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DISC1 a key molecular lead in psychiatry and neurodevelopment: No-More Disrupted-in-Schizophrenia

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Since the middle of the past century, we have serendipitously come across treatment regimens that can partially ameliorate psychosis and depression. Nonetheless, the mechanisms underlying such severe mental conditions still remain elusive. Such lack of mechanistic insight into major mental illnesses has hampered the establishment of precise diagnostic framework, precluding further discovery of fundamental treatments for these disorders. Meanwhile, understanding of the brain at the molecular level has dramatically expanded, in particular by the identification of neurotransmitters and their receptors in the second half of the 20th century.

If we retrospectively view the scientific situation when the current century started, we can recall how scientists felt serious dilemma in the lack of understanding of several mental conditions at the molecular level, although the basic molecular neuroscience had advanced. In the year 2000, a group reported a molecule with the fascinating name, Disrupted–in-Schizophrenia 1 (DISC1), based on the unique finding of a familial aggregation of major mental illnesses.[1] It was very reasonable that people suddenly jumped onto this fascinating molecular lead, given that there had been a long-term gap in understanding molecular neuroscience and psychiatry.

DISC1 since 2000: two challenges

The findings were based on only a single Scottish family, and the segregation with schizophrenia and other psychiatric disorders due to the same chromosomal abnormality was unclear. Nonetheless, many groups suddenly began to explore the function of DISC1 to look for a clue for any severe mental condition. After the first paper providing a clear hint of DISC1's role in neurodevelopment,[2] many groups have demonstrated the crucial involvement of DISC1 in multiple processes of early brain development. The link between a

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molecule underlying psychiatric manifestation and neural development and signaling was featured among the top breakthrough discoveries in 2005.[3, 45]

Since then, multiple papers were featured in prominent scientific journals for a while.[6] However, when we retrospectively review the history of DISC1 research, we need to point out that the biological studies have moved forward by holding uncertainty in two scientific questions: first, it is unclear whether genetic variation of *DISC1* is involved in sporadic cases of schizophrenia; second, although DISC1 is a multifunctional intracellular hub protein, we still do not know which specific function of DISC1 underlies each endophenotype or phenotype in mental conditions.

To address the first question on genetic validity, Sullivan[7] pointed out that *DISC1* is unlikely to be an important "genetic" factor for schizophrenia defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM). This discussion is fairly valid, and we agree with this statement and conclude as "No-More *Disrupted-in-Schizophrenia*." Regarding the second question, Tsuboi et al.[8] have recently encouraged the field to reinforce the evidence that supports the role for DISC1 in early development.

Critical roles of DISC1 in early brain development: further validation now available

In response to the encouragement, a recent collaborative effort by multiple laboratories aimed to ascertain the validity of the role of DISC1 in early development of the cerebral cortex. In contrast to the Tsuboi group[8] that used a mouse model with deletion of exons 2 and 3 of the *Disc1* gene, the new study utilized a model in which a much larger deletion of the *Disc1* gene was accomplished through encompassing the region before exon 1 to exon 3 including a large intron 2 and introducing a spontaneous 25 base pair deletion in exon 6 [*Disc1* locus impairment model (*Disc1* LI model)].[9, 10] DISC1 is known to have many isoforms,[11] and it is crucial to deplete the genetic locus as long as possible to provide rigorous evidence of the maximal perturbation of the *Disc1* gene. In the *Disc1* LI model, the collaborative group now shows clear evidence of defects in progenitor cell proliferation and neuronal migration (Supplementary Figures 1 and 2).

Furthermore, the present study precludes potential off-target effects elicited by an RNAi construct[12, 13] that was used to show the involvement of DISC1 in progenitor cell proliferation and neuronal migration: The DISC1 RNAi construct does not affect the migration of *Disc1* LI mice in which the target sequences of RNAi were genetically depleted (Supplementary Figure 3).

Thus far, perturbation of DISC1 in early development has been linked to behavioral and cognitive changes in adulthood.[6] Thus, further validation of DISC1's role for early brain development in the present study reinforces the concept that functions of DISC1 in early brain development are very important to account for mental manifestations.

The bright promise of DISC1 protein as a molecular driver for the biology of mental illnesses

In the history of molecular psychiatry, DISC1 emerged as one of the most popular leads to explore molecular pathways underlying the pathophysiology of major mental conditions.[6] Although its significance in the unique Scottish pedigree is still undoubted, great advances in genome-wide association studies on schizophrenia and other major mental illnesses have dramatically changed the landscape in psychiatric genetics,[14] and have concluded that *DISC1* is not valid as a common risk gene for the DSM-diagnosed schizophrenia. However, despite the fact that multiple genetic loci have been reported by many genome-wide association studies, concrete molecular entry points for investigating biological mechanisms of mental illnesses remain obscure.

