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Review

Understanding the Role of DISC1 in Psychiatric Disorders

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ABSTRACT

In a Scottish family with major psychiatric disorders such as bipolar and schizophrenia, the chromosome 1;11 translocation was assumed to be related to schizophrenia. Although this discovery has the potential to shed light on schizophrenia, later research has revealed that disrupted-in-schizophrenia 1 (DISC1) gene is not affected in all cases of schizophrenia, and that not all aberrant DISC1 results in schizophrenia.With increased studies relating DISC1 to various mental disorders, it is becoming increasingly necessary to investigate the relationship between functional abnormalities in psychiatric patients and DISC1. DISC1 has been found to be involved in processes that deteriorate in psychiatric disorders, such as cell migration, proliferation, differentiation, mitochondrial transport, neuronal growth, and synaptic transmission control, according to investigations on its mechanism. Although genetic linkage studies have identified DISC1 mutations as a general risk factor for schizophrenia, schizoaffective disorder, bipolar disorder, major depression, and autism spectrum disorders, more research is needed to determine which functions of the protein are responsible for the risk factor. The purpose of the review was to discuss the relationship between DISC-1 and psychiatric disorders.

Keywords: Bipolar disorder, DISC1, psychiatric disorders, schizophrenia

A Scottish family with major depression and schizophrenia was the subject of segregation research in a study. Individuals with a karyotype containing the balanced translocation (1;11) (q42.1;q14.3) in the q42 region of the 1st chromosome were diagnosed with significant depression and schizophrenia, while those without the karyotype did not show symptoms.[1] The disrupted-in-schizophrenia 1 (DISC1) gene has been named for the gene at the point of balanced translocation, which is likely to be deficient in schizophrenia. It encodes a multifunctional scaffold protein.[2] The DISC1 protein interacts with several proteins and is involved in essential nervous system functions. DISC1 is highly expressed during the early stages of brain development. It's also found in the hypothalamus, olfactory bulb, cortex, hippocampus, cerebellum, and brain stem, among other places.[3] The dentate gyrus of the hippocampus is regarded to have the highest gene expression in adults.[4] In studies, DISC1 was found to be expressed in glial cells. [5]

DISC1 PROTEIN STRUCTURE

The first 350 amino acids of DISC1, a lengthy protein with 854 residues, are irregular, according to bioinformatics research, while the remaining area is rich in a-helix and helix-helix patterns.[6] At least three phosphorylation sites have been identified in this gene: threonine 50 (T50), serine 58 (S58), and serine 713 (S713).[7]

There is no significant sequence similarity between the 98 kDa protein and other known proteins.[8] A globular region near the protein's N-terminus is rich in charged amino acids (35 negatively charged and 38 positively charged), glycine (12.6%), and serine (15.2%).[9] The C-terminal contains two double helix structures and two leucine zippers, as well as a series of helices that mediate protein-protein interactions.[6] In diverse variations and settings, DISC1, which is known to be in an oligomeric structure under

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normal conditions, reveals conformation changes relatively quickly. The centrosome[10], cytoskeleton[11], mitochondria[12], cytoplasm[8], axon, and synapses[13] have all been found to contain DISC1 protein. DISC1 has been implicated in numerous stages of neuronal development, including maturation, migration, morphogenesis, and synaptic integration, according to research.[14-16] Depletion of endogenous DISC1 or expression of mutDISC1 inhibits neurite outgrowth and normal cerebral cortex development, according to another study.[16]

DISC1 is involved in synapse development and formation[17], as well as synaptic vesicle transit.[18-22] DISC1 is thought to play a role in neuronal excitability and synaptic function maintenance, according to recent research.[23,24] The protein's primary roles are assumed to involve the regulation of basic processes in early brain development. According to several studies, abnormalities with this gene are linked to cognitive issues. When using functional magnetic resonance imaging (fMRI) to evaluate various cognitive activities, the cys704ser polymorphism located in exon 10 of DISC1 was found to be related to diminished hippocampal gray matter and N-acetylaspartate (NAA) signaling, as well as aberrant hippocampus involvement. In schizophrenia, this circumstance is linked to cognitive deficiencies.[25-27]

