Ndel1, Nudel (\textsuperscript{3}Noodle): Flexible in the Cell?

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Nuclear distribution element-like 1 (Ndel1 or Nudel) was firstly described as a regulator of the cytoskeleton in microtubule and intermediate filament dynamics and microtubule-based transport. Emerging evidence indicates that Ndel1 also serves as a docking platform for signaling proteins and modulates enzymatic activities (kinase, ATPase, oligopeptidase, GTPase). Through these structural and signaling functions, Ndel1 plays a role in diverse cellular processes (e.g., mitosis, neurogenesis, neurite outgrowth, and neuronal migration). Furthermore, Ndel1 is linked to the etiology of various mental illnesses and neurodegenerative disorders. In the present review, we summarize the physiological and pathological functions associated with Ndel1. We further advance the concept that Ndel1 interfaces GTPase-mediated processes (endocytosis, vesicles morphogenesis/signaling) and cytoskeletal dynamics to impact cell signaling and behaviors. This putative mechanism may affect cellular functionalities and may contribute to shed light into the causes of devastating human diseases.© 2011 Wiley Periodicals, Inc.

Key Words: Ndel1; cytoskeleton; cell signaling, molecular cellular biology; neurological diseases

Introduction

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Ndel1 (also termed Nudel and pronounced phonetically as “noodle”) is a 345 amino acids coiled-coil protein with remarkable evolutionary conservation: homologs have been identified in diverse non-mammalian species including fungus and zebrafish [Morris et al., 1998; Efimov and Morris, 2000; Niethammer et al., 2000; Reiner, 2000; Sasaki et al., 2000; Hoffmann et al., 2001; Reiner et al., 2002; Drerup et al., 2007]. Ndel1 participates in cytoskeletal organization, intracellular transport, membrane trafficking, enzymatic reactions, and cell signaling [Nguyen et al., 2004; Shu et al., 2004; Liang et al., 2004, 2007; Hayashi et al., 2005; Guo et al., 2006; Kamiya et al., 2006; Mori et al., 2007, 2009; Shen et al., 2008; Shim et al., 2008; Toth et al., 2008; Yamada et al., 2008; Ma et al., 2009; Zhang et al., 2009]. Research on Ndel1 has gained further momentum with the discovery of Ndel1-binding proteins linked to human diseases such as Lis1 [Reiner, 2000; Reiner et al., 2002], the protein mutated in human lissencephaly, and the neurofilament light (NF-L) subunit [Nguyen et al., 2004] and Dynamin 2 (Dyn2) GTPase [Chansard et al., 2011], both mutated in Charcot–Marie–Tooth disease [Niemann et al., 2006]. Disrupted-in-schizophrenia 1 (DISC1), another Ndel1-interacting partner, is now recognized as a strong risk factor for schizophrenia, bipolar disorder, and major depressions [Porteous et al., 2006; Brandon, 2007; Camargo et al., 2008; Wang et al., 2008]. While Ndel1 is an essential protein in vivo, reviews describing its functions refer to Ndel1 as a protein auxiliary to many other cellular pathways. Thus, an integrated picture of the roles of Ndel1 is still missing. In this review, we emphasize on the cytoskeletal and signaling functions of Ndel1 in normal and diseased conditions (Fig. 1). We expand the functions of Ndel1 in association with GTPases and advance the idea that Ndel1 may interdependently control GTPase-mediated processes and cytoskeletal dynamics to impact cell signaling and behaviors (Figs. 2–4).

An Organizer of the Cytoskeleton

Ndel1 was originally identified as a binding partner for Lis1 in yeast two-hybrid screenings [Morris et al., 1998; Efimov and Morris, 2000; Niethammer et al., 2000;
Mitosis and Neurogenesis

The embryonic lethality of Ndel1 null mice, combined with the in vitro findings of impaired growth of Ndel1 null blastocyst and defects in the inner cell mass growth, revealed that Ndel1 is essential for cell proliferation and cell survival [Sasaki et al., 2005]. In dividing cells, prior to mitotic entry at G2/M phase, Ndel1 is necessary for centrosomal separation and maturation through phosphorylation at serine 251 [Mori et al., 2007]. These two functions may also require cytoplasmic dynein-dependent and dynein-independent protein assembly at the centrosome and may occur via Ndel1’s association with the centrosomal proteins pericentrin, γ-tubulin, PCM-1, TACC3, and Su48 [Guo et al., 2006; Hirohashi et al., 2006a,b]. During mitotic progression, Ndel1 interacts with the nuclear matrix protein Cenp-F and localizes to the kinetochores in a Cenp-F-dependent manner [Vergnolle and Taylor, 2007]. Cenp-F is critical for microtubules (MTs)-kinetochore interaction and spindle checkpoint activation. At the kinetochore, Ndel1 activates the dynein-mediated retrograde transport of proteins, stabilizes the kinetochore-MTs interface and ensures chromosomes alignment and segregation without involving checkpoint activation [Liang et al., 2007; Vergnolle and Taylor, 2007]. Independently of its roles at the kinetochores, Ndel1 also regulates spindle assembly through several other mechanisms. For instance, during MTs aster formation, Ndel1 recruits Lis1 for the dynein-dependent MT organization. Furthermore, Ndel1 is a substrate of protein phosphatase 4C (PP4C). Loss of PP4C results in temporal deregulation of cyclin-dependent kinase 1 (Cdk1) in interphase, resulting in hyperphosphorylation of Ndel1, excessive recruitment of katanin to the centrosome, and ultimately, disorganization of MTs and disorganized MTs array [Toyo-oka et al., 2005, 2008]. The MT phenotypes can be rescued with inhibition of either one of the three components of the cascade (i.e., katanin, Ndel1, or Cdk1). Thus, the death of proliferative cells associated with the loss of Ndel1 is very likely to be attributed to these multifaceted roles of Ndel1 during mitotic entry and progression (see Fig. 1 for a summary of the mitotic functions of Ndel1).

