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DISC1 as a therapeutic target for mental illnesses

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Abstract

Introduction—Many genetic studies have indicated that *DISC1* is not merely “*disrupted-in-schizophrenia*,” but is more generally implicated in various brain dysfunctions associated with aberrant neurodevelopment and intracellular signaling pathways. Thus, the *DISC1* gene is mildly associated with a variety of brain disorders, including schizophrenia, mood disorders, and autism. This novel concept fits with the results from biological studies of *DISC1*, which include cell and animal models.

Areas covered—We review the molecular structure and functions of *DISC1*, particularly those in conjunction with its important interactors. Functions of these interacting proteins are also introduced under the concept of the “*DISC1* interactome.” Finally, we discuss how the *DISC1* interactome can provide potential therapeutic targets for mental illnesses.

Expert opinion—Modulation of *DISC1* stability and post-transcriptional modifications may be key targets to address *DISC1*-related pathology. In addition, modulation of *DISC1* interactors and the mechanisms of their interactions with *DISC1* may also provide drug targets. *Disc1* rodent models can subsequently be used as templates for *in vivo* validations of compounds designed for *DISC1* and its interacting proteins. Furthermore, these rodents will serve as genetic models for schizophrenia and related conditions, especially in conjunction with their pathologies during the neurodevelopmental trajectory.

Keywords

DISC1; interactome; schizophrenia; depression; bipolar disorder; autism; mental illnesses; psychiatric diseases; mouse models

1. Introduction

Since the initial report that described a translocation mutation segregating with major mental illnesses in a Scottish pedigree, Disrupted-in-schizophrenia 1 (*DISC1*) has been expected as a “special” molecule in psychiatry [1–3]. Has *DISC1* met this expectation? A recent meta-analysis did not strongly support the idea that common variants of the *DISC1* gene are associated with schizophrenia [4]. Furthermore, genome-wide association studies have failed to identify *DISC1* as a promising gene associated with schizophrenia and bipolar disorder

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[5–8]. In contrast, accumulating studies have shown that genetic variations of *DISC1* affect general brain structure and function, including cortical thickness, hippocampal gray matter volume, white matter integrity, auditory event-related potential, and prefrontal-associated cognitive functions [9–21]. Furthermore, recent studies have associated *DISC1* with a variety of mental and physical diseases, such as mood disorders (e.g., bipolar disorder and major depression), schizoaffective disorder, autism, Asperger syndrome, chronic fatigue syndrome, and callosal agenesis [12, 22–30]. Recent biological approaches studying cellular functions of *DISC1* have shown that *DISC1* is a multifunctional protein involved in long-term neurodevelopmental processes [31]. Dissection of these functions and dysfunctions will be required when considering *DISC1* as a therapeutic target in mental illnesses.

2. Structure and function of *DISC1* and its key interactors

Before we discuss the potential of *DISC1* as a drug target, we will briefly introduce the structure, motifs, and post-translational modifications of *DISC1*. In addition, as *DISC1* functions via interactions with a range of other proteins, we will introduce the key protein interactors.

2.1. Structure, motifs, and post-translational modifications of *DISC1*

The human *DISC1* protein has 854 amino-acid residues in the full-length form, but also exists as a variety of isoforms (see a review by Ishizuka *et al* [32]). It has no clear functional domains, such as specific enzymatic domains (e.g., kinase and catalytic domains) and transmembrane domains that may imply a possible function as receptor or transporter. However, *DISC1* has conserved nuclear localization signals (Fig. 1). Amino acid substitutions in nuclear localization signal-1 (NLS1; amino acids 35–43) abolish nuclear localization of *DISC1* [33]. NLS2 (amino acids 331–346) and nuclear export signals (NESs; amino acids 504–513, 546–555, and 621–631, respectively) also affect the cellular/nuclear distribution of *DISC1* [33]. In patients with sporadic schizophrenia, major depression, and substance/alcohol abuse, a nuclear form of *DISC1* is increased [34]. This finding suggests that modulation of the nuclear localization/export signals of *DISC1* has significant functional consequences and may be a potential therapeutic strategy.

