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DISC1 as a key lead in studying cortical development and associated brain disorders

Soumya Narayan¹, Kazunori Nakajima², and Akira Sawa¹

¹Department of Psychiatry, Johns Hopkins University School of Medicine

²Department of Anatomy, Keio University School of Medicine

Abstract

For the past decade, DISC1 has been studied as a promising lead to understand the biology underlying major mental illnesses, such as schizophrenia. Consequently, many review papers on DISC1 have been published. In this article, rather than repeating comprehensive overviews of research articles, we will introduce the utility of DISC1 in the study of cortical development in association with a wide range of developmental brain disorders. Cortical development involves cell autonomous and cell non-autonomous mechanisms as well as host responses to environmental factors, all of which involve DISC1 function. Thus, we will discuss the significance of DISC1 in forming an overall understanding of multiple mechanisms that orchestrate corticogenesis and can serve as therapeutic targets in diseases caused by abnormal cortical development.

Keywords

DISC1; cortex; development; corticogenesis; probe

Development of the human cortex is essential for normal cognitive function (Guerrini and others 2008). Dysfunction in proper development is the root of many devastating neurodevelopmental disorders, highlighting the importance of understanding the mechanisms that regulate corticogenesis (Francis and others 2006; Gupta and others 2002; Manzini and Walsh 2011). Corticogenesis is a complex multi-step process regulated at distinct stages by various regulatory mechanisms. How these diverse mechanisms functionally interact with one another, remains largely unclear, but necessary in developing a comprehensive picture of cortical development and insight into disease states. In this review we propose DISC1, a risk gene for major mental illness with substantial roles in early brain development, as a probe to study corticogenesis and its implication in a wide range of developmental brain disorders. We will begin by introducing major mechanisms underlying cortical development, and propose to classify these mechanisms into three distinct categories: cell-autonomous mechanisms, cell non-autonomous mechanisms, and mechanisms of host responses to environmental stressors. Although roles for DISC1 in neurodevelopment have been summarized and described in detail in recent reviews (Brandon and Sawa 2011; Johnstone and others 2011; Porteous and others 2011), we will organize these roles of DISC1 into the three mechanisms categorized above. Finally, we will propose the idea of DISC1 as a powerful gateway into exploring the development of the human cortex, especially in the context of disease.

Cortical Development: Three Distinct Mechanisms

Cortical development begins at distinct proliferative zones in the embryonic brain. Specialized neuroepithelial cells give rise to a pool of progenitor cells that undergo successive cell divisions, eventually differentiating into immature post-mitotic migratory neurons (Dehay and Kennedy 2007). Appropriate control of cell division is essential as progenitor cell expansion regulates the size and thickness of the cerebral cortex. Dysregulation of normal mitotic activity, which affects proliferation, can result in altered neurogenesis and eventual neuropsychiatric conditions (Mahmood and others 2011; Mochida and Walsh 2004; Thornton and Woods 2009; Yingling and others 2008).

Following cell cycle exit, post-mitotic cells migrate to their sites of action in the developing cortex (Dehay and Kennedy 2007). Neurons migrate from the proliferative zones along one of two routes referred to as: radial migration and tangential migration. Radially migrating cells, which become excitatory neurons, are derived from neural progenitors/precursors in the ventricular zone (VZ) and subventricular zone (SVZ). Depending on the stage of embryonic development, these cells use a combination of multiple modes of migration, such as somal translocation, multipolar migration, locomotion, and terminal translocation (Nadarajah and others 2001; Noctor and others 2004; Rakic 1972; Sekine and others 2011; Sekine and others 2012; Tabata and others 2009; Tabata and Nakajima 2003). The majority of neurons born in the VZ reside for half a day in this zone before transforming into multipolar cells. These cells then accumulate within a narrow band above the VZ called the multipolar cell accumulation zone (Tabata and others 2009), extending and retracting multiple processes in a dynamic manner (Tabata and Nakajima 2003). As they enter the lower intermediate zone, they move in various directions, eventually approaching the cortical plate (Tabata and Nakajima 2003).

