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NEUROGENESIS

Assisted birth with DISC1

Mutations in the gene disrupted in schizophrenia 1 (*DISC1*) have been associated with increased risk for schizophrenia as well as other mental disorders, including bipolar disorder and major depression. DISC1 is known to regulate diverse processes in postmitotic neurons during development, such as maturation and migration, but Tsai and colleagues now show that it also regulates the proliferation of both embryonic and adult neuronal progenitor cells by modulating glycogen synthase kinase 3β (GSK3β)–β-catenin signalling.

The authors used short hairpin RNAs (shRNAs) directed against *DISC1* to silence *DISC1* expression *in vitro* and *in vivo*. DISC1 knockdown decreased the proliferation of progenitor cells cultured from the hippocampus of adult mice and reduced the number of cells in the ventricular and subventricular zones — regions where neurogenesis takes place — in embryonic mouse brains. Moreover, decreased bromodeoxyuridine labelling in these embryonic brains indicated an increase in the number of cells exiting the cell cycle, suggesting that DISC1 knockdown caused premature differentiation of progenitors and a depletion of the progenitor pool. Overexpression of DISC1 had the opposite effect, confirming a role for DISC1 in regulating cell proliferation.

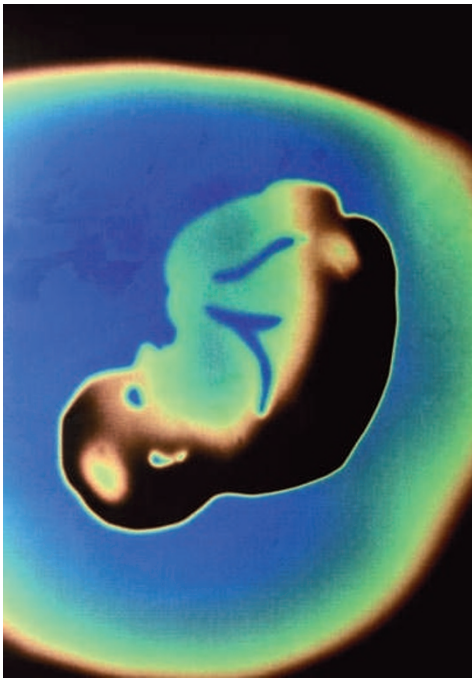
Wnt signalling plays an important part in neural development, and the authors therefore investigated whether DISC1 interacts with this pathway. DISC1 knockdown reduced Lef–Tcf activation — a read-out of canonical Wnt signalling activity — whereas DISC1 overexpression increased Lef–Tcf activation; this effect was dependent on the Wnt effector β-catenin, as it was abolished by silencing β-catenin expression with shRNAs.

As expected, β-catenin overexpression potentiated Lef–Tcf activity *in vitro*, and this potentiation was reduced by DISC1 knockdown. Interestingly, however, silencing DISC1 had no effect on Lef–Tcf activity *in vitro* or on progenitor proliferation *in utero* if a degradation-resistant form of β-catenin was expressed. This suggested that DISC1 regulates β-catenin levels; indeed, *in vitro* knockdown of DISC1 decreased β-catenin levels.

The authors next established that DISC1 regulates β-catenin levels by inhibiting GSK3β, an enzyme that targets β-catenin for proteasomal degradation. A GSK3β inhibitor rescued the reduced proliferation caused by DISC1 silencing *in vitro* and *in utero*. Conversely, overexpression of GSK3β in embryonic mouse brains reduced progenitor proliferation, and this was normalized by co-expression of DISC1.

Importantly, these results could be reproduced in the adult hippocampal dentate gyrus *in vivo*: injections of a lentivirus expressing DISC1 shRNA decreased cell proliferation in this region, and treatment with a GSK3β inhibitor restored it.

Finally, the authors tested the behavioural consequences of manipulating the DISC1–GSK3β signalling pathway. Knockdown of DISC1 in adult dentate gyrus resulted in hyperactivity in an open field test and increased immobility in a forced-swim test, which are thought to model schizophrenia- and depression-like behaviours, respectively. The behavioural effects were normalized by treatment with a GSK3β inhibitor.



These findings broaden our understanding of the central role of DISC1 and GSK3β in neural development and mental disorders. The finding that GSK3β inhibitors can abolish the behavioural and cellular effects of DISC1 knockdown in adulthood suggests that the GSK3β–β-catenin pathway could be a promising target for the treatment of these disorders.

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ORIGINAL RESEARCH PAPER Mao, Y. *et al.* Disrupted in schizophrenia 1 regulates neuronal progenitor proliferation via modulation of GSK3β/β-catenin signaling. *Cell* **136**, 1017–1031 (2009)