DISC1 appears to play an important role in other subcellular compartments, e.g. mitochondria [35, 36] and centrosome [37, 38], as well as in the presynaptic terminal [39], and dysfunctional localization may contribute to disease phenotypes. In addition, it has recently been shown that *DISC1* can form protein aggregates, reminiscent of the proteinopathy observed in Alzheimer's and Parkinson's disease [40, 41]. This aggregation can affect a wide variety of *DISC1* functions, for example, disrupt its role in the intracellular transport of mitochondria [40].

DISC1 contains a self-association domain in the middle portion of the protein (amino acids 403–504), which harbors a well-conserved coiled-coil motif (Fig. 1). *DISC1* forms a protein homodimer via the self-association domain [38]. The mutation in the Scottish pedigree may give rise to a putative C-terminal-truncated *DISC1*, which leads to misdistribution of wild-type *DISC1* by their dimerization via the self-association domain, and results in a dominant-negative function [38].

DISC1 has post-translational modifications, which contribute significantly to the function of this protein. Human *DISC1* has at least three phosphorylation sites: threonine 50 (T50), serine 58 (S58) and serine 713 (S713); the two serine phosphorylation sites are conserved as S54 and S710 in mouse *DISC1*, respectively (Fig. 1). The functional influences of phosphorylation at S713 have been well studied [42]. Unphosphorylated *DISC1* normally binds to glycogen synthase kinase 3 β (GSK3 β) and upregulates Wnt/ β -catenin signaling

activity to promote progenitor proliferation [42]. However, phosphorylation of DISC1 triggers an interaction with Bardet-Biedl Syndrome (BBS) proteins at the centrosome, and activates the developmental switch from progenitor proliferation to postmitotic neural migration [42].

Thus far, many studies have indicated that DISC1 is a scaffold protein that is involved in many biological processes via various interacting proteins [3, 31, 32, 43, 44]. The structural motifs described above appear to underlie the regulation of these protein-protein interactions, and may point to potential therapeutic targets.

2.2. DISC1 interacting proteins

DISC1 binds over one hundred proteins, including many structural proteins as well as those involved in critical signaling pathways [3, 31, 32, 43, 44]. Here, we introduce some of these proteins that may be particularly relevant to drug discovery for mental illnesses. Fig. 1 shows the binding sites for these interacting proteins, and Fig. 2 shows the DISC1 binding partners in the interactome.

2.2.1. cAMP-dependent phosphodiesterase 4 (PDE4)—DISC1 interacts with cAMP-dependent phosphodiesterase 4 (PDE4), an enzyme that degrades cyclic adenosine 3', 5'-monophosphate (cAMP) [45, 46]. Cyclic AMP is a ubiquitous signaling molecule with many roles throughout the central nervous system, but is particularly relevant to cognitive functions via the prefrontal cortex (PFC) [47, 48], amygdala [49] and hippocampus [50–52], and plays a key role in mental illnesses [48]. Four genes, *PDE4A/B/C/D*, encode the PDE4 family of proteins [46]. DISC1 has two common binding sites for all isoforms (amino acids 190–230 and 611–650) and three PDE4B-specific binding sites (amino acids 31–61, 101–135, and 266–290) [45, 53]. Cyclic AMP plays a key role in cognitive function and its impairment in mental illnesses [47, 48]. Thus, the DISC1/PDE4 interaction may be particularly important for regulating cAMP signaling in the pathophysiology of mental illnesses [45].

2.2.2. Glycogen synthase kinase 3 β (GSK3 β)—Mao *et al* [54] have found that two different domains of DISC1 (amino acids 1–220 and 356–595) are directly associated with purified GSK3 β in an *in vitro* binding assay. The DISC1 fragment at amino acids 195–238 directly regulates GSK3 β / β -catenin/Wnt signaling by inhibiting GSK3 β catalytic activity, which in turn reduces β -catenin phosphorylation and stabilizes β -catenin [54]. The GSK3 inhibitor SB-216763 can normalize the impairment of progenitor proliferation as well as schizophrenia- and depression-like behavioral defects induced by a *Disc1* knockdown in adult mice [54], indicating that the DISC1-GSK3 β interaction is a possible therapeutic target for mental illnesses.

