that defects in this region are associated with schizophrenia, it is not understood how these defects develop.

DISC1 is a so-called 'signalling scaffold protein' because it acts as a control centre by recruiting other types of proteins, attracting them to its surface where they generate and interpret signals able to control brain development and function.

Professor Miles Houslay, of the Institute of Neuroscience & Psychology at the University of Glasgow, said: "While it is now well-recognised that

DISC1 is a major susceptibility factor for these brain diseases, we still don't understand enough about the range of processes it controls and how they go wrong in mental illness."

However, as reported in the latest edition of the journal *Nature*, the Glasgow team, working with colleagues from John Hopkins University, Duke University and Keio University, Tokyo, have shown that DISC1 acts as a molecular switch that controls two key stages in the development of the cortex.

One stage involves how cells in the cortex multiply in development and the other stage relates to how brain cells migrate within the cortex to specific locations that allow for correct functioning.

Prof Houslay added: "These processes are critical for normal brain function. However, as these new results show that DISC1 is a protein whose function can be dynamically regulated, it opens up the possibility of pharmaceutical and biotech companies designing new medicines able to correct defects in DISC1 that lead to the debilitating disease of schizophrenia.

"Schizophrenia, mood disorders and autism cause great emotional and financial hardships for individuals, their families and for society as a whole. Because of this we desperately need to know what goes wrong in the brain that leads to these debilitating conditions."

More information: DISC1-dependent switch from progenitor proliferation to migration in the developing cortex, Nature, Volume: 473, Pages: 92–96 Date published: 05 May 2011. DOI: doi:10.1038/nature09859 www.nature.com/nature/journal/ … ull/nature09859.html

Abstract

Regulatory mechanisms governing the sequence from progenitor cell proliferation to neuronal migration during corticogenesis are poorly understood. Here we report that phosphorylation of DISC1, a major susceptibility factor for several mental disorders, acts as a molecular switch from maintaining proliferation of mitotic progenitor cells to activating migration of postmitotic neurons in mice. Unphosphorylated DISC1 regulates canonical Wnt signalling via an interaction with GSK3β, whereas specific phosphorylation at serine 710 (S710) triggers the recruitment of Bardet–Biedl syndrome (BBS) proteins to the centrosome. In support of this model, loss of BBS1 leads to defects in migration, but not proliferation, whereas DISC1 knockdown leads to deficits in both. A phospho-dead mutant can only rescue proliferation, whereas a phospho-mimic mutant rescues exclusively migration defects. These data highlight a dual role for DISC1 in corticogenesis and indicate that phosphorylation of this protein at S710 activates a key developmental switch.

Provided by University of Glasgow

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