PSYCHIATRIC DISORDERS

The risk of DISC — at the synapse

Disrupted in schizophrenia (DISC1) is an emerging risk factor for several psychiatric disorders, including schizophrenia, but its role in the aetiology of these disorders is not completely understood. As defective synaptic function has been linked to complex psychiatric conditions and as DISC1 is localized to the synapse, Brandon *et al.* investigated the role of DISC1 by studying its interaction with another synaptic protein, TRAF2 and NCK-interacting kinase (TNIK). This interaction, previously identified by yeast two-hybrid studies, caught the authors' attention because *TNIK* has also been strongly implicated as a susceptibility gene for schizophrenia and related conditions. But does this interaction occur *in vivo* and, if so, what is its biological importance at the synapse?

Initial immunohistochemistry analysis of mouse brain sections showed that both proteins colocalized in dendritic spines in hippocampal area CA1 and in the somatosensory cortex. This was an interesting result given that these areas are crucial anatomical substrates in schizophrenia. Furthermore, cell fractionation experiments confirmed that both proteins were enriched in postsynaptic density (PSD) fractions and, crucially, co-immunoprecipitation experiments verified the endogenous interaction between TNIK and

DISC1 in whole-cell lysates from rat brains. Together, these results indicate that these proteins interact *in vivo*, and their most likely site of interaction is the PSD.

Does this interaction modulate the function of either or both proteins? Brandon *et al.* reported that cell rounding — a phenomenon dependent on the kinase activity of TNIK — was inhibited by co-transfection with DISC1, suggesting that DISC1 might inhibit the kinase activity of TNIK. The authors mimicked the DISC1–TNIK interaction by treating cells with a DISC1-derived peptide (DISC1-pep-WT-tat) and showed that this markedly inhibited TNIK kinase activity *in vitro*. Moreover, treatment with DISC1-pep-WT-tat led to a dramatic reduction not only of TNIK but also of other key synaptic proteins, including the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor subunit GluR1, the transmembrane AMPA receptor regulatory subunit stargazin and the PSD scaffold protein PSD95. Similar decreases were also noted when the production of endogenous TNIK was prevented using lentivirus-expressed small hairpin RNA (shRNA). Crucially, by measuring the amplitude and frequency of isolated AMPA receptor miniature excitatory postsynaptic currents following TNIK inhibition

by shRNA or DISC1-pep-WT-tat, the authors showed that TNIK inhibition modified synaptic connectivity.

These data suggest a working model in which DISC1 negatively regulates synaptic strength by inhibiting the TNIK-dependent stabilization of key postsynaptic proteins. Given that synaptic function is an essential determinant of complex psychiatric disorders, a deeper understanding of both proteins might help to identify strategies for the prevention and treatment of these diseases.

Safia Ali Danovi

ORIGINAL RESEARCH PAPER Wang, Q. *et al.*
The psychiatric disease risk factors DISC1 and TNIK interact to regulate synapse composition and function. *Mol. Psychiatry*. 14 Sep 2010
(doi:10.1038/mp.2010.87)