2.2.3. Traf2 and Nck-interacting kinase (TNIK)—Wang *et al* [55] have reported that Traf2 and Nck-interacting kinase (TNIK) interacts with DISC1 via a 13-amino acid region (amino acids 335–347). TNIK is a serine/threonine kinase from the Ste20 kinase family, and has been associated with schizophrenia and bipolar disorder by independent studies [7, 56, 57]. DISC1 and TNIK colocalize in the brain and are enriched in postsynaptic density (PSD) fractions, and DISC1 inhibits the kinase activity of TNIK in cells [55]. Inhibition of TNIK has been shown to reduce PSD proteins and excitatory synaptic transmission, while knockdown of *Disc1* leads to an increase in some of the PSD proteins [55]. Thus, inhibition of TNIK is likely to restore at least some aspects of this interaction to treat excitatory synaptic dysfunction frequently observed in many mental illnesses [58–60].

2.2.4. Kalirin-7—DISC1 interacts directly with kalirin-7 (Kal7), a GDP/GTP exchanging factor (GEF) for Ras-related C3 botulinum toxin substrate 1 (Rac1), which regulates spine morphology and plasticity in an activity-dependent manner [61]. Hayashi-Takagi *et al* [62] have reported that DISC1 augments Kal7/PSD-95 interaction in the spine via the Kal7-binding domain of DISC1 (amino acids 350–394). Activation of NMDA-type glutamate receptors results in the dissociation of this DISC1-Kal7-PSD-95 protein complex, allowing Kal7 to bind to Rac1 to induce proper spine enlargement. The effects of constitutively active Rac1 on dendritic spine resemble those elicited by knockdown of *Disc1*, in which activation of Rac1 initially leads to rapid spine growth, but continuous activation eventually results in spine shrinkage [62]. These results indicate that DISC1/Kal7/Rac1 signalosome regulates glutamatergic synaptic transmission and spine morphology, which are disturbed in schizophrenia [58–60, 63, 64].

2.2.5. Activating transcription factor 4 (ATF4)/cAMP response element binding protein 2 (CREB2)—Immuno-electron microscopy in the human neocortex have revealed that a pool of DISC1 protein is localized in the nucleus in association with chromatin structures [65]. In the nucleus of mammalian cells, DISC1 colocalizes with promyelocytic leukemia (PML), a main component of nuclear body-mediating gene transcription [33]. DISC1 also interacts with activating transcription factor 4 (ATF4)/cAMP response element binding protein 2 (CREB2) and the nuclear receptor corepressor N-CoR, and then modulates cAMP response element (CRE)-mediated gene transcription [33]. Sleep homeostasis is known to be regulated, at least in part, via CREB signaling [66]. Transgenic fruit flies with exogenous human DISC1 expressed in the nucleus show disturbances in sleep homeostasis [33]. These two independent observations may be interpreted by the hypothesis that nuclear DISC1 is involved in sleep. Three functional *cis*-elements, NLS1, nuclear export signal 2 (NES2) and the leucine zipper (LZ) domain, in the DISC1 protein appear to regulate the balance of nuclear and non-nuclear DISC1 [67]. As sleep disturbances are observed in many mental illnesses [68], these *cis*-elements may be targeted to restore the appropriate nuclear localization of DISC1. Whether to increase or decrease the accumulation of nuclear DISC1 would depend on the nature of the DISC1 mutation, and is yet to be determined *in vivo*.

2.2.6. Nuclear distribution protein nudE-like 1 (Ndel1)—DISC1 and nuclear distribution protein nudE-like 1 (Ndel1) interact at the centrosome, and this interaction mediates neurite outgrowth, neuronal migration in cortical development, and adult newborn neuron development in the dentate gyrus [69, 70]. Ndel1 binds the C-terminal domain of DISC1 (amino acids 802–835) [35], and this binding site is lost in the putative truncated protein in the *DISC1* translocation mutation in the Scottish pedigree, in which *DISC1* was initially discovered [71]. Ndel1, also known as endo-oligopeptidase A (EOPA), is a cysteine protease and has oligopeptidase activity, which is inhibited by DISC1 in *in vitro* assays [72]. Ndel1/EOPA inactivates bioactive peptides such as bradykinin and neurotensin, and converts opioid oligopeptides into enkephalins [73–75]. A recent study has shown that the endo-oligopeptidase activity of Ndel1 plays a crucial role in the differentiation process of PC12 cells to neurons [76]. Inhibitors for Ndel1-EOPA activity may thus be a candidate target for mental illnesses [77]. Furthermore, it has recently been found that the DISC1-NDEL1 pathway is complemented by a parallel interaction between DISC1 and Fasciculation and Elongation Protein Zeta-1 (FEZ1) [78].