Studies on DISC1 with a t(1;11) balanced translocation have indicated that it is related to impaired white matter integrity in the frontal lobe[28], cortical thickness is similar to schizophrenia[29], and diminished gyrification in the prefrontal cortex[30]. Furthermore, this translocation disrupts the gene balance in the 1st and 11th chromosomes, as well as neuronal migration, which is one of DISC1's key tasks.[31] Studies linking DISC1 to negative mood-related anhedonia, frontal lobe-related memory, cortical thickness, hippocampus, gray matter volume, and white matter integrity issues are critical for understanding its role in psychiatric disorders.[25,32-39] This gene also organizes axonal development[40,41], modulates neuroblast migration[7,14], and organizes newborn neurons in adults.[15] The studies that found it to be significant are also encouraging. On the other hand, the Q31L point mutation, which causes the replacement of glutamine with leucine at amino acid 31 in DISC1, has been linked to alterations in pro- and anti-inflammatory cytokine density in multiple brain regions, pointing to a variety of neurodevelopmental psychiatric disorders.[42] Through signaling connections with phosphodiesterase 4B (PDE4B) and kalirin-7 (Kal-7), mutations in the N-terminus of DISC1 are hypothesized to be important in adult plasticity. Its immediate impact on plasticity, however, is uncertain.[43] It's crucial since loss of neuroplasticity function is common in mental disorders.

Early Development Period

Progenitor cell proliferation and postmitotic neuronal migration are hypothesized to be regulated by DISC1. It prevents progenitors from differentiating and exiting the cell cycle early.[44]

DISC1 inhibits glycogen synthase kinase 3 (GSK3), which reduces catenin phosphorylation and stabilizes the protein. It interacts with proteins in dynein motor complexes linked with microtubules and centrosomes in postmitotic neurons, including Bardet-Biedl Syndrome (BBS) proteins that mediate neuronal migration.[16,45]

DISC1's affinity for GSK3 declines while the association with BBS proteins increases as DISC1 protein levels are reduced by short-hairpin RNA (shRNA) at embryonic stage E13 and corticogenesis progresses. When Wnt/-catenin activity is inhibited, a switch from neural progenitor proliferation to neuronal migration occurs. To put it another way, DISC1 is involved in neuronal migration and proliferation, as well as the transitions between the two.[7] Early brain development appears to play a role in the development of schizophrenia, albeit it is not the sole cause.[46,47] Studies on schizophrenia show that DISC1 plays an important role in early development.

Neonatal Neurons in Adults

Downregulation of DISC1 was linked to aberrant morphological development and malposition of new dentate granule cells, as well as faster neural integration. Newborn neurons with DISC1 knockdown exhibited quicker dendritic growth, higher excitability, and synapse formation, according to the same study.[14]

The loss of DISC1 in neonatal granule cells creates issues in axonal targeting and the development of synaptic outputs in the adult brain, according to a study undertaken to understand the molecular processes that regulate the axonal output of new neurons in the adult brain.[15]

DISC1 is also involved in regulating the maturation rate of newborn neurons in the adult brain, according to the same study. Although the mechanism of neonatal neurons in adults is still unknown, studies have offered information on the involvement of

DISC1 in mental illnesses, given that neuronal activity in these diseases differs.

