News Release

Title

Disrupted-in-schizophrenia 1 regulates transport of *ITPR1* mRNA for synaptic plasticity

Key Points

- DISC1 interacts with RNA-binding proteins that act as components of RNA-transporting granules.
- DISC1 regulates the dendritic transport of *ITPR1* mRNA in hippocampal neurons.
- Studies with *Disc1*-knockout mice provide novel function of DISC1 in synaptic plasticity.

Summary

Prof. Kozo Kaibuchi (Department of Cell Pharmacology) and his team led by Dr. Daisuke Tsuboi (Assistant Professor) in Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.) revealed that Disrupted-In-Schizophrenia-1 (DISC1) regulates transport of inositol 1,4,5-trisphosphate receptor type 1 (*ITPR1*) mRNA for synaptic plasticity.

Schizophrenia is a devastating psychiatric disorder affecting 1% of the population worldwide. *DISC1* gene is a promising susceptibility factor for schizophrenia. To examine the role of DISC1 during neurodevelopment, we have previously generated a *Disc1* knockout (*Disc1*$^{-/-}$) mouse. The *Disc1*$^{-/-}$ mouse shows altered synaptic plasticity and abnormal emotional behaviors. However, the molecular mechanism of DISC1 underlying the synaptic plasticity remained to be unsolved. In this study, using a proteomic analysis, we identified several RNA-binding proteins including HZF as DISC1-interactors. We revealed that DISC1, together with HZF, regulates the dendritic transport of *ITPR1* mRNA for synaptic plasticity.

Summary

Disrupted-in-schizophrenia 1 regulates transport of *ITPR1* mRNA for synaptic plasticity. DISC1 is a promising genetic risk factor to schizophrenia. However, the patho-physiological functions of DISC1 are not fully understood. Tsuboi et al. identified several RNA-binding proteins including HZF as DISC1-interactors by proteomic approach. They reveal that DISC1, together with HZF, regulates the dendritic transport of *ITPR1* mRNA for synaptic plasticity.

Research Background

Schizophrenia is a devastating psychiatric disorder affecting 1% of the population worldwide. The *DISC1* gene locus was originally identified at the breakpoint of a balanced (1;11) (q42;q14) chromosome translocation that co-segregates with schizophrenia, bipolar

disorder, and recurrent major depression in a large Scottish family. Further analysis indicates that inheritance of the translocation was causal and increased the risk of these psychiatric disorders by 50-fold. Therefore, *DISC1* gene is a promising susceptibility factor for schizophrenia.

The studies *in vitro* and in intact cells have shown that DISC1 is involved in neurogenesis, neuronal migration, axon/dendrite formation, and synapse formation through interactions with various partners. To examine the role of DISC1 during neurodevelopment, we have previously generated a *Disc1* knockout (*Disc1*$^{-/-}$) mouse. The *Disc1*$^{-/-}$ mouse displays no gross abnormalities in the brain's cytoarchitecture, whereas it shows altered synaptic plasticity and abnormal emotional behaviors (Kuroda et al., Hum Mol Genet. 2011), suggesting that DISC1 regulates synaptic plasticity and cognitive functions.

Research Results

In the present study, using a proteomic analysis, we identified RNA-binding proteins including HZF as novel DISC1-interactors. HZF is a component of the RNA granules with inositol 1,4,5-trisphosphate receptor type 1 (*ITPR1*) mRNA, which acts as a key regulator for synaptic plasticity. DISC1 co-localized with HZF and *ITPR1* mRNA in hippocampal dendrites. Furthermore, DISC1 directly associated with several mRNAs including that of *ITPR1*. The impairment of DISC1 function prohibited the dendritic transport of *ITPR1* mRNA and caused altered synaptic plasticity (Figure 1).

Research Summary and Future Perspective

In summary, this study describes a novel role of DISC1 in mature neuron and provides an intriguing clue regarding the molecular mechanism underlying synaptic plasticity. In the future, we will focused on the structural plasticity and alternation of cell signaling at the activated synapses of *Disc1*$^{-/-}$ mouse.

<Article>

Tsuboi D, Kuroda K, Tanaka M, Namba T, Iizuka Y, Taya S, Shinoda T, Hikita T, Muraoka S, Iizuka M, Nimura A, Mizoguchi A, Shiina N, Sokabe M, Okano H, Mikoshiba K, Kaibuchi K. Disrupted-in-schizophrenia 1 regulates transport of *ITPR1* mRNA for synaptic plasticity. Nature Neuroscience (Advanced online publication; Mar 30, 2015)

Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2014/itpr1_20150331jp.pdf

(Figure 1)

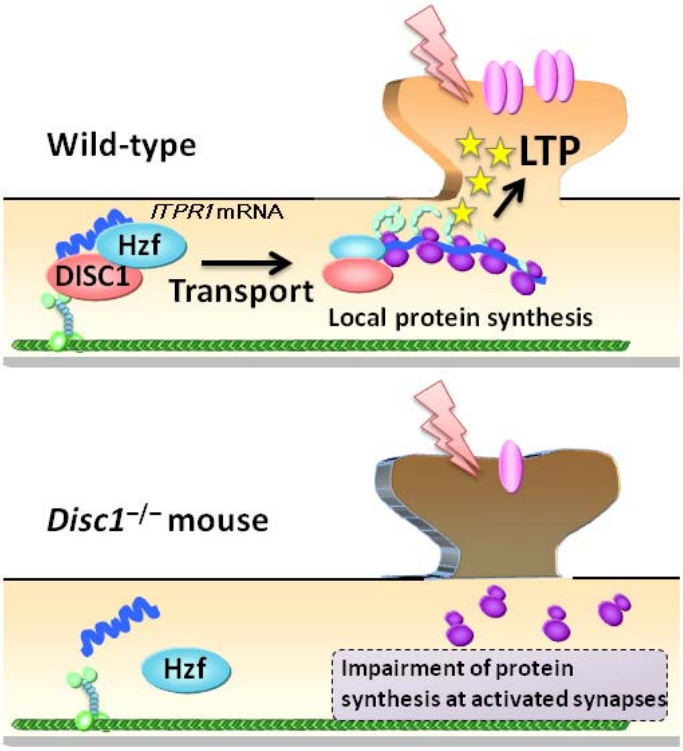

Figure 1 Novel function of DISC1 in synaptic plasticity.
We propose that DISC1 binds ITPR1 mRNA with HZF, thereby regulating its dendritic transport for synaptic plasticity. DISC1 forms a complex with HZF and ITPR1 mRNA, resulting in stable RNA granules. Because DISC1 can link kinesin-1 to HZF and ITPR1 mRNA, DISC1 may be involved in the conversion from static RNA granules to motile ones (namely, RNA-transporting granules). The localized mRNAs would be translated at activated spines, and then newly synthesized proteins would contribute to synaptic plasticity. DISC1 depletion impaired the dendritic transport of *ITPR1* mRNA and caused altered synaptic plasticity.