3. Expert opinion

Basic studies of DISC1 and its interactors will provide critical information for developing novel therapies in at least two respects: first, these molecules can become drug targets; second, animal models in which these molecules are manipulated reportedly display behavioral and neurochemical changes relevant to mental illnesses, such as schizophrenia.

These models can then be utilized to aid drug discovery, in addition to serving as tools to understand how DISC1 and its interactors function in the brain.

3.1. Drug discovery by direct modulation of DISC1

3.1.1 Modulation of DISC1 protein stability—The significance of the Scottish mutation has been debated [3, 79]: this truncation in the middle of the open reading frame of the *DISC1* gene may result in degradation of the protein, leading to “haploinsufficiency” [45]. Alternately, a C-terminal truncated DISC1 protein may be generated. Several studies have indicated that this putative truncated protein has a “dominant-negative” function, impairing functions of the wild-type allele [35, 38]. These hypotheses are reconciled by the notion that, in either scenario, an overall loss of DISC1 function underlies the pathology elicited by the Scottish mutation [38]. Consistent with this notion, many studies have shown aberrant brain development and functions in the presence of *Disc1* RNAi, (knockdown of *Disc1*) [38, 54, 80]. These results indicate that, at least, loss of DISC1 is not favorable for proper brain function. Therefore, compounds that directly or indirectly stabilize the DISC1 protein may be powerful drug candidates.

3.1.2 Modulations of post-translational modifications of DISC1—Phosphorylation and other post-translational modifications likely modulate DISC1 function. For example, phosphorylation at the S713 residue of the human DISC1 protein (S710 of mouse DISC1) facilitates a switch from progenitor proliferation to postmitotic neuronal migration in the developing cortex [42]. The phosphorylation status of DISC1 also determines the subcellular distribution of DISC1 and its interactors: Phospho-DISC1 at S713 co-localizes with BBS proteins at the centrosome, whereas non-phosphorylated DISC1 is more widely distributed in the cytoplasm [42]. Post-translational modifications of other residues of DISC1 can modulate its nuclear targeting, and possibly affects interactions of nuclear DISC1 with ATF4/CREB2 (Ishizuka, Sawa: unpublished observations). Given that the disturbance of proper protein-protein interactions within the DISC1 interactome is appreciated as a possible mechanism for mental illness [3], modulation of such post-translational modifications of DISC1 may be a useful therapeutic target. For example, the S713 residue of DISC1 can be phosphorylated by both protein kinase A (PKA) and cycline-dependent kinase 5 (cdk5) [42]. Cdk5 inhibitors CP-681301 and CP-668863 have been considered as potential therapeutics for Alzheimer’s disease [81], and may also target other neural and cognitive dysfunctions [82]. The role of phosphorylation and other post-translational modifications of DISC1 at the synapse remain elusive, but will likely play key roles in synaptic transmission. Further basic studies on post-translational modifications of DISC1 proteins may open many avenues to utilize these paradigms for future drug discoveries for mental illnesses.

3.2. Drug discovery by modulating DISC1 interacting proteins

DISC1 is by nature a scaffold protein that interacts with many other proteins with a variety of functions. Thus, many experts of drug discovery may hesitate to modulate its function directly, due to the potential for unintended effects on other DISC1-mediated signaling pathways. However, DISC1 modulates many signaling cascades via its many protein interactors, many of which have been independently associated with mental illnesses. These pathways can then be specifically targeted to normalize aberrant neural mechanisms in these disorders. In fact, for some of these proteins that are enzymes, activators and inhibitors are already available in clinical trials. In addition, small molecule microarray screening pioneered by the Haggarty group is a promising approach to find compounds that can modulate specific protein-protein interactions [83].