NEUROGENESIS

DISC1 is hypothesized to be involved in the process of neurogenesis. This finding is significant because aberrant neurogenesis plays a role in the pathophysiology of psychiatric diseases including schizophrenia and autism. The rate of hippocampus neurogenesis is accelerated once DISC1 knockdown is degraded shRNA, resulting in quicker stem cell turnover and dendritization of new neurons. The interaction between depolarizing gamma-aminobutyric acid (GABA) signaling and DISC1 was reported to be activated during both stress-induced preterm postnatal neurogenesis and normal adult neurogenesis, and converge in the mammalian target of rapamycin (mTOR) pathway, according to a study focusing on the connection between GABA and DISC1 in the context of neurogenesis.[48]

WNT SIGNALLING PATHWAYS

The fetal forebrain-hippocampus and midbrain dopaminergic systems, which are the most frequently disturbed in schizophrenia and bipolar disorder, are involved in the Wnt family of pathways. Studies have also found that patients with schizophrenia have impaired Wnt signaling pathway functions.[49,50]

DISC-1 interacts directly with GSK3, a key component of the Wnt signaling pathway, and serves as a major positive modulator of the canonical Wnt pathway.[44] It accomplishes this by lowering beta-catenin phosphorylation and stabilizing the protein. By inhibiting GSK3, DISC1 controls progenitor proliferation and adult brain progenitor proliferation. GSK3 activity is inhibited by a 15-mer domain on the N-terminus of DISC1 that interacts with GSK3. These factors are known to enhance neural stem cell proliferation by blocking early cell cycle exit and neuronal differentiation. Indeed, psychiatric medications inhibit GSK3 function through a variety of methods.[51]

The GSK3 activity is influenced by antipsychotic medications, mood stabilizers, and lithium through several pathways. In terms of pharmacological embroidery, this points to the DISC1 gene.[51] By interfering with GSK3, DISC1 regulates cytokine production induced by basal or maternal immune activation.[52] Wnt signaling is also implicated in DISC1-mediated neurogenesis.[44,53] Studies have also shown that the interaction of DISC1 and GSK-3 increases the number of neural progenitors.[44,54]

Singh et al.[55] studied DISC1 single-point polymorphisms in order to establish if there was a link between canonical Wnt signaling and DISC1. While DISC1 promotes canonical Wnt signaling in human and mouse cell lines, single nucleotide polymorphisms change the interaction of DISC1 with GSK-3, lowering canonical Wnt signaling and resulting in a corresponding decrease in neural progenitor cell proliferation, according to the findings.

Many psychiatric disorders have been linked to the Wnt signaling pathway. In bipolar patients' lymphoblasts, for example, Wnt signaling was shown to be weaker than in controls.[55] This finding is in line with previous research that found lithium regulates adult hippocampus progenitor growth via the canonical Wnt pathway.[56] Many studies have linked defects in the Wnt signaling pathway to Alzheimer's disease.[57]

Overall, it appears that understanding the mechanism of DISC1 in the Wnt signaling pathway is critical.

DISC1 AND GLUTAMATE

DISC1 interacts with exocyst complex components involved in glutamate receptor trafficking.[65] The interaction of DISC1 with Kal-7 controls the activation of N-methyl-D-aspartate (NMDA)-type glutamate receptors.[66] The activation of DISC1, which is known to be located at the synapse, as well as Kal7, is crucial. A decrease in Kal7 has been documented in the autopsy brains of schizophrenic patients[67] in research conducted with a Japanese population.[70] The glutamate system is destabilized in psychiatric disorders; therefore, these findings are significant.

DISC1 AND DOPAMINERGIC SYSTEM

Dopamine's role has long been recognized, particularly in psychotic disorders.[71]

DISC1 is a dopamine system scaffolding protein that interacts with other proteins. Studies show that DISC1 affects both presynaptic and postsynaptic dopaminergic function (tyrosine hydroxylase levels, dopamine transporter levels, and dopamine levels at baseline and after amphetamine treatment) (dopamine D1 and D2). There has been evidence that DISC1 has a direct effect on dopamine release in the nucleus accumbens and presynaptic and postsynaptic transmission.[72]

The Akt–GSK3 pathway, with which DISC1 interacts, has been linked to the modulation of dopamine neurotransmission.[73,74]

