Discovery of Schizophrenia Drug Targets from DISC1 Mechanisms
Atsushi Kamiya M.D., Ph.D.

Assistant Professor
Department of Psychiatry and Behavioral Sciences
Johns Hopkins University School of Medicine
akamiya1@jhmi.edu

How does neurobiology offer novel treatment interventions?

Outline
• Discovery of the Disrupted in Schizophrenia 1 (DISC1) gene
• Potential therapeutic strategies based on structure and motif of DISC1 protein
• DISC1-associated pathways as drug targets
• Molecular complexities of DISC1
Discovery of the Disrupted in Schizophrenia 1 (DISC1)

THE LANCET

Association within a family of a balanced autosomal translocation with major mental illness

D. S. Craig, RPCPhD, IC. Blochowicz, MRCPhD, P. W. Mue, MRCPhD, P. M. Walker, MRCPhD, O. D. Clapham, V. M. Ullman, A. Cleghorn, PhD, G. Spain, PhD, C. Giedan, PhD, H. J. Evans, PhD

*Department of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, United Kingdom

Abstract

262 pedigrees in the MRC Cytogenetics Registry, Edinburgh, with familial autosomal anomalies were examined for the presence of associated mental illness. In one large pedigree there were 25 cases of mental and/or behavioral disorders meeting Research Diagnostic Criteria. 34 of the 71 family members available for cytogenetic analysis carried a balanced translocation t(1:11) (q21;q21). Psychiatric diagnoses had been recorded for 16 of the 34 members with the translocation compared with only 5 of the 34 without it. The four outcomes (organic brain lesion of the translocation with mental illness) were greatest when the mental disorders in the phenotype were restricted to schizophrenia, schizoaffective disorder, resistant major depression, and adolescent conduct and emotional disorders. Although the mental illness in this family may not be typical of that in the general population, the findings suggest that the q21-22 region of chromosome 11 may be a promising area to examine for genes predisposing to major mental illness.

The Scottish t(1;11) family

Brandon et al., Nat Rev Neurosci, 2002
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Disrupted in Schizophrenia 1 (DISC1)
- Scottish family
- (1; 11)(q42;q14) translocation
- DISC1 gene
- DISC1 protein

Possible pathological effects of the DISC1 Scottish mutation
- Wild-type
- C-terminal
- C-terminal
- C-terminal
- C-terminal
- No protein

Potential therapeutic strategies based on structure and motif of DISC1 protein
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Structure and motif of DISC1 protein
- NLS: nuclear localization signal
- NES: nuclear export signal
- LZ: leucine zipper motif
- p: crude nuclear pellet
- s: postnuclear supernatant

Modulation of nuclear localization/export signaling may have potential for treatment of major mental conditions

Loss of DISC1 function impairs brain development
- Kamiya et al., Nat Cell Biol 2005
- Taniguchi et al., Neuroscientist 2012

Scottish mutant of DISC1 phenocopies knockdown effect of DISC1
- Loss of function of DISC1 may have pathological effect in the Scottish pedigree
- Stabilization of DISC1 protein may have therapeutic effect

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Loss of function DISC1 animal models for drug discovery

DISC1-associated pathways as drug targets

DISC1; diverse cellular compartment and multiple protein interactors

Amended from Ishizuka et al., Biol Psychiatry, 2006

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Multiple protein interactors of DISC1

- As an adaptor protein, DISC1 may regulate various cellular cascades during and after neurodevelopment.

Multiple protein interactors of DISC1 (2)

DISC1 regulates neural progenitor proliferation via GSK3β signaling
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**DISC1 regulates neural progenitor proliferation via GSK3β signaling (2)**

- SB-216763 normalizes defects and behavioral abnormalities induced by knockdown of DISC1
- Lithium, clozapine, risperidone, valproic acid

**Phosphorylation of DISC1 at S710 is switch signaling from proliferation to migration**

**Phosphorylation of DISC1 at S710 is switch signaling from proliferation to migration (2)**

Modulation of enzymatic activity for post-translational modification of DISC1 may be useful in finding therapeutic strategies

PKA and Cdk5

Progenitor proliferation

Neuronal migration

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DISC1-NDEL1 interaction for neuronal migration and neurite outgrowth

Kamiya et al., Hum Mol Genet 2006

NDEL1 as endooligopeptidase

• NDEL1 has the ability to inactivate bioactive peptides, such as bradykinin and neurotensin
• Binding of NDEL1 with DISC1 regulates its enzymatic activity
• Enzymatic activity of NDEL1 is required for neurite outgrowth
  (Hayashi et al., Mol Cell Neurosci 2010)

Modulation of endooligopeptidase activity of NDEL1 may be useful in finding therapeutic strategies

Multiple roles for DISC1 in the developmental trajectory

Developmental processes
- Purification
- Neuronal maturation
- Synaptic signaling

Kamiya et al., Front Psychiatry 2012
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DISC1 and cAMP signaling

- PDE4 inhibitors – side effects
- Isoform-specific PDE4 inhibitors are expected
- Alternatively, modulation of DISC1-PDE4B interaction may be a useful approach

DISC1 and synaptic signaling

Brandon et al., Nat Rev Neurosci 2011

Multiple drug targets in DISC1 mechanisms

Modified Kamiya et al., Front Psychiatry 2012
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Molecular complexities of DISC1

Multiple variants of DISC1

How can we address molecular complexity and pathological roles of DISC1?

- Pathological roles of DISC1 mutation in Scottish pedigree
  - Characterization of Scottish mutation using iPSCs-derived neurons from patients in Scottish pedigree
- Multiple variants of DISC1
  - RNA sequencing to uncover entire mRNA structures of DISC1
  - RNAi approach with multiple targets and rescue experiments
- DISC1 animal models
  - Conditional DISC1 knockout mice (deletion of entire exons of DISC1 by chromosome engineering)
Summary

• Recent progress for understanding DISC1 function may provide us new avenues to find novel therapeutic targets.
• Modulation of DISC1 itself (e.g., protein stability, cell compartmentalization, post-transcriptional modification) and molecules associated with DISC1 pathways may be useful.
• DISC1 is a good entry point to explore potential drug targets; however, further understanding molecular complexities of DISC1 and its pathological roles is critical to understand how DISC1 affects disease susceptibility.