Perspectives on disrupted-in-schizophrenia 1 signaling in neurogenesis

New neurons are generated and integrate into existing circuitry within the hippocampal dentate gyrus and the olfactory bulb of most mammals (Gage and Temple, 2013). Neurogenesis in the hippocampus persists through adulthood, and while its function and importance remains unclear, it appears to be required in the formation of specific types of learning and memory that may be compromised in neurological disorders (Gage and Temple, 2013). A balanced translocation in Disrupted-in-Schizophrenia 1 (DISC1) was discovered in a large Scottish family with a high incidence of schizophrenia, bipolar disorder and major depressive disorder (Millar et al., 2000), and several independent animal models demonstrate that DISC1 mediates multiple aspects of embryonic and adult neurogenesis. Here, we will discuss the data linking DISC1 to neurogenesis, and define some of the questions that remain unanswered regarding DISC1 function.

DISC1 function in the subependymal zone (SEZ) and subgranular zone (SGZ): Neural stem cells (NSCs) are prominent in two regions of the mammal brain: along the ependyma of the lateral wall of the lateral ventricle (SEZ, also known as subventricular zone/ SVZ), and below the granule cell layer of the dentate gyrus (SGZ). In contrast to their highly mitotic state during embryogenesis, stem cells are relatively quiescent in the adult brain, and maintain a dynamic pool of neurons by generating highly proliferative intermediate (or amplifying) progenitors that mature into neuroblasts, before differentiating into an immature neuron (Figure 1).

One important mediator of neural progenitor homeostasis in both neural stem cell niches is Gycogen synthase kinase-3 (GSK-3), which in mammals is present as two isoforms (GSK-3α and GSK-3β). Deletion of both GSK-3 isoforms in mice leads to cell hyperproliferation due to augmented β-catenin expression, suggesting that inhibiting GSK-3 activity can promote cell division and enhance neurogenesis (Kim et al., 2009). The first clue linking DISC1 to the wnt/β-catenin pathway came from the observation that DISC1 can bind to and inhibit GSK-3β, stabilizing β-catenin expression, and maintaining cell homeostasis (Mao et al., 2009). Reducing the inhibition of GSK-3β through RNAi mediated knockdown of DISC1 in the embryonic SVZ and adult SGZ led to a loss in proliferating cells, and delineated a role for DISC1 in the NSC pathway. Interestingly, shRNA reduction of DISC1 also led to the generation of immature neurons in the SGZ with exaggerated dendritic arbors, and ectopic placement within the granule cell layer suggesting that DISC1 could affect multiple cell populations within the niche (Duan et al., 2007; Mao et al., 2009).

Several mouse models have demonstrated an important role for DISC1 in the SEZ and SGZ, and indicate that DISC1 activity is important during both early embryogenesis as well as adult neurogenesis. DISC1 knockout mice generated through a partial deletion of the second and third exon display a mild cognitive impairment, but otherwise show grossly normal physiology (Kuroda et al., 2011). Mice with a germline insertion of a premature stop codon that maintains solely a short N-terminal DISC1 protein, however, display working memory deficits associated with hippocampal dysfunction, impaired neurogenesis, and yield mature dentate granule neurons with less developed dendritic arbors and decreased spine density (Kvajo et al., 2008). The possibility that expression of an N-terminal DISC1 fragment potentiates a toxic effect is supported by a mouse model of DISC1 dysfunction that overexpresses two copies of Disc1 exons 1–8 on the wild-type background, and which show behavioral abnormalities and a loss of proliferating cells in the embryonic SVZ (Shen et al., 2008).

To further explore DISC1 function in neurogenesis, we examined two different N-terminal Disc1 missense mutants generated through N-ethyl-N-nitrosourea (ENU) mutagenesis that did not affect the expression of full length DISC1, but yielded distinct behavioral phenotypes (Clapcote et al., 2007). Notably, mice carrying a homozygous Q31L mutation had a depressive-like phenotype, while mice with a homozygous L100P mutation had a more schizophrenia-like phenotype. Previously, a loss in neurons in the embryonic SVZ as well as neuronal migration defects across the embryonic cerebral cortex in both Disc1100P/100P and Disc1100P/100P mice were reported (Lee et al., 2011), but whether the DISC1 mutations affected any cell populations in the SGZ was unknown.

We were surprised to see that adult hippocampal tissue from the Disc1100P/100P mice had a nearly two fold loss in neurosphere forming ability, an index of neural stem cells, when compared to either Disc1100P/100P mice or littermate controls (Chandran et al., 2014). When we probed tissue sections from the Disc1 mice with an antibody raised against T-box brain gene 2 (Tbr2), a marker for intermediate progenitors that arise from neural stem cell division (Figure 1), we noted a similar two-fold loss in the Disc1100P/100P mice compared to both the Disc1100P/100P mice and littermate controls. However, when we labelled the mitotic neuroblasts and post-mitotic immature neurons with doublecortin (DCX), we noted that Disc1100P/100P mice compared to either Disc1100P/100P mice or Disc1100P/100P mice had reduced numbers of DCX positive neurons present in the Disc1100P/100P mice compared to wild-type controls. Furthermore, alterations in neurogenesis were not unique to the adult SGZ, as Disc1100P/100P mice also showed deficits in proliferating cells in the adult SEZ as well as reductions in neurosphere formation in early postnatal (P0) mice in both niches (unpublished observations). Overall, the data obtained from the Disc1 missense mutants supports the other DISC1 mouse models that show that DISC1 can influence multiple cell populations in the NSC lineage.

DISC1, mental illnesses, and targets for therapy: Nearly fifteen years ago, three researchers proposed a link between oscillations in hippocampal neurogenesis and the etiology of clinical depression (Jacobs et al., 2000). Mouse models and postmortem tissue obtained from patients suggest that impaired neurogenesis may be relevant in a wider spectrum of mental illnesses (Gage and Temple, 2013). In the adult brain,
the majority of NSCs are quiescent, and are activated in response to a specific cellular stress (Gage and Temple, 2013). Identifying the molecules that can activate the NSCs can therefore be an important step towards developing a neural regeneration therapy. Our data using a colony forming assay, adapted to the generation of neurospheres, in the Disc1<sup>m31L/m31L</sup> mice indicate the existence of a link between the DISC1-dependent perturbation of the behavior of the NSC population and the depression-like phenotype, though whether this is mediated through an increase in NSC quiescence which leads to a loss of intermediate progenitors, is still unknown. A platform for developing regenerative therapies based on the SGZ may be dependent on future studies investigating how DISC1 exerts an effect on the NSCs, and whether this can be optimized.

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Figure 1 Neurogenesis in the subgranular zone.
Lineage tracing experiments indicate that the neural stem cells in the SGZ generate new granule neurons, which extend processes across the granule cell layer, through a step of amplification (generation of fate restricted Tbr2<sup>+</sup> intermediate progenitors) and neuronally committed DCX<sup>+</sup> neuroblasts. SGZ: Subgranular zone; Tbr2: T-box brain gene 2; DCX: doublecortin.