According to research, DISC1 plays a crucial role in the activity and affinity of the dopamine transporter protein (DAT).[75]

The dopamine D2 receptor (DISC1-D2R) complex has been shown to enhance GSK3 signaling and prevent agonist-induced D2R internalization in a study.[76] The discovery of a decrease in dopaminergic neurons in the substantia nigra, which is involved in many mental disorders, is significant.[77]

DISC1 AND MITOCHONDRIA

Many psychiatric disorders, including Parkinson's, Huntington's, and Alzheimer's diseases, have been linked to mitochondrial malfunction.[79,80] DISC1 has been found to be effective in the function of defective mitochondria in a variety of psychiatric disorders.[81,82] DISC1 is primarily found in mitochondria.[83] It interacts with the mitochondrial Rho (Miro) and trafficking kinesin protein (TRAK) proteins to regulate mitochondrial transport.[39,80]

DISC1 AND MICROTUBULES

DISC1, which has been shown to interact with microtubules and related complexes including nuclear distribution protein nudE-like 1 (NDEL1), nuclear distribution gene E homolog 1 (NDE1), lissencephaly 1 protein (LIS1), 14-3-3, dynactin, the microtubule-interacting protein associated with TRAF3 (MIPT3), and microtubule-associated protein 1A (MAP1A), is expected to have similar roles.[12,65]

It is thought to be significantly concentrated in the centrosome, which regulates microtubules. Furthermore, it was found that DISC1 regulates microtubules in neurodevelopmental processes such as neural migration when it was discovered that it interacts directly with them.[8,85] By regulating microtubule dynamics in the centrosome structure, DISC1 coordinates neuronal migration in the developing brain. DISC1 interacts with MIPT3, a protein that binds microtubules to both proteins via its central domain, and with MAP1A via its amino terminus, showing that DISC1 is important for microtubules. Microtubule failure is linked to problems with receptor location and neuronal transmission, both of which are common in schizophrenia.[16,86]

DISC1 regulates the dynein protein complex in the centrosome, modulating microtubular dynamics. This suggests that DISC1 is involved in microtubule transport, neuronal migration, neurite outgrowth, and axon development.[87] Neuronal migration, axonal extension, and neurite outgrowth are all affected by microtubule dysfunction. Reduced DISC1 binding may alter NDEL1-mediated microtubule organization, according to certain research.[88]

DISC1 AND ASTROCTES

Astrocytes provide energy to neurons by producing lactate from glucose and ketones via glycolysis or glycogenolysis. Pathologies in astrocytes, the most numerous cell in the brain, have been linked to cognitive and behavioral impairments in studies.[89,90] Reduced DISC1 expression was found to influence astrocyte glucose absorption and lactose synthesis in studies. This scenario is assumed to be the cause of impaired glucose tolerance in individuals with documented first-episode psychosis[91], decreased energy metabolism in the dorsolateral prefrontal cortex (DLPFC) in schizophrenia[92], and the reduction of high-energy phosphates in bipolar disorder[93,94]; According to the study, DISC1 is involved in the regulation of lactate generation in astrocytes in order to support neuronal activity and related behaviors.[95]

INTERACTION BETWEEN NDEL1 AND DISC1

DISC1 is considered to interact with the NDEL1 to coordinate processes such as cortical neuron migration, neurite outgrowth, and adult neonatal neuron development in the dentate gyrus.[14,96] With 100 amino acids at the C-terminus of DISC1, it interacts with NDEL1 for the centrosomal association.[97]

The leucine zipper domain complex generated by DISC1 and NDEL1 after birth is plentiful, although it declines in adulthood. It also helps to generate trimolecular by coordinating the binding of LIS1 and DISC1. The NDEL1-DISC1 complex is hypothesized to be involved in neuronal migration and is linked to schizophrenia pathophysiology.[11]