These multipolar migrating neurons then transform into bipolar cells and adopt a mode of migration known as locomotion, where they migrate along radial glial fibers over long distances through the intermediate zone and cortical plate (Bystron and others 2008). Locomotion occurs in a saltatory manner with intervals of no movement between periods of rapid forward movement. During locomotion, neurons extend a leading process away from the soma, whose length remains relatively constant. This leading edge is thought to survey the microenvironment for guidance cues including the radial fibers to interpret the direction of migration. Once the leading process is consolidated, nucleokinesis begins (Ayala and others 2007). The centrosome moves into the leading edge and extends microtubules back towards the nucleus, enveloping it into a “cage”-like structure, pulling it forward. This process culminates in the retraction of the trailing edge (Tsai and Gleeson 2005).

When the migrating cells reach the outermost region of the cortical plate or beneath the primitive cortical zone in the top of the cortical plate, they switch from locomotion to terminal translocation (Sekine and others 2011). The soma moves in a radial-glia-independent manner and the tips of the leading processes retain their attachment to the marginal zone, completing their migration to just beneath the marginal zone (Nadarajah and others 2001; Sekine and others 2011). Upon arrival at their final destination, these cells differentiate into mature neurons with axons and dendrites, that are formed from growing neurites, establishing the laminar cytoarchitecture of the cortex (Ayala and others 2007). Although the distance of migration is very small for terminal translocation, this final step is essential for development of the eventual pattern of neuronal layering (Sekine and others 2011; Sekine and others 2012).

In contrast, GABAergic interneurons are derived from ganglionic eminences and the preoptic area (POA) at the ventral forebrain, and migrate to the cortex in a path tangential to

that of excitatory neurons (Anderson and others 1997; Gelman and others 2009; LoTurco and Bai 2006; Maricich and others 2001; Marin and Rubenstein 2001; Nakajima 2007; Tamamaki and others 1997). The majority of cortical interneurons (65–70%) are derived from progenitor cells in the medial ganglionic eminence (MGE) and the remainders arise from the caudal ganglion eminence (CGE) and POA (Gelman and others 2009; Kanatani and others 2008; Xu and others 2004; Yozu and others 2005). However, other subpallial sources, including the lateral ganglionic eminence (LGE), may also account for a small proportion of them (Wonders and Anderson 2006). Interneurons from the MGE populate the cortex in an inside-out pattern while interneurons from the CGE migrate to the superficial layers independent of their time of birth. The migration of cortical interneurons is characterized by successive cycles of nucleokinesis and neurite branching. The MGE also contributes to interneurons in the hippocampus while the LGE gives rise to interneurons directed towards the olfactory bulbs (Ayala and others 2007). Since much more is known about the mechanisms underlying the development of excitatory neurons, our focus in this review will predominantly be on these cells.

Insights from disorders of abnormal cortical development, influenced by several developmental processes such as progenitor proliferation and neural migration, have been invaluable in identifying mechanisms that orchestrate early brain development. Here we propose to categorize multiple mechanisms that regulate cortical development into the following three subclasses as follows.

Cell Autonomous Mechanisms Regulate Cortical Development

Key components of the neuronal cytoskeletal machinery are tightly regulated in cortical development. Proper positioning of the centrosome and microtubule dynamics are important for progenitor proliferation, migration, and axon elongation (Heng and others 2010; Vallee and others 2009). Intracellular proteins that regulate microtubule networks and have essential roles in cortical development include lissencephaly protein (LIS1), nuclear distribution element 1 (NDE1), nuclear distribution element-like 1 (NDEL1), pericentriolar material 1 (PCM1), and bardet-biedl syndrome proteins (BBS) (Badano and others 2005). Their intracellular regulation of the cell cytoskeleton can be classified as “cell autonomous mechanisms regulating cortical development.”

