DISCLOSURE
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Neuronal signaling pathways: genetic insights into the pathophysiology of major mental illness

Psychiatric genetics has turned a corner—increasingly robust findings can be placed in a neurobiological context, with practical implications for understanding disease pathogenesis and developing of therapeutics. A milestone in this effort was the discovery of the *DISC1* (disrupted in Schizophrenia 1) gene, found via analysis of a large Scottish family with a high rate of schizophrenia and psychotic affective disorder. All affected members of the family carry a (1;11)(q42.1; q14.3) translocation; the chromosome 1 translocation break point falls between exon 8 and 9 of *DISC1*, presumably resulting in loss of *DISC1* expression. This finding has launched an entire subfield of schizophrenia genetics and neurobiology, with an emphasis on the role of the *DISC1* gene product and its protein interaction partners in neurodevelopment and synaptic function (Chubb *et al*, 2008).

In the past year, DISC1 has been put into the context of key signal transduction pathways and other genetic findings. In one critical study (Mao *et al*, 2009), DISC1 was shown to modulate the 'canonical' Wnt-signaling pathway. This pathway (Komiya and Habas, 2008) is activated when a member of the *Wnt* family of secreted glycoproteins binds a member of the Frizzled receptor family along with coreceptors. Pathway activation reduces GSK3β kinase activity, resulting in diminished phosphorylation of β-catenin. Unphosphorylated β-catenin accumulates in the cytoplasm and is translocated into the nucleus, where it functions as a transcriptional coactivator. Among other effects, this transcriptional activity can drive neuronal neurogenesis. DISC1 directly interacts with GSK3β, inhibiting GSK3β phosphorylation of β-catenin and thus increasing β-catenin-induced transcriptional activity. The effect is to mimic Wnt pathway activation. Loss of DISC1 inhibits β-catenin-induced transcription, providing a potential mechanism by which *DISC1* loss of function mutations might exert their effect.

DISC1 has also been linked to pathways involving Neuregulin-1 (*NRG1*), one of the most robust candidate genes for schizophrenia (Mei and Xiong 2008). Extracellular NRG1, cleaved from Pro-NRG1, interacts with and activates the ErbB family of receptor protein kinases (ErbB2, 3, 4, and EGFR), starting a cascade that activates a number of partially overlapping pathways, including Raf—MEK–ERK and PI3K–Akt. NRG1 signaling has been implicated in neuronal migration, axon guidance, synapse formation, myelination, and oligodendrocyte development. NRG-1 activated Akt inhibits GSK3β, tying NRG1 signaling to Wnt and DISC1 activity. The related effects of DISC1 and NRG1 have been highlighted in a zebrafish model, in which DISC1 loss produced developmental deficits very similar to loss of NRG1 signaling, including failure of normal oligodendrocyte development and near total failure of olig2-positive cerebellar neuron development (Wood *et al*, 2009). The effect of psychotropic agents on these pathways provides an additional link to major mental illness. For instance, lithium activates Akt and inhibits GSK3β, whereas antipsychotic agents, by antagonism of D2 receptors, block the stimulatory effect of dopamine on Akt.

Overall, the convergence of genetic, pharmacological, and neurobiological data have opened the door to multiple novel potential therapeutic targets in the DISC1–Wnt–NRG1 systems, and this neurogenetic approach holds considerable promise for future research. For instance, the recent association of the MHC locus on chromosome 6p with schizophrenia (e.g., Stefansson *et al*, 2009) supports the long standing concept that environmental factors such as infection may have a role in schizophrenia, and provides a rationale for models of disease that encompass both genetic and environmental factors. Associations of neurogranin on 11q24.2 and transcription factor 4 (*TCF4*) on 18q21.2 with schizophrenia (Stefansson *et al*, 2009) may lead to new pathways with additional therapeutic targets. Psychiatric research has entered an era in which genetic findings implicate specific signaling pathways, leading to new insights into disease pathogenesis and the development of new approaches to therapeutics.

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Antidepressants, age, and neuroprogenitors

New neurons are generated in the granule cell layer of the dentate gyrus (DG) of the hippocampus in adult humans (Eriksson *et al*, 1998). Our knowledge of adult neurogenesis in humans is quite limited and it could differ from adult neurogenesis in lower mammals. In rodents, neurogenesis is necessary for learning, and some antidepressant effects are lost in the absence of adult neurogenesis, which increases with environmental enrichment and exercise (Olson *et al*, 2006), as well as with antidepressant treatment (Couillard-Despres *et al*, 2009).

We reported (Boldrini *et al*, 2009) that selective serotonin reuptake inhibitors and tricyclic antidepressants increase dividing and neural progenitor cells (NPCs) in the DG of depressed subjects (MDD), compared with untreated MDD patients or controls. In humans, antidepressants increase the number of mitotic cells of all phenotypes in the DG, regardless of age. On the other hand, replication of NPCs, as in lower mammals, decreases with age (Couillard-Despres *et al*, 2009). This might explain why there is a poor antidepressant response in the elderly.

The functional relevance of the enhancement of neurogenesis by antidepressants needs to be ascertained by determining whether increased cell proliferation is associated with improvement of symptoms in MDD. In our study (Boldrini *et al*, 2009), a significant proportion of subjects died by suicide, which would argue against the benefits of antidepressant-induced cell proliferation, as opposed to the potential benefits of cell maturation, survival, and integration into functional neural networks, which should have a greater role in the potential beneficial impact of adult neurogenesis. Exposure to enriched environments, learning, and neurotrophins improve the survival and differentiation of newborn cells. Factors regulating cell survival and integration should be considered when examining the role of adult neurogenesis for antidepressant efficacy.

Another open question is the role of neurogenesis in the pathogenesis of MDD. Adult neurogenesis decreases with stress in rodents and is enhanced by environmental enrichment, exercise, and antidepressants. However, blunted cell replication alone does not induce depression-like behavior in mice. Growth factors, which affect neurogenesis, are decreased in MDD. Therefore, impaired hippocampal plasticity may be involved in the pathogenesis of MDD, not merely because of impaired cell replication but also because of impaired cell connectivity and functional integration into brain circuits that regulate emotional responses to the environment.

In our study, the antidepressant-induced increase in NPCs and dividing cells was associated with a larger volume of DG. Antidepressant treatment is known to increase hippocampal volume in posttraumatic stress disorder (Bossini *et al*, 2007), but no similar data are available in depression, although patients with MDD have a smaller hippocampus. The volume increase could be related to a restoration of cell number or neuropil, as antidepressants reverse dendritic shrinkage and improve cell survival, activating the antiapoptotic protein Bcl-2 and brain-derived neurotrophic factor expression in mammals.

Future studies must determine whether antidepressant response is linked to increased neurogenesis, but assessing adult neurogenesis *in vivo* is challenging. In a recent study, magnetic resonance spectroscopy was proposed as a possible method, but the specificity of the molecule used to identify NPCs was questioned and the results have not been replicated. Positron emission tomography has the limitation of low resolution and the unknown consequences of radiolabeling newborn cells. Cerebral blood volume, which correlates with angiogenesis, may prove to be a viable method for detecting neurogenesis *in vivo* (Pereira *et al*, 2007). Linking neurogenesis to improvement in depression symptomatology would justify seeking new treatments that increase not only neurogenesis but also plasticity, cell survival, and integration into functional networks.

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