NDEL1 deficiency has been linked to aberrant cortical histogenesis.[98] It has been proven in experimental animal investigations on the issue that disruption of the interaction of Mutant DISC1 with NDEL1 causes abnormalities in cellular distribution and functions[16], as well as a severe behavioral disorder phenotype in mice.[99]

DISC1 AND ATF4

Binding is accomplished by DISC1's coil-to-coil domain (DISC1-CC; aa 765–852) and activating transcription factor 4 (ATF4)'s leucine zipper domain (ATF4-LZ; aa 314–349). DISC1's carboxy terminus has a 157-amino-acid domain that interacts with the ATF4 and ATF5 proteins, which are involved in receptor trafficking, localization, and signal transduction.[100] According to one study, DISC1 truncated with exon 9 (aa 607-628) was unable to bind with ATF4, which is ATF4-DISC1. exon's role in its action is highlighted.[101] The loss of exon 9 is most likely due to misfolding.[102] Dysregulated gene expressions and synaptic dysregulation are shown in the presence of mutant DISC1, while ATF4 binds to DNA targets more.[103] Many more investigations on the significance of ATF4-DISC1 interaction in psychiatric disorders are needed, as studies have shown its importance in synapse function.

DISC1 AND FEZ1

One of the earliest identified associated proteins of DISC1 to trigger neurite outgrowth was fasciculation and elongation protein zeta-1 (FEZ1).[104] The interaction between DISC1 and FEZ1 has been shown to increase during neural differentiation.[105] FEZ1 was found to be co-localized with DISC1 in neuronal development cones in the same study. According to the findings of Lipska et al.[106], FEZ1 mRNA levels in the schizophrenic hippocampus and dorsolateral prefrontal cortex are significantly lower. There is a link between FEZ1 mRNA levels and the DISC1 genotype. Nerve growth factor (NGF) regulates the DISC1–FEZ1 signaling, which is involved in neurite elongation.

DISC1 STUDIES IN PSYCHIATRIC DISORDERS

The discovery that DISC1 is linked to schizophrenia was promising in terms of understanding schizophrenia. The fact that this gene is not always defective in the following processes in schizophrenia has redirected focus to the mechanism of DISC1 and its link with other mental disorders. Studies on samples carrying psychiatric disorders have risen as a result of this process. In a recent study, insoluble DISC1 proteins were discovered in the postmortem brains of a sporadic sample of people with significant depression, schizophrenia, and bipolar disorder.[107] Furthermore, studies using the P300 value and DISC1 impairment in electrophysiological methods, which are both impaired in schizophrenia and are commonly employed to test attention-dependent information processing in mental disorders, have generated a lot of interest.[108,109] While the expression levels of the DISC1 gene in peripheral blood mononuclear cells in people with schizophrenia were shown to be greater than in people without schizophrenia, 12-week antipsychotic treatment did not reduce this level.[110] The DISC1 gene polymorphism was found to be related to schizophrenia in an Iranian population study.[111] In attention-deficit schizophrenia patients, two DISC1 single-nucleotide polymorphisms (SNPs) (rs11122324 and rs2793091) have been discovered.[112] The SNP rs821597 variant has been linked to schizophrenia in those over the age of 40.[113]

While a 4 bp deletion was detected at the extreme 3' end of DISC1 exon 12, it was reported that this mutation was found in a sibling with schizophrenia, a sibling with schizoaffective disorder, and an unaffected father, and no mutation was detected in 424 control individuals in a study conducted in an American family with comorbid schizophrenia and schizoaffective disorder. A frameshift mutation resulted from the loss, but nine aberrant amino acids were added to the C-terminus.[114] A study found a connection between several haplotypes located between exon 1 and exon 9 regions and schizophrenia, bipolar disorder, and schizoaffective disorder in their DISC1 study. They discovered a strong link between schizoaffective disease and a "missense" mutation in the exon 9. [115] DISC1 was identified as one of six issue gene areas in a study of a family with bipolar disorder who had a negative lithium reaction.[116] DISC1 gene variants were found to be risk factors for autism in a Chinese population investigation.[117] In another study conducted in families with autism spectrum disorder,[118] The DISC1 variant was found.[119] Repeated DNA sequences in the DISC1 gene were discovered in a Finnish family with autism and Asperger's syndrome.[120] In the same sample, people diagnosed with Asperger's syndrome had a high rate of single nucleotide changes.