Although the functions ascribed to Ndel1 in mitotic cell cultures are thought to take place in vivo, little work on Ndel1 has been performed in constitutively proliferative tissues. Instead, probably due to its higher expression, Ndel1 has been extensively studied in the brain, particularly at embryonic stages during neurogenesis when neuronal progenitors undergo massive proliferation. These precursor cells [for reviews on neurogenesis, see Gotz and Huttner, 2005; Huttner and Kosodo, 2005; Buchman and Tsai, 2007; Fietz and Huttner, 2010], Ndel1 and Lis1 influence the dynein-dependent nuclear envelope invagination that precedes nuclear envelope breakdown [Hebbar et al., 2008]. The Ndel1/Lis1 complex is also important for spindle assembly and orientation in neuronal progenitors in vivo via dynein-mediated cortical MTs capture. For instance, alterations in the orientation of the spindle following Lis1 depletion alter the fate of these cells or induce apoptosis. These effects can be rescued by overexpressing Ndel1 [Yingling et al., 2008]. Thus, by virtue of its functions in dividing cells, investigation of Ndel1’s implication in aberrant cell cycle progression in cancers would be interesting.

Structurally, two distinct dynein-binding domains have been found in Ndel1 to account for its double role in the dynein/Lis1 complex [Torisawa et al., 2011]. The first domain lies within the first 80 amino acids of Ndel1 [Wang and Zheng, 2011], nearby the Lis1-binding region, while the second domain is located in the C-terminus [Torisawa et al., 2011]. On one hand, the binding of the C-terminus of Ndel1 to dynein dissociates the motor from the MTs [Torisawa et al., 2011]. On the other hand, the recruitment of Lis1 by Ndel1 (two supercoiled alpha helices of Ndel1 binding cooperatively to a Lis1 homodimer [Derewenda et al., 2007]) relieves the suppression exercised by Lis1 dimers on dynein activity [Torisawa et al., 2011; Zykiewicz et al., 2011]. Concomitantly, binding of Ndel1 to dynein via dimerization of its coiled-coil domain results in activation of dynein motility [Torisawa et al., 2011]. This mechanism is under refinement and it appears to take place in most cellular functions mediated by the Ndel1/Lis1/dynein protein complex described above such as during MTs aster formation [Zykiewicz et al., 2011]. It is compatible with a model in which suppression of dynein activity by Lis1 account for the plus-end-directed kinesin-1-dependent transport of cytoplasmic dynein/Lis1 on MTs [Yamada et al., 2008].

Reiner, 2000; Sasaki et al., 2000; Hoffmann et al., 2001; Reiner et al., 2002; Drerup et al., 2007]. This interaction was confirmed in mammalian systems and studied in context of dynein protein complex activation/motility [for a review on dynein, see Hook and Vallee, 2006; Vallee et al., 2009; Hirokawa et al., 2010] and microtubule dynamics [Morris et al., 1998; Efimov and Morris, 2000; Niethammer et al., 2000; Reiner, 2000; Sasaki et al., 2000; Hoffmann et al., 2001; Reiner et al., 2002; Drerup et al., 2007]. Later, Ndel1 was found to organize intermediate filaments (IFs) through direct interaction with monomers or indirect association with polymers via molecular motors [Nguyen et al., 2004; Shim et al., 2008; Toth et al., 2008]. Ndel1 also impacts microfilament (MF) dynamics via actin-regulating proteins [Shen et al., 2008; Chansard et al., 2011]. Through remodeling of the cytoskeleton, Ndel1 controls key cellular processes in mitotic cells (centrosome maturation, spindle assembly/orientation, neurogenesis) and post-mitotic neurons (neuronal migration, neurite outgrowth, neuronal maintenance).
Neuronal Migration