Many of the genes encoding these molecules have unique evolutionary significance. For example, the genes encoding LIS1, NDEL1, and NDE1 are homologues of a highly conserved family of genes in fungi that regulate nuclear migration, which resembles neuronal migration in humans (Kardon and Vale 2009). LIS1, NDEL1, and NDE1 interact with motor complexes at various time points during neurodevelopment to regulate their activity (Ayala and others 2007; Shu and others 2004). This complex plays an important role in mediating functions of the microtubule network and centrosome in a cell, for proper mitosis during cell proliferation and nucleokinesis in neuronal migration (Grabham and others 2007; Higginbotham and Gleeson 2007; Shu and others 2004).

In proliferating cells, the centrosome contributes to the assembly and organization of mitotic spindles (Nigg and Stearns 2011). During the proliferative stage, NDE1 and LIS1 bind dynein motors at the centrosome to mediate spindle formation and chromosome attachment for mitotic division (Faulkner and others 2000; Feng and Walsh 2004; Li and others 2005). Cortical progenitor cells from mice with *Nde1* mutations exhibit deficits in mitotic-spindle formation and chromosome positioning (Feng and Walsh 2004). In contrast, a network of microtubules couples the centrosome to the nucleus in postmitotic neuronal migration. For example, NDEL1 and LIS1 binding stimulate dynein motor activity which is important for pulling microtubules and the centrosome forward during nucleokinesis (Shu and others 2004; Vallee and others 2009). Knockdown of NDEL1 or LIS1 results in neuronal

positioning impairments and uncoupling of the nucleus from the centrosome (Grabham and others 2007; Shu and others 2004; Tsai and others 2007). Furthermore, LIS1 and NDEL1 also interact with the motor protein kinesin in neurites to regulate axon elongation (Taya and others 2007).

PCM1, a part of centriolar satellites associated with the centrosome, is important for progenitor proliferation and neuronal migration. Ge and colleagues (Ge and others 2010) showed a role for PCM1 in interkinetic nuclear migration through Hook3 interaction. This process is regulated by microtubule dynamics and is important for maintaining the progenitor pool during proliferation. In addition, PCM1 knockdown experiments in mice showed neuronal migration deficits in the developing brain (Kamiya and others 2008). The BBS4 protein is required for localization of PCM1 to the centrosome, which mediates the anchoring of microtubules to the centrosome and localization of centrosomal proteins (Kim and others 2004).

Mutations in genes encoding these proteins can result in devastating developmental disorders with compromised cortical development (see Table 1). Lissencephaly caused by haploinsufficiency of the *LIS1* gene, results in impaired migration, abnormal cortical layering, and a lack of cortical folds in the developing brain (Reiner and others 1993; Wynshaw-Boris 2007). Mutations in the *NDEL1* gene also result in a severe form of microcephaly with lissencephaly, indicative of aberrant cell proliferation and neurogenesis during development (Alkuraya and others 2011; Feng and Walsh 2004). The *PCM1* gene has also been reported as a risk factor for schizophrenia (Datta and others 2010; Gurling and others 2006; Kamiya and others 2008).

Cell Non-Autonomous Mechanisms Regulate Cortical Development

In addition to intrinsic factors inside cells, extracellular factors that bind cells initiating signaling events or facilitating cell-cell interactions, are also critical in the regulation of cortical development. Signaling elicited by extracellular Wnt is one such pathway that has roles in proliferation of cortical progenitors and patterning of the developing cortex (canonical Wnt/ β -catenin pathway) (Chenn and Walsh 2002; Hirabayashi and others 2004; Woodhead and others 2006). β -catenin, a key downstream intracellular component of the Wnt pathway, is highly expressed in neural progenitors in the VZ during early development (Chenn and Walsh 2002; Clevers and Nusse 2012). One of the key regulators of β -catenin is glycogen synthase kinase-3 β (GSK3 β). When β -catenin is overexpressed in progenitor cells of the developing mouse brain, the cortical surface area increases from a rise in precursor cell numbers and cell cycle re-entry (Chenn and Walsh 2002). In contrast, downregulation of β -catenin expression leads to premature cell cycle exit. These experimental data indicate that Wnt/ β -catenin signaling is important for mediating proliferation versus differentiation during cortical development through regulation of the cell cycle.