There is numerous research that suggests a link between DISC1 and depression. While the R37W polymorphism in the DISC1 gene was found in investigations with people with persistent depression, mice with the DISC1-Q31L polymorphism showed enhanced emotionality, impulsivity, aggression, and habenular neurons.[121]

There are other findings that contradict research that show a relationship between DISC1 and psychiatric disorders. In a large-scale genetic investigation with a total of 11 thousand patients,

for example, no relationship was observed between any version of DISC1 and schizophrenia. not discovered.[122] Another study on schizophrenia found that DISC1 did not have a significant effect either alone or in functional relationships.[123] According to genome-wide association studies (GWAS), DISC1 is a low significant risk factor for schizophrenia or bipolar disorder, and there is no substantial link between DISC1 and schizophrenia.[124-127]

DISC1 STUDIES IN EXPERIMENTAL ANIMALS MODELS

Experimental animal models are critical for understanding the mechanisms of mental disorders. In this context, the results of animal tests on the DISC1 gene are equally noteworthy. The connectivity between the prefrontal cortex and the hippocampus was destroyed in research performed on compromised DISC1 mice models, for example, and memory and attention were affected.[46,128,129] Prefrontal-hippocampal maturation is hampered by aberrant DISC1 expression, according to another study.[130]

The loss of DISC1 function produced a decrease in brain progenitor cell proliferation and the appearance of schizophrenia and depressive-like behaviors in adult mice in a study conducted in the dentate gyrus (region of the hippocampus).[131] In another study, it was discovered that down-regulation of the DISC1 gene induces anxiety-like behavior and social dysfunction in mice, as well as reducing synaptic plasticity and impairing recognition memory.[132]

Rats with the N-terminal of DISC1 truncated had decreased risk aversion behavior and showed less sociability in the triple recognition test, according to a study.[133] In another investigation on DISC1 malfunction, mice in the forced swimming test displayed depression-like behavior.[44] While working memory has been shown to be reduced in mice[134], spatial memory has not been affected, and mice with DISC1 are more depressed when compared to the forced swimming test, which is a depression marker. In psychosis, executive dysfunction is a common symptom. [135, 136]

In conclusion, following the discovery that DISC1 was linked to schizoaffective disorder, bipolar disorder, and schizophrenia in families with schizophrenia, a slew of studies on the gene's role in disorders and physiological activities were done. This protein's functional relationship with proteins engaged in diverse brain activities related to neurodevelopment and intracellular signaling pathways is particularly notable. It plays a significant role in neurodevelopment, synaptic formation, newborn neurons, centrosome and microtubule structure, and astrocyte organization, all of which have previously been linked to psychiatric disorders. It is frequently expressed in areas of the brain linked to psychiatric disorders, such as the hypothalamus, olfactory bulb, cortex, hippocampus, and cerebellum brain stem, forming associations with proteins linked to psychiatric disorders, such as FEZ1-NDEL1-ATF4, participating in Wnt and cAMP signaling pathways, and interacting with disease-related glutamate and dopamine receptors, providing an important perspective for the role of this It's worth noting, however, that large-scale investigations have indicated that DISC1 is unrelated in research including people with the condition. It is clear that mental disorders are complicated, including connections between the environment and genes. Psychiatric disorders, also, involve multi genetic components, according to studies. In many clinical circumstances, DISC1 is expected to be one of the multi-genetic variables. However, more research is needed to completely understand the significance of DISC1.

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