PSYCHIATRIC DISORDERS

DISC1 drives development through girdin

Mutations in disrupted in schizophrenia 1 (DISC1) are a risk factor for multiple psychiatric and mental disorders, and DISC1 regulates diverse aspects of neuronal physiology. However, the molecular mechanisms by which DISC1 mediates its effects are largely unknown. Enomoto *et al.* and Kim *et al.* have begun to dissect these signalling pathways, revealing a central role for the actin-binding protein girdin (also known as KIAA1212) in DISC1's regulation of neuronal growth and migration in the postnatal and adult hippocampus.

DISC1 binds to a host of different proteins — known as the 'DISC1 interactome' — making it important to discover which of these interactions underlie its diverse roles. In 2007, a yeast two-hybrid screen revealed girdin as a potential DISC1-interacting protein. This interaction was confirmed in both of the new papers *in vitro* with co-immunoprecipitation and pull down assays and by Kim *et al. in vivo*. Together with the expression of girdin in hippocampal dentate granule cells (DGCs) and pyramidal neurons observed by Enomoto *et al.*, this suggests a role for girdin in DISC1's effects on the development of newborn hippocampal neurons in the postnatal period and adulthood.

Enomoto *et al.* investigated this link in the brains of girdin$^{-/-}$ mice and cultured hippocampal neurons in which girdin was knocked down using short hairpin RNA, and found that girdin, like DISC1, is important for DGC neurite growth. Further experiments suggested that DISC1 might stabilize or anchor girdin in axonal growth cones. Loss of girdin also disrupted DGC migration and positioning. This effect could be mimicked by inhibiting DISC1–girdin binding, which confirmed the importance of this interaction for DGC development.

Girdin has been shown to enhance the activation of the signalling kinase Akt, and Kim *et al.* found that DISC1–girdin binding suppressed Akt activation in HEK293 cells. Furthermore, short hairpin RNA-mediated knockdown of DISC1 in mouse hippocampal neurons increased Akt activation, suggesting that suppression of Akt signalling might underlie the effects of DISC1 on DGC development. Indeed, overexpressing girdin or constitutively active Akt, or knocking down PTEN — a negative regulator of Akt signalling — mimicked many of the effects of DISC1 knockdown, including accelerated and increased dendritic growth and abnormal migration.

To investigate the pathways downstream of Akt that mediate DISC1's effects, Kim *et al.* used pharmacological inhibitors of two major Akt effectors, mammalian target of rapamycin and glycogen synthase kinase 3β. Only disruption of mammalian target of rapamycin signalling was able to rescue neurons from the effects of DISC1 knockdown or girdin overexpression, suggesting a role for this pathway in DISC1's regulation of adult-born neurons.

These studies reveal that DISC1–girdin interactions are crucial for several aspects of neural development in the adult hippocampus. Some aspects of this regulation require further clarification — for example, the two groups found different domains of girdin to be important for DISC1 binding. Nevertheless these studies have begun to pick apart the signalling mechanisms by which DISC1 mediates its diverse effects, and this may lead to new insights into the pathophysiology of the disorders with which it is associated.

Katherine Whalley

ORIGINAL RESEARCH PAPERS Kim, J. Y. *et al.* DISC1 regulates new neuron development in the adult brain via modulation of AKT-mTOR signaling through KIAA1212. *Neuron* **63**, 761–773 (2009) | Enomoto, A. *et al.* Roles of disrupted in schizophrenia 1-interacting protein girdin in postnatal development of the dentate gyrus. *Neuron* **63**, 774–787 (2009)