Several selective PDE4 inhibitors (e.g., cilomilast and roflumilast) are already being explored to treat inflammatory respiratory diseases, such as chronic obstructive pulmonary

disease (COPD), although these compounds appear to have low blood-brain barrier permeability [84]. Another inhibitor, rolipram, has been clinically tested for depression [85], and has also been found to readily cross the blood-brain barrier [86]. A major drawback of PDE4 inhibitors is that they show significant side effects, including nausea and emesis, due to inhibition of the PDE4D isoform [87]. Possible isoform-specific PDE4 inhibitors have been reported [88], which may minimize these side effects. Basic knowledge of how DISC1 regulates PDE4 activities will aid the development of more optimized compounds, and will help to treat cognitive dysfunction observed in many mental illnesses.

DISC1 inhibits the activity of GSK3 β to promote progenitor proliferation in the brain. Tideglusib (previously known as NP-12) is a selective GSK3 β -inhibitor in the phase IIb clinical trial for Alzheimer's disease [89]. In addition, lithium, frequently used for the treatment of bipolar disorder and related conditions, may exert its therapeutic effects in part via inhibition of GSK3 β [90].

DISC1 regulates Kal7 [62], which is known to activate Rac1 and p21-activated kinase (PAK) [91]. The Rac inhibitor, NSC23766, and the PAK1 inhibitor, 2,2'-dihydroxy-1,1'-dinaphthylidene (IPA-3), are preclinical reagents for a novel oncologic therapy [92, 93]. It may be worthwhile to test whether such compounds can block synaptic pathologies relevant to mental illnesses, including deterioration of synapses induced by *Disc1* knockdown [38].

Finally, TNIK and Ndel1 comprise kinase and endopeptidase activities, respectively. We are not aware of currently available compounds for these targets. However, compounds that target these enzymatic activities may aid in treating disorders associated with impaired excitatory synaptic transmission, such as schizophrenia. As mentioned above, a TNIK inhibitor may help to restore excitatory synaptic function, while a Ndel1 inhibitor may normalize such processes as neurite outgrowth, neuronal migration and adult neuronal development.

3.3. DISC1 animal models as templates for *in vivo* assays

Thus far, ten different types of *Disc1* rodent models have been published [54, 80, 94–100]. The detailed descriptions of each model and comparisons of their phenotypes have been fully reviewed in recent articles, including the complexities of DISC1 isoforms among different strains [3, 31]. Therefore, here, we highlight the phenotypes that can form the basis for *in vivo* validation of target compounds for mental illnesses.

3.3.1. Behavioral changes—The majority of *Disc1* mouse models show overlapping behavioral phenotypes (Table 1A). For example, they show deficits in prepulse inhibition, a measure of sensory-motor gating function [80, 94, 95, 100], as well as impairments in working memory and latent inhibition [95, 96, 98, 101]. These findings indicate that *Disc1* mouse models have common pathological changes related to the prefrontal cortex. In addition, many *Disc1* animal models show increased immobility in the forced swim test [54, 94–96, 98, 102], which is used to test the efficacy of antidepressants [103]. As the *DISC1* mutation initially discovered in the Scottish pedigree is associated with both mood disorders and schizophrenia [104, 105], these mouse models may be utilized as templates for schizophrenia, mood disorders, or mixed conditions of these two clinical manifestations. Interestingly, Clapcote *et al* [95] have presented two *Disc1* missense mutant mice that have distinct behavioral, biochemical, and pharmacological phenotypes. In particular, mice with a Gln31Leu mutation show reduced responsiveness to rolipram relative to mice with a Leu100Pro mutation [95]. These findings suggest that such genetic models can be used for pharmacogenomic studies of *Disc1*.

3.3.2. Histological changes—Many *Disc1* mouse models have modest but significant histological changes (Table 1B). Reduction of parvalbumin immunoreactivity in the interneurons in the medial prefrontal cortex is observed in several *Disc1* animal models [80, 94, 97, 98]. In addition, pyramidal neurons in some mouse models show abnormalities in dendrite and spine density [80, 106]. In addition, some models show impaired adult hippocampal neurogenesis [70, 107]. Finally, brain MRI scans reveal signs of reduced brain volume and enlarged lateral ventricle in some *Disc1* models [94, 95, 97], and thus may be useful in testing the efficacy of compounds that may ameliorate these changes.