Neurons in the cortex are arranged into layers in an inside-out manner corresponding to their time of birth (Ayala and others 2007). The *reeler* mouse, with a spontaneous mutation in the gene encoding for the extracellular protein Reelin (Bar and others 1995; Barinaga 1996; D'Arcangelo and others 1995; Hirotsune and others 1995; Ogawa and others 1995), exhibits "inversion" of cortical layers ("outside-in" pattern) and severe cerebellar ataxia. While it is obvious that Reelin plays an essential role during cortical layer formation, and a number of downstream cascades of Reelin signaling have been reported, the physiological functions of Reelin in migrating neurons *in vivo* remain controversial. Indeed, several different hypotheses, some of which appear to conflict with each other, still exist (Rice and Curran 2001). Recently, Sekine and colleagues (Sekine and others 2012) demonstrated a molecular mechanism for Reelin signaling in neuronal positioning. After Reelin binds to its receptors ApoER2 and VLDLR, it activates integrin $\alpha 5 \beta 1$ through the intracellular Dab1-Crk/CrkL-

C3G-Rap1 pathway, promoting adhesion of neurons to fibronectin through integrin $\alpha 5\beta 1$. Since fibronectin is localized in the marginal zone, the activation of integrin $\alpha 5\beta 1$ on leading processes then controls terminal translocation. Therefore, Reelin-dependent activation of neuronal adhesion to the extracellular matrix is crucial for the eventual birth-date-dependent layering of the cortex.

Neuregulin (NRG) and its receptor ErbB families also play key cell non-autonomous roles in neurodevelopment (Corfas and others 2004; Mei and Xiong 2008). NRG1 and ErbB receptors are expressed in areas of the brain undergoing active cell proliferation both in the developing and adult brain (Mei and Xiong 2008). NRG1 has been shown to promote proliferation of neural stem cells in culture but does not stimulate cell proliferation in ErbB4 conditional null mice (Ghashghaei and others 2006; Liu and others 2005). These results suggest a role for NRG1-ErbB signaling in progenitor cell proliferation and neurogenesis. NRG1-ErbB has also shown to mediate interactions between neurons and glial cells. NRG1 contributes to the formation and differentiation of the radial glial scaffold during development for radial migration of neurons to the cortex (Rio and others 1997; Schmid and others 2003). Additionally, NRG1 can act as a guidance cue for tangentially migrating interneurons, which express ErbB4 receptors (Flames and others 2004; Marin and others 2010).

Genes in the Wnt signaling cascade have been shown to associate with mood disorders and schizophrenia (Lachman and others 2007; Matigian and others 2007; Zandi and others 2008). More specifically, genetic polymorphisms in the gene coding for GSK3 β have been reported with anatomical changes in the brains of patients with recurrent major depression disorder (Inkster and others 2009, 2010). Disruption of Reelin signaling has been identified in disorders such as Norman-Roberts syndrome, autism, bipolar disorder, depression and schizophrenia (Fatemi and others 2000; Guidotti and others 2000; Hong and others 2000; Persico and others 2001). Mutations in the Reelin gene and in its receptor VLDLR have been implicated in lissencephaly and cerebral ataxia, respectively (Boycott and others 2009; Chang and others 2007). In addition, genes coding for NRG1, NRG3, and ErbB4 are also associated with schizophrenia and related disorders in a reproducible manner (Chen and others 2009; Stefansson and others 2002; Walsh and others 2008; see Table 1).

Environmental Factors Regulate Cortical Development

There exists a body of work documenting a role for environmental factors such as drugs, neurotoxins, obstetric complications and viral infection in abnormal brain development (Stolp and others 2012; see Table 1). For example, fetal hypoxia associated with obstetric complications, has major consequences for perinatal brain development (Rees and Inder 2005; Rees and others 1999). Hypoxic conditions during critical periods in cortical development lead to proliferation and migration deficits along with impairments in axon guidance (Pan and Garriga 2008; Pocock and Hobert 2008; Zechel and others 2005; Zhu and others 2005). The cellular and molecular mechanisms by which these impairments occur still remains uncertain.

