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The potential of DISC1 protein as a therapeutic target for mental illness

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1. Brief review of DISC1 history

The *DISC1* locus and its protein product(s) have received broad attention during the past 15 years in the context of psychiatric illness [1]. The initial impetus was the original discovery of a balanced translocation that segregated in a pedigree with schizophrenia and depression [2]. In more recent years, the interrogation of large cohorts with psychiatric illness has found modest, sometimes contradictory, evidence for the role of *DISC1* as a “genetic” contributor to sporadic cases of schizophrenia [3]. At the same time, studies in cells and model organisms highlighted both the transcriptional and translational complexity of the locus and its involvement in biological processes critical for neurodevelopment and homeostasis [1]. These findings have become directly relevant to our understanding of disease processes; compelling evidence now indicates that several pathways involving DISC1 and its protein network play pivotal roles in the pathobiology of overlapping mental illnesses that include schizophrenia, autism, and mood disorders [1,4]. As such, irrespective of the hotly-debated “genetic” question of whether *DISC1* common or rare variants provide major genetic burden of schizophrenia, the potential value of the DISC1 protein as a “biological” beacon for rational drug discovery towards a variety of neuropsychiatric illnesses is clear.

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Declaration of interest

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2. DISC1 interacting proteins: addition of several exciting molecules

Consistent with its broad role(s) in brain development and homeostasis, DISC1 can bind to over 100 proteins. In the context of neuropsychiatric disorders, several members of signaling pathways that affect higher brain function have merited particular attention. These include cAMP-dependent phosphodiesterase 4 (PDE4), glycogen synthase kinase 3 β (GSK3B), Kalirin-7, and pericentriolar material 1 (PCM1) [1,5,6]. Excitingly, some of these targets are amenable to therapeutic intervention, with data suggesting efficacy in modulating brain function, at least in preclinical models. For example, a PDE4 inhibitor rolipram has been validated for depression and anxiety in preclinical models. Furthermore, this compound was tested clinically for depression. A major drawback of PDE4 inhibitors is that they show significant side effects, including nausea and emesis, due to inhibition of some PDE4 isoform(s). Thus, development of isoform-specific PDE4 inhibitors that may minimize such side effects is being considered. In the context of DISC1-GSK3B, Tideglusib (aka NP-12) and lithium are known GSK3B inhibitors, albeit with debatable specificity. Finally, the DISC1-PCM1 interaction and the postulated role in ciliary-driven neuropsychiatric disorders have raised the possibility that emergent ciliary therapeutic agents, such as sulforaphane, might be of benefit [7].

More recently, two intriguing reports suggested additional lines of investigation for candidate therapeutics. One report identified dopamine D2 receptors (D2Rs) as novel protein interactors of DISC1 [8]. The major molecular targets of current antipsychotic drugs include D2Rs. However, such drugs also elicit side effects, most notably extra-pyramidal symptoms (EPS) and metabolic problems. Thus, identifying a specific D2R signaling pathway that could be targeted for antipsychotic effects without inducing EPS, would be a significant improvement in the treatment of schizophrenia. The study reports that the D2Rs form a protein complex with DISC1 that modulates D2R-mediated GSK3B signaling and inhibits agonist-induced D2R internalization [8]. An increase in the levels of D2R-DISC1 interaction and a reduction in the levels of GSK3A/B (Ser21/9) phosphorylation have been observed in both postmortem brains from patients with schizophrenia and in a genetically-engineered model for *Disc1* (Disc1-L100P mutant mice) [8]. Administration of an interfering peptide that disrupts the D2R-DISC1 complex reverses behavioral deficits in the model without inducing catalepsy, a strong predictor of EPS in humans [8].

The second report focused on the potential of the DISC1-Kalirin-7 interaction for new drug discovery avenues [9]. Disturbances in the signaling downstream of the DISC1- Kalirin-7 lead to the deterioration of glutamatergic synapses via dysregulation of p21-activated kinases (PAKs). Synaptic pathologies, in particular those involving the glutamatergic neurotransmission, have been observed frequently in brains from patients with schizophrenia [10]. Thus, selective PAK inhibitors were used to test whether they could block synaptic changes elicited by DISC1 knockdown. One of these PAK inhibitors (FRAX486), which penetrates the blood brain barrier well, prevented progressive synaptic deterioration in adolescence as shown by *in vivo* two-photon imaging, and ameliorated a behavioral deficit in prepulse inhibition in adulthood in a DISC1 knockdown mouse model. Daily administration of FRAX486, but not that of vehicle, between postnatal day 35 (P35) and

P60, significantly blocked the exacerbated spine loss during adolescence, and also showed a trend of enhanced spine generation [9].

In summary, because DISC1 is a hub protein of neurosignaling that underlies higher brain function, drug discovery stemming from the understanding of molecular cascades involving DISC1 may be a promising strategy.

