Biological Psychiatry: Celebrating 50 Years

DISC1 and Its Protein Interactomes for Mental Function

Akira Sawa

Advances in psychiatric genetics in the past decade have been amazing. The team effort at the global level has provided an invaluable encyclopedia. Furthermore, this information may be useful in identifying biomarkers and stratifying patients. Thus, its clinical utility may be high in the coming years. Nevertheless, it is unclear how much such rich information has contributed to a mechanistic understanding of disease pathophysiology. One concern is that the effect size of almost all genes identified by genome-wide association studies may be too small to generate model animals in an effective manner.

In research for neurological disorders, such as Alzheimer's disease and Parkinson's disease, in which biological and mechanistic dissection have been made successfully, variants found in rare familial cases have been used effectively. In parallel, investigators have examined tissues from patients and identified biological changes associated with the pathophysiology, such as aberrant phosphorylation of tau protein in patients with Alzheimer's disease. Key mediators in the disease pathophysiology may not necessarily be discovered through genetic studies. Together, successful research accomplishment in biology for neurological disorders may guide the future direction of biological psychiatry by looking beyond only genetic studies to identify key proteins and pathways that mediate the pathophysiology of psychiatric phenotypes. In short, well-balanced perspectives between genetic and nongenetic approaches may be productive for the future direction.

***DISC1:* No More *Disrupted in Schizophrenia*.** *DISC1* was first reported under the name "disrupted in schizophrenia" in a Scottish pedigree in which patients with major mental illnesses such as mood and psychotic disorders are extremely enriched (1). It is unclear why this gene was named *DISC1*, as the breakpoint of the balanced chromosomal translocation where the gene is disrupted was linked to several major mental illnesses, not specifically to schizophrenia. This initial report should be highly appreciated as a pioneering effort that brought molecular biology to psychiatry. Nevertheless, because of technical reasons in human genetics, Sullivan (2) noted that there is still some level of uncertainty whether we can solely attribute the occurrence of major mental illnesses to the disruption of the *DISC1* "gene." Furthermore, at least when we stand on the DSM-based categorical approach, we fail to observe a positive association between schizophrenia and the *DISC1* "genetic" locus (2).

In contrast, neurobiology built on a working hypothesis that the DISC1 "protein" may play a key role in the processes in a wide range of major mental illnesses has been productive (3). In this context, genetically engineered models for DISC1 have been used not to test the pathogenic or constructive validity of the gene for specific mental illness, such as schizophrenia; instead, they are used to validate how the DISC1 protein contributes to the biological processes or disease pathophysiology underlying major mental illnesses and neurodevelopmental disorders (4). Thus, biological study of DISC1 for mental illnesses, not specifically for schizophrenia, is well justified in analogy to successful precedence in biological study of tau for various neurodegenerative disorders.

DISC1 Protein in Major Mental Illnesses and Neurodevelopmental Disorders. The justification of studying DISC1 in biological psychiatry can stand on its implication at the protein level. Molecular implication in the protein context implies not only the level of the protein but also the post-translational modifications (e.g., phosphorylation, ubiquitination, and SUMOylation) and interaction with other proteins, called the protein interactome. Recent studies have reported the stability of DISC1 protein in conjunction with ubiquitination and interaction with other proteins (5,6). The regulatory mechanisms for DISC1 protein stability seem to be perturbed in pathological conditions, such as hypoxia (5), suggesting that this line of study is significant in the research of brain disorders. Phosphorylation of DISC1 at a specific amino acid residue plays a fundamental regulatory role in cortical development that may underlie key behavioral constructs associated with neurodevelopmental conditions (7). A comprehensive assessment of protein interactomes involving DISC1 was initially pioneered more than a decade ago by Camargo *et al.* (8). On the basis of such a fruitful history of research on the DISC1 protein, the article by Wilkinson *et al.* (9) in this issue of *Biological Psychiatry* addresses DISC1 protein interactomes in a cell type–specific manner by combining the cutting-edge technologies of human stem cell and clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 genetic engineering.