Cytomegalovirus (CMV) infection is a common cause of central nervous system disorders resulting in neurological defects at birth including mental retardation and hearing loss. (Cheeran and others 2009). While the mechanisms by which infection leads to brain abnormalities are largely unknown, several studies have demonstrated that CMV targets progenitor cells lining the ventricular zone, influencing proliferation and migration during cortical development (Kosugi and others 2000; Shinmura and others 1997; Tsutsui and others 2008). An *ex vivo* study of infected brain slices showed decreased progenitor cell growth and ability to differentiate into neuronal cell types (Shinmura and others 1997). In addition, injection of mouse embryos with CMV upon embryonic day 15.5 (E15.5) resulted

in abnormal neuronal migration suggesting an effect of viral infection in cortical development (Shinmura and others 1997).

DISC1 and Cortical Development

The *DISC1* gene was originally identified at the breakpoint of a hereditary chromosomal translocation, and disruption of the gene was strongly associated with occurrence of major mental illnesses, such as depression and schizophrenia (Blackwood and others 2001; Millar and others 2000; Thomson and others 2012). Following the identification of the *DISC1* gene in the Scottish pedigree, various groups have addressed whether genetic variations in the *DISC1* gene affect brain anatomy and related functional changes. Multiple studies report that *DISC1* polymorphisms correspond to anatomical changes such as reduced gray matter volume, white matter integrity, or cortical thickness along with electrophysiological changes (Brauns and others 2011; Callicott and others 2005; Cannon and others 2005; Carless and others 2011; Hashimoto and others 2006; Kahler and others 2012; Sprooten and others 2011; Szeszko and others 2008; Takahashi and others 2009; Whalley and others 2012). In addition to these findings in the human brain, effects of *DISC1* variants were also shown in mouse models where variants were associated, at least with impairments in Wnt signaling (Singh and others 2011). Biochemically, *DISC1* variants at Ser704Cys were also demonstrated to influence protein binding of NDE1 and NDEL to *DISC1* (Burdick and others 2008; Kamiya and others 2006). These results indicate on different levels, that *DISC1* is involved in multiple processes in the development of the brain, and are also supported by biological studies of *DISC1* in rodent models (Brandon and Sawa 2011; Johnstone and others 2011; Porteous and others 2011). Interestingly, *DISC1* is indeed involved in brain development, playing key roles in the three mechanisms of cortical development classified and described above.

DISC1 in Cell Autonomous Mechanisms Regulating Cortical Development

Biochemical studies, especially those with yeast two-hybrid screening, have indicated that *DISC1* is a scaffolding protein with multiple interacting partners, many of which are known to have important roles in neurodevelopment, including: LIS1, NDEL1, PCM1, GSK3 β , and BBS proteins (Brandon and Sawa 2011). A pool of *DISC1* occurs in the dynein motor complex, interacting with LIS1, NDEL1, PCM1, and BBS proteins (Kamiya and others 2008; Kamiya and others 2005; Morris and others 2003; Taya and others 2007). Consistent with classic reports that knockdown of LIS1 and NDEL1 affect neuronal migration in the developing cortex (Shu and others 2004; Tsai and others 2007), knockdown of *DISC1* also results in migration deficits when shRNA to *DISC1* is introduced via *in utero* gene transfer in both mouse and rat models (Kamiya and others 2005; Young-Pearse and others 2010). This is a representative mechanism whereby *DISC1* regulates cortical development in a cell autonomous mechanism.

In addition to neuronal migration, *DISC1*, NDEL1 and microtubule-associated motor complexes may also have roles in neurite outgrowth (Hayashi and others; Kamiya and others 2006; Miyoshi and others 2003; Taya and others 2007). Although this notion is proposed with the evidence from cell culture *in vitro* thus far, knockdown of *DISC1* or expression of dominant-negative *DISC1* inhibits neurite outgrowth (Kamiya and others 2006; Ozeki and others 2003; Taya and others 2007).