3. Modulation of DISC1 protein stability

The biological significance of the Scottish mutation (disruption of the *DISC1* gene open reading frame) has been discussed in multiple ways. However, one clear consensus derived from biological studies is that loss of DISC1 function can result in molecular cellular disturbances in the pathology of mental illness (e.g., synaptic and dendritic changes) which then lead to behavioral deficits relevant to schizophrenia and depression, as seen in multiple clinical models [1]. In addition to the use of RNAi technology, at least three hereditary mouse models that were designed to achieve haploinsufficiency of DISC1 (e.g., knocking out some exons) have represented, at least to reasonable extent, key features of neuropsychiatric conditions [11–13].

Therefore, modulating the protein stability of DISC1 may be a target for understanding underlying pathology and for an alternative drug discovery by using these loss-of-function cellular and animal models as templates. Motivated by these ideas, some studies have explored the half-life of the DISC1 protein in the context of possible posttranslational modifications known to regulate protein stability, such as ubiquitination and SUMOylation. For example, a recent report suggested that the half-life of DISC1 was affected by its subcellular conditions (e.g., interaction with other proteins and subcellular distribution), as well as by environmental conditions, such as hypoxic stress. More concretely, in undifferentiated PC12 cells, the half-life of DISC1 protein (2.7 h) is significantly prolonged by co-expression of PDE4B2 (> 6 h), whereas hypoxic stress robustly reduces the DISC1 protein level in PC12 cells as compared to the normoxic condition [14]. As such, screening compounds that directly or indirectly interact with DISC1 and affect its stability may be an interesting approach to drug discovery for mental disorders as well as, more broadly, for brain conditions that involve hypoxia. Note that DISC1 is intrinsically amyloidogenic [1], and this nature may also need to be taken into consideration.

4. Technical cautions in biological experiments on DISC1

DISC1 is an attractive tool molecule to help us understand the biology of higher brain function and the pathobiology of major mental illness, with obvious potential investigative extensions into drug discovery. At the same time, it is important to highlight several technical challenges that persist and can hinder or confuse investigations. First, the *DISC1* locus encodes multiple isoforms, the relative functionality of which is not yet clear, in part because antibodies against this molecule (and its variants) are either unavailable or partially characterized [1,15]. Such technical challenges have occasionally caused debates in the scientific data, in particular in the context of the specificity of RNAi-derived phenotypes [1,13]. To overcome such challenges and to help normalize the reproducibility of

observations, experts in this area have come together to propose a set of experimental standards [1]: the use of multiple RNAi constructs targeting different regions of DISC1 is recommended; the RNAi experiments should be combined with a rescue experiment by co-expressing a known DISC1 isoform, such as full-length isoform L; if one needs to rely on antibodies, at least pairs of antibodies against DISC1 should be used in immunoprecipitation-Westerns. Major studies that have established the roles for DISC1 in neurodevelopment and synaptic signaling have satisfied the criteria [1].

5. Expert opinion

In this editorial, we provide general perspectives of DISC1 in possible drug discovery, by highlighting recent articles that may directly influence the strategy. The major findings of DISC1 research for the past 15 years include the protein network involving DISC1 that mediates higher brain functions, whereas there are several technical limitations, as described above. One of the intriguing examples that utilizes the scientific knowledge is to interfere with the DISC1 and D2R protein interactions, which reportedly blocks aberrant behaviors relevant to major mental illness, without eliciting adverse effects, at least in a preclinical animal model. Likewise, the ultimate goal of this field is to apply basic information of the DISC1 protein network to therapeutic intervention strategies.

In the Scottish pedigree in which the *DISC1* gene was originally identified, the disruption of the gene leads to a wide range of major mental illnesses, rather than one specific disorder. Meanwhile, the disruption is tightly associated with the alteration of an event related potential P300 [2]. This finding is reminiscent of a recent proposal by the Research Domain Criteria (RDoC), in which molecular signatures are considered to underlie physiological and behavioral characteristics, rather than disease entities categorized by operational diagnostic criteria, such as Diagnostic and Statistical Manual of Mental Disorders (DSM) [4]. We believe that the drug discovery stemming from DISC1 and its protein interactors will target specific behavioral and biological constructs that underlie mental illnesses (e.g., working memory deficits and social cognition), rather than single disorder (e.g. schizophrenia or depression).

DISC1 is a hub protein with a variety of binding partners. Thus, it is important to reinforce the scientific knowledge in regard to the specificity of DISC1 and each protein partner, which includes information on specific binding domains of DISC1 for each protein. It is also crucial to point out how the DISC1 protein network overlaps and interacts with the biological pathways that have been highlighted by comprehensive genetic studies. Intervening with “specific” biological pathways and protein interactions is a novel opportunity for drug discovery, but the validation of the “specificity” will be the most crucial issue and challenge in order to avoid unexpected side effects. Given that induced pluripotent stem cells and genetically-engineered mice of DISC1 are currently available [1], these models will serve as useful templates to validate the specificity and potential side effects elicited by the intervention through DISC1 and its protein interactors. We optimistically predict that the novel protein network-based strategy, different from classical approaches that directly target receptors, channels, and enzymes, will open a new window in translational psychiatry.

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