There are molecules that play critical roles in a wide range of brain pathological conditions beyond specific diagnostic classification in categorical approaches, such as the DSM. For example, the microtubule-associated protein Tau is the most crucial biological lead to study the pathology of Alzheimer's disease, and is also involved in other neurodegenerative conditions. Nonetheless, extensive human genetic studies have not provided any strong evidence that the *Tau* gene provides a common genetic risk for sporadic cases of Alzheimer's disease. This is pretty analogous to DISC1 in mental illness (weak “genetic” validity in sporadic cases of a specific disorder, but strong as a tool to study “biology” underlying a range of brain conditions). Interestingly, like the Tau protein,[15] phosphorylation of the DISC1 protein has a crucial role in brain function.[12] In summary, as of 2016, we can build further research on the bright promise of DISC1 “protein” as a molecular driver for the biology of mental illness (Figure 1).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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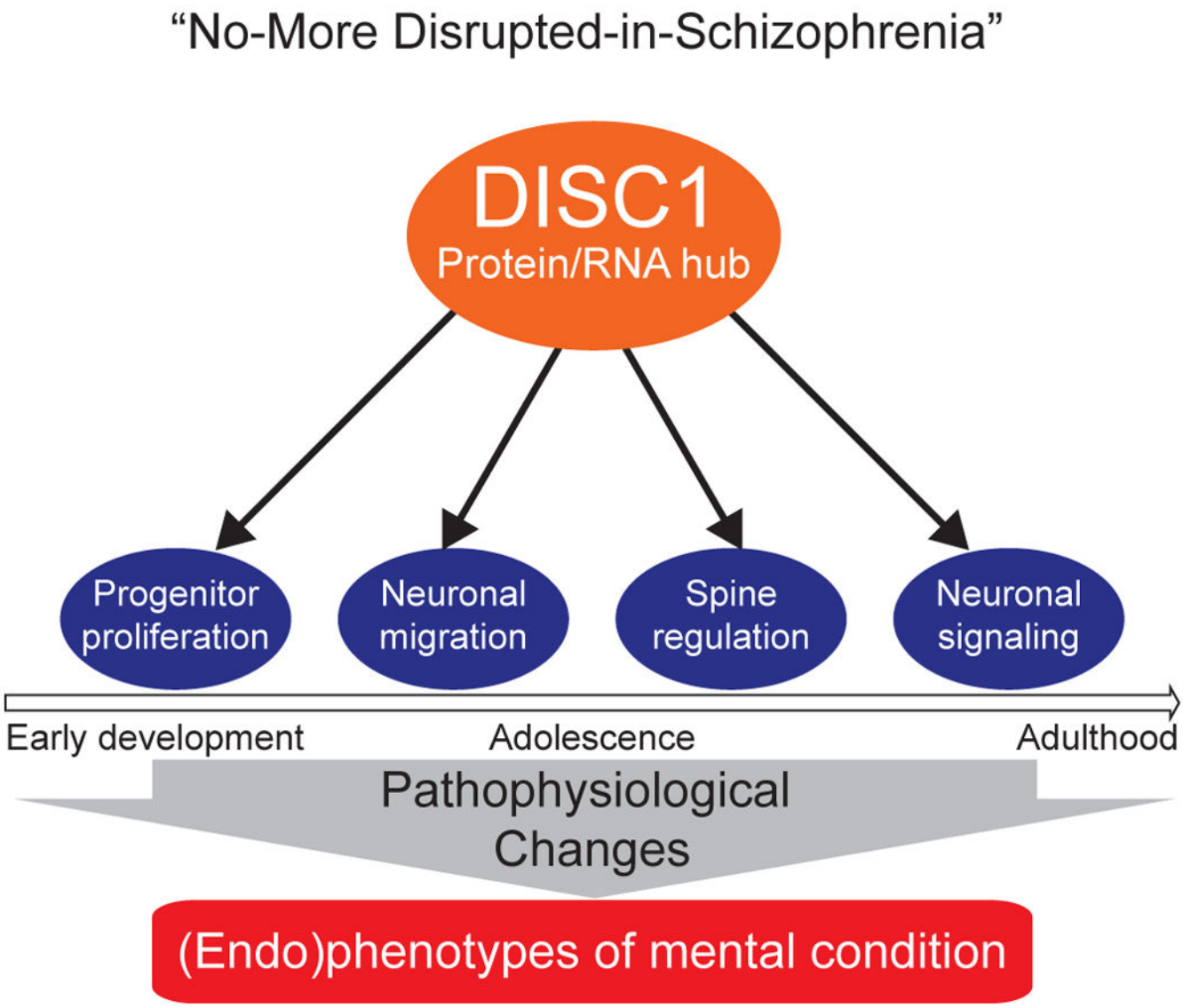

Figure 1.

DISC1 is an intracellular hub for protein/RNA networks that regulates progenitor proliferation, neuronal migration, dendritic spine formation, synaptic regulation, and neuronal signaling. Many lines of evidence have indicated that deficits of these neuronal processes, in particular those in early development, underlie circuitry and behavioral (endo)phenotypes relevant to a wide range of mental illness.