DISC1 in Cell Non-Autonomous Mechanisms Regulating Cortical Development

In early development, *DISC1* interacts with GSK3 β , inhibiting the kinase activity that is required for canonical Wnt signaling, which controls progenitor cell proliferation (Ishizuka and others 2011). This mechanism was originally demonstrated by using shRNA-mediated

DISC1 knockdown (Mao and others 2009). Similar observations are observed in two distinct genetic animal models for DISC1 (Lipina and others 2011; Lipina and others 2012).

Seshadri and colleagues (Seshadri and others 2010) reported that NRG1 and NRG2, but not NRG3, increase expression of an isoform of DISC1 in primary neurons. Receptors ErbB2 and ErbB3, but not ErbB4, are responsible for transducing this effect, and PI3K/Akt signaling is also required. In *Nrg1* knockout mice, this DISC1 isoform is selectively down-regulated during neurodevelopment. This is another example of how DISC1 is involved in neurodevelopment via a cell non-autonomous mechanism (see Fig. 2).

DISC1 may be involved in multiple stages of Reelin signaling. DISC1 forms a possible ternary complex with amyloid precursor protein (APP) and disabled-1 (Dab1), and plays a role in migration together with APP in the developing cortex (Young-Pearse and others 2010). As described, in response to Reelin signaling, phospho-Dab1 and LIS1 interact and play a role in corticogenesis (Assadi and others 2003). Given that DISC1 has been shown to bind with both Dab1 and LIS1 in the context of migration, it is highly probable that DISC1 may function downstream of Reelin signaling in the developing cortex (see Fig. 2).

Finally, a recent study explored how DISC1-associated cell autonomous and cell non-autonomous mechanisms are associated with each other (Ishizuka and others 2011). As described, DISC1 interacts with GSK3 β , which underlies regulation of progenitor cell proliferation (Mao and others 2009). Meanwhile, interactions of DISC1 with several proteins in the dynein motor complex regulate postmitotic neuronal migration (Kamiya and others 2005). DISC1 is phosphorylated at serine 710 (S710) in mice (of note, this corresponds to serine 713 in humans), and this phosphorylated form is enriched in postmitotic neurons whereas non-phosphorylated DISC1 at S710 is prominent in proliferating progenitor cells (Ishizuka and others 2011). Furthermore non-phosphorylated DISC1 at S710 preferentially binds with GSK3 β and regulates progenitor proliferation via the Wnt/ β -catenin signaling pathway, whereas DISC1 interacts with the BBS1/dynein protein complex by phosphorylation at S710 (Ishizuka and others 2011). Thus, this phosphorylation event switches DISC1 from having a cell non-autonomous role to adopting a cell autonomous role at neuronal differentiation (see Fig. 2).

DISC1 in Environmental Factors Regulating Cortical Development

It is well known that environmental factors influence cortical development (Stolp and others, 2012). Interestingly, the impacts of such environmental factors are different in DISC1 genetically-engineered models compared with those in normal controls. Two groups reported the differences in response among various DISC1 genetic models to the administration of polyriboinosinic-polyribocytidylic acid (polyI:C), which mimics innate immune responses elicited by viral infection early in development (Abazyan and others 2010; Ibi and others 2010; Nagai and others 2011). This suggests that DISC1 may participate in the processes by which environmental factors affect corticogenesis.

DISC1 as a Lead for Further Understanding Corticogenesis and Associated Disease Conditions

While we understand many aspects of cortical development, we still do not understand the mechanisms in their entirety. For example, how do external signaling pathways and environmental factors influence cell intrinsic factors, such as cytoskeletal dynamics, the overall of which contribute to cortical development? Furthermore, although mutations in genes associate with various types of developmental brain disorders, we do not know how specific phenotypes associated with individual disorders are driven by mutations or their

relationships. To develop a clearer picture of brain development and subsequently therapeutic targets for disease due to brain malformation, it is important to understand the mechanisms by which these pathways function and interact with one another as part of a larger network that orchestrates cortical development.