3.3.3. Developmental trajectory: a possible template to develop preventive medications?—Although drug-induced models of mental illnesses, such as those with phencyclidine (PCP) in adulthood [108, 109], are useful as templates for drug discovery, these models may not reflect an important pathological feature of major mental illnesses, that is, the neurodevelopmental trajectory of their pathology [31, 110, 111]. As many studies have indicated, DISC1 is highly expressed in the developing brain and plays a key role in neurodevelopment [31, 32, 112]. Thus, a major advantage of genetically-engineered *Disc1* models is that they can potentially mimic neurodevelopmental deficits, which eventually contribute to the neurochemical and behavioral abnormalities in adulthood. For example, transient knockdown of *Disc1* in pyramidal neurons of the frontal cortex during early development leads to behavioral and neurochemical abnormalities after puberty [80]. This model thus resembles the time course of the onset of schizophrenia in humans. *Disc1* models have also proven to be useful for examining potential gene-environment interactions in disease etiology: administration of polyriboinosinic polyribocytidylic acid (polyI:C) during early development, which mimics innate immune activation, augments the behavioral and histological phenotype of *Disc1* mutant mice [102, 113]. Therefore, *Disc1* models are particularly useful when testing compounds that may target neurodevelopmental processes underlying the pathology of mental illnesses, including those that possibly prevent or delay the onset of the disease.

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Article highlights

- *DISC1* gene is associated with a variety of brain disorders.
- DISC1 has many biological functions via its post-transcriptional modifications and interactions with various binding partners, which may provide therapeutic targets for mental illnesses.
- *Disc1* rodent models may be useful as genetic models that may mimic neurodevelopmental trajectory and some endophenotypes underlying of major mental illnesses.

Fig. 1. Functional domains and interactors of DISC1 protein

The self-association domain, phosphorylation sites, leucine zipper (LZ) motif, nuclear localizing signals (NLSs), and nuclear export signals (NESs) are indicated. Amino acid numbers of the binding sites in human DISC1 protein are indicated for its interacting molecules [33, 53–55, 62, 69]. PDE4, phosphodiesterase 4; B, PDE4B isoform; B/D, PDE4B and D isoforms; GSK3β, glycogen synthase kinase 3β; TNIK, Traf2- and Nck-interacting protein kinase; ATF4, activating transcription factor 4; Kal7, kalirin-7; Ndel1, nuclear distribution protein nudE-like 1.

Fig. 2. Potential therapeutic candidates in the DISC1 interactome

DISC1 interacts with its binding partners to modulate cellular signaling and other biological functions. Several inhibitors for enzymes that are modulated by DISC1 signaling pathways may be therapeutic candidates for mental illnesses. cAMP, cyclic adenosine 3',5'-monophosphate; EOPA, endo-oligopeptidase A; Rac1, Ras-related C3 botulinum toxin substrate 1; Pak1, p21-activated kinase 1.

Table 1Common phenotypes in *Disc1* mouse models.

	Assays	Phenotypes in DISC1 mice	References
A. Behavioral changes	Startle response test	Deficits in prepulse inhibition	[80, 94, 95, 100]
	Delayed non-matching to place test	Deficits in working memory performance	[95, 96, 101]
	Fear conditioning	Deficits in latent inhibition	[95, 98]
	Forced swim test	Increased immobility	[54, 94, 95, 96, 98, 102]
B. Histological changes	Immunohistochemistry of interneurons	Reduction of parvalbumin immunoreactivity in mPFC	[80, 94, 97, 98]
	Golgi staining	Reduced spine density of pyramidal neurons in the frontal cortex	[106]
	GFP labeling by in utero gene transfer	Impaired dendritic formation of pyramidal neurons in mPFC	[80]
	<i>in vivo</i> MRI scan	Reduced brain volume and enlargement of lateral ventricles	[94, 95, 97]

mPFC, medial prefrontal cortex; GFP, green fluorescent protein; MRI, magnetic resonance imaging