Cell Type-Specific DISC1 Interactomes: Its Implication in Biological Psychiatry. DISC1 protein is expressed not only in neurons but also in astrocytes and other glial cells (3). Although most studies on DISC1 thus far have been made in the context of neurons and progenitors, a number of studies have explored the role of DISC1 protein in nonneuronal cells, such as astrocytes. For example, astrocytic DISC1 but not neuronal DISC1 is involved in the negative impact of exposure to a cannabis constituent (Δ^9-tetrahydrocannabinol) during adolescence on recognition memory in adulthood in a cell type–specific fashion (10). Thus, addressing cell type–specific DISC1 protein interactomes may be the first step of addressing the biological mechanisms.

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Wilkinson *et al.* (9) inserted a 3X-FLAG coding sequence at the C-terminal end of the endogenous *DISC1* gene using CRISPR/Cas9 genome engineering in human induced pluripotent stem cells that differentiated into neural progenitors and astrocytes, respectively. Endogenous DISC1 binding partners were determined by immunoprecipitation of DISC1-FLAG followed by high-pressure liquid chromatography coupled to tandem mass spectrometry in cell type–specific settings. Wilkinson *et al.* (9) clustered three types of DISC1 protein interactors: those common to both cell types, those that are neural progenitor specific, and those that are astrocyte specific. Importantly, in the DISC1 interactome in neural progenitors, a significant enrichment of de novo nonsynonymous mutations in patients with schizophrenia and a suggestive enrichment of the mutations in patients with intellectual disability were observed when compared with control subjects. In summary, Wilkinson *et al.* (9) provide an example of how complementary knowledge of neurobiology and psychiatric genetics is fruitfully integrated to provide a mechanistic insight for major mental illnesses and neurodevelopmental disorders.

Significance in Studying DISC1 Protein in Biological Psychiatry: Future Perspectives. DISC1 protein serves as a critical hub to regulate multiple proteins, like a conductor of a symphony orchestra (3). Any conductor by her/himself is silent in generating individual sound, like the *DISC1* gene with no significant signals in most of genetic studies. Minor tuning problems with each member of the orchestra (e.g., a mutation with a modest effect size in each gene) may not result in a prominent issue by itself. However, at the level of overall functional coordination, the failure of the conductor in dealing with individual tuning problems, even if each problem is minor, may lead to a devastating outcome. Likewise, the deficits of DISC1 protein and its interactomes play a fundamental role in the pathophysiology of major mental illnesses.

Based on this conceptual framework, what will be near-future perspectives in research of biological psychiatry when we appreciatively use DISC1 protein as a molecular lead? First, we need to learn how the DISC1 protein coordinates the overall function of its interactome when multiple genetic variations impact the interactors at the mechanistic levels. Second, it is crucial to know how disease-relevant environmental stressors may influence posttranslational modifications of DISC1, such as phosphorylation, ubiquitination, and oxidation. Accordingly, DISC1 may mechanistically serve as a hub of gene and environmental interactions. Third, because protein interactomes include cell type–specific nature as featured here (9), the knowledge will help understand the disease mechanisms from a neuron–glia interaction viewpoint.

In conclusion, whom do you care for more: Leonard Bernstein, or each individual player in the New York Philharmonic? Probably both, which may be my answer. However, some may say, “I love Lenny.”

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Article Information

From the Departments of Psychiatry, Neuroscience, Mental Health, and Biomedical Engineering, Johns Hopkins University School of Medicine and Bloomberg School of Public Health, Baltimore, Maryland.

Address correspondence to Akira Sawa, M.D., Ph.D., Johns Hopkins University School of Medicine and Bloomberg School of Public Health, Departments of Psychiatry, Neuroscience, Mental Health, and Biomedical Engineering, 600 N Wolfe St, Baltimore, MD 21287; E-mail: asawa1@jhmi.edu.

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