Here we propose DISC1 as a promising lead in studying cortical development and associated brain disorders for the following major reasons. Firstly, DISC1 in nature is an intracellular hub protein with many protein interactors and therefore is involved in multiple pathways. DISC1 is widely expressed throughout the developing cortex both spatially and temporally (Schurov and others 2004). A very important feature of DISC1 as a hub protein is binding various complexes and localizing them to their correct sites for proper function (Bradshaw and others 2008; Camargo and others 2007; Miyoshi and others 2003; Morris and others 2003; Ozeki and others 2003). Furthermore, as described in the cases of Reelin, NRG cascades, and Wnt signalling (Ishizuka and others 2011; Seshadri and others 2010; Young-Pearse and others 2010), DISC1 serves as a convergence point between cell autonomous and cell non-autonomous pathways. Important efforts carried out by many investigators thus far are to map specific domain(s) of DISC1 with each protein interactor to dissect how these distinct domains converge the signals of cell autonomous and non-autonomous pathways through DISC1 interacting proteins. (Brandon and Sawa 2011). Thus, it would be reasonable to have an optimistic perspective that DISC1 can be a useful probe to study complex relationships.

Secondly, animal models provide a crucial tool for studying the developing brain and multiple varieties of genetically-engineered animal models for DISC1 are available that are not lethal during early development and display unique phenotypes, especially in response to environmental stressors. Thus far, many groups have attempted to develop genetically-engineered models, especially knockout mice, for key molecules in corticogenesis. A drawback in such efforts has been in the fact that in many cases homozygous knockout mice for these molecules become lethal in the embryonic stage. This is a barrier to study the notion of how deficits in corticogenesis may result in disease phenotypes in later stages, including adulthood. A possible reason for this embryonic lethality may be that molecules thus far targeted are involved in the executive processes rather than regulatory processes in the corticogenesis. In contrast, DISC1, possibly serving as a regulatory unit for the executive machinery, has significant effects that do not cause lethality. Accordingly, nine different DISC1 animal models have been generated thus far (Brandon and Sawa 2011; Clapcote and others 2007; Hikida and others 2007; Koike and others 2006; Kuroda and others 2011; Li and others 2007; Niwa and others 2010; Pletnikov and others 2008; Shen and others 2008). By using these valuable resources, an important area of research will be addressing how environmental and genetic factors interact pre- and peri-natally to affect developmental outcomes.

Animal models provide an avenue to explore the effects of environmental insults such as viral infection or hypoxia on genetic factors during early development. For example, data of DISC1 genetically-engineered mice under exposure to polyI:C, indicate that DISC1 participates in the host response to such environmental stressors for corticogenesis (Abazyar and others 2010). It is also possible to infect viruses that can penetrate the placenta, such as CMV, and see how direct viral infections may affect corticogenesis in the fetus. In this context, viruses may rely on the cell cytoskeleton and the dynein and kinesin motors to enter the host cell's nucleus and carry out the viral life cycle (Dohner and Sodeik 2005; Dohner and others 2005), which DISC1 may modulate. Moreover DISC1 also interacts with transcription factors such as activating transcription factor 4 (ATF4), a regulator of the hypoxia pathway (Malavasi and others 2012; Sawamura and others 2008), suggesting a possible mechanism whereby DISC1 plays a role in neonatal hypoxia. In order to address

mechanistic detail in the molecular cross-talks, introduction of *in utero* gene transfer for various molecules in DISC1 genetic models may serve as an important tool (Niwa and others 2010; Taniguchi and others 2012).

In this review, rather than focusing on providing a comprehensive overview of research articles on the subject, we aim to introduce the function of DISC1 in the study of cortical development in association with a wide range of developmental brain disorders. To address this goal, we have tried to reorganize reported roles for DISC1 in cortical development into the three categories: cell autonomous and cell non-autonomous mechanisms as well as host responses to environmental factors. We hope that this novel perspective on the utility and value of DISC1, beyond its narrower classification as the “disrupted-in-schizophrenia” gene, assists in developing an overall understanding of multiple mechanisms orchestrated in corticogenesis. We hope that this will ultimately help to identify therapeutic targets in diseases caused by abnormalities in cortical development.

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Figure 1. DISC1 in Cell Autonomous Mechanisms Regulating Cortical Development

Cell autonomous mechanisms are important for regulating progenitor proliferation and neuronal migration during cortical development. In both processes, DISC1 plays a key scaffolding role, localizing and maintaining many regulatory proteins at the centrosome. During the proliferation of neural progenitor cells, DISC1 occurs at the centrosome binding with NDE1, LIS1 and the dynein motor complex to mediate spindle formation and chromosome attachment. In nucleokinesis, an important process in the migration of neurons, the nucleus and cell body move forward into a leading edge. This process requires proper positioning of the centrosome, reorganization of the microtubule network, and dynein motor complex activity, which are regulated by several proteins including LIS1, NDE1, PCM1

and BBS. A pool of DISC1 occurs at the dynein motor complex where it interacts with LIS1, NDEL1, PCM1, and BBS, localizing and maintaining these proteins at the centrosome for proper migration.

Figure 2. DISC1 in Cell Non-Autonomous Mechanisms Regulating Cortical Development

Cell non-autonomous mechanisms that regulate cortical development consist of cell signaling events initiated by extracellular factors in the cytoplasm or through cell-cell interaction. Three key cell non-autonomous mechanisms involving DISC1 are the NRG1/ErbB and canonical Wnt pathways which play a role in progenitor proliferation, and the Reelin cascade which is important for neuronal migration and positioning. Roles for DISC1 have been reported in each of these pathways, suggesting that DISC1 may be an important molecule in studying how these pathways interact with one another. In the NRG1/ErbB signaling pathway, binding of NRG1 to its receptors ErbB2/3 activates PI3K/Akt signaling which increases expression of DISC1 in primary neurons. DISC1 also inhibits the formation

of the β -catenin degradation complex by binding GSK3 β , therefore leading to β -catenin stabilization and up regulation of Wnt signaling. DISC1 and APP interact with phosphorylated Dab1, a key downstream target of Reelin. Together with LIS1, which also interacts with phosphorylated Dab1, DISC1 is likely to play a role in modulating intracellular downstream signaling of Reelin.

Figure 3. DISC1 in Environmental Factors Regulating Cortical Development

Exposure of the developing fetus to various environmental factors can influence corticogenesis at critical periods. Obstetric complications such as hypoxia and viral infection by cytomegalovirus for example, have shown to influence progenitor proliferation and neuronal migration. DISC1 mouse models show aberrant stress responses to environmental factors during early development, including those for corticogenesis.

Table 1

Mechanisms and factors regulating cortical development and their associated disease pathology

Mechanism	Factors	Associated Pathology	References
Cell autonomous	LIS1	Lissencephaly	(Lo Nigro and others 1997)
	NDEL1	Microcephaly	(Alkuraya and others 2011)
	PCM1	Schizophrenia	(Gurling and others 2006)
	BBS	Bardet-Biedl syndrome	(Katsanis and others 2001)
Cell non-autonomous	NRG1/ErbB	Schizophrenia	(Corfas and others 2004)
		Bipolar disorder	(Cassidy and others 2006)
	Reelin signaling	Norman-Roberts syndrome	(Hong and others 2000)
		Autism	(Persico and others 2001)
	Wnt signaling	Schizophrenia	(Zandi and others 2008)
		Bipolar disorder	(Okerlund and Cheyette 2011)
Environment	Viral infection	Autism	(Libbey and others 2005)
		Schizophrenia	(Pearce 2001)
	Ethanol exposure Hypoxia	Fetal alcohol syndrome	(Ikonomidou and others 2000)
		Cerebral palsy	(Derrick and others 2007)
DISC1	DISC1	Schizophrenia	(Millar and others 2000)
		Schizoaffective disorder	(Hodgkinson and others 2004)
		Bipolar disorder	(Hodgkinson and others 2004)
		Major depression	(Millar and others 2000)
			(Hashimoto and others 2006)

We would like to apologize to many authors whom we were unable to cite due to limitations in space.