While Ndel1 plays critical roles in mitotic cells, it is robustly expressed in developing and mature neurons of the brain. In the developing neocortex, Ndel1 is essential for neuronal migration, the process that governs the inside-out layering of the brain [for a review on neuronal migration, see Ayala et al., 2007]. During this process, Ndel1 and Lis1 act in a common pathway with dynein to regulate nucleokinesis. Nucleokinesis [Buchman and Tsai, 2008] is divided into two mechanically distinct phases: the first phase consists into the extension of the leading process that relies on a MFs/MTs interplay at the cell edge and is responsive to external stimuli; the second step is the pulling of the nucleus toward the centrosome following the extension of the leading process. During these steps, Ndel1 recruits Lis1 to dynein anchored on the nuclear membrane to activate the motor complex. Consequently, the motor walks retrogradely towards the centrosome, pulling the nucleus into the direction of the centrosome. Migrating neurons depleted of Ndel1 by RNAi using in utero electroporation exhibit an uncoupling between the leading process extension and nucleokinesis: the leading process extension is unaffected but the distance between the centrosome and the nucleus is much bigger in Ndel1 RNAi-treated cells vs. control RNAi-treated cells. As a result, Ndel1-depleted neurons (as Lis1-depleted neurons) failed to migrate to their destination and remain stuck in the ventricular/subventricular zones in vivo [Shu et al., 2004]. These RNAi data concord with the defects in migration observed with the hypomorph null Ndel1 mice showing a reduction of 70% and in Ndel1 and Lis1 null compound mice [Sasaki et al., 2005]. Of note, using chimeric mice, a recent study found that Ndel1 is involved in migration into the target lamina, possibly in concert with the proline-directed serine/threonine kinase cyclin-dependent kinase 5 (Cdk5) [Hippemeyer et al., 2010]. In addition to nucleokinesis, LIS1 and Ndel1 display non-cell autonomous roles during neuronal migration that remain to be determined [Hippemeyer et al., 2010].

In brain slices, total loss of Ndel1 also inhibits nuclear migration while neurons with a 65% depletion showed diverse branched migration modes with multiple leading processes, suggesting problems in cell polarity/adhesion [Youn et al., 2009]. Consistent with this idea, Ndel1 has been shown to be important for cell adhesion through passillin: an elegant experiment with fused Ndel1–passillin constructs transfected in cells demonstrated stable Ndel1 protein at nascent focal contacts and great reinforcement in adhesion [Shan et al., 2009]. This effect is abolished by activated focal adhesion kinase (FAK) in a passillin-dependent manner [Shan et al., 2009]. This mechanism has not been investigated in migrating neurons but one could speculate that it would occur based on the conservation of Ndel1 molecular complexes in mitotic and post-mitotic cells, and the implication of FAK in neuronal migration [Xie et al., 2003].

As for mitosis, the functions of Ndel1 during neuronal migration are also regulated by post-translational modifications. Ndel1 is phosphorylated by Cdk5 upon binding to its co-activator p35 [Niethammer et al., 2000]. p35/Cdk5 also phosphorylates the actin-binding protein and wingless-int (WNT) signaling component Dixo1 to facilitate its association with Ndel1 and DISC1, another molecular event required for neuronal migration [Singh et al., 2010]. Consistently, both p35 and Ndel1 null mice show defects in neuronal migration [Chae et al., 1997], further supporting the importance of the p35/Cdk5-dependent phosphorylation of Ndel1 in neuronal migration [Niethammer et al., 2000]. Finally, palmitoylation of Ndel1 reduces dynein activity, thereby impeding neuronal migration in vivo [Shmueli et al., 2010]. This result is in agreement with the idea that Ndel1 recruits Lis1 to dynein to activate the motor complex [Shu et al., 2004; Shim et al., 2008]. Altogether, they suggest that Ndel1 may be involved in the activation of dynein’s ATPase and, perhaps, may display some inherent ATPase activity typical of chaperones. These two rather provocative hypotheses remain to be tested.

Neurite Outgrowth, Neuronal Differentiation, and Maturation

As the brain matures, the expression of Ndel1 increases progressively [Niethammer et al., 2000], hinting to important roles for Ndel1 in differentiating neurons. Ndel1 is important for neurite outgrowth as indicated by loss of function experiments using RNAi or dominant negative forms of the protein. Several Ndel1 proteins complexes related to cytoskeletal organization have been characterized during neurite outgrowth of neuroblastoma cells and primary neurons (see Fig. 1). The interactions between Ndel1, DISC1, and FEZ-1 have been implicated in this process. A mutated version of DISC1 found in patients with neuropsychiatric disorders that no longer associates with Ndel1 impairs neurite outgrowth in differentiating PC12 cells [Kamiya et al., 2006]. A kinases-microtubule-associated proteins (MAPs) cascade promoting neurite extension and involving the protein kinase C zeta (PKCζ) and Aurora-A kinase has been recently discovered [Lefkowitz and Gleeson, 2009; Mori et al., 2009]. This cascade culminates in the activation of Aurora A, phosphorylation of Ndel1 at serine 251 and its recruitment at the axon hillock to promote MT stabilization [Mori et al., 2009]. Pharmacological or molecular alteration of the cascade at single step level results in severe impairment of neurite extension, probably caused by decrease in the frequency of MTs emanation from the MTs organizing center [Mori et al., 2009]. Ndel1 also favors neurite extension by promoting the dynein-mediated transport of the vimentin, an IF implicated in axon regeneration [for a review on IFs,
see Fuchs and Cleveland, 1998; Julien, 1999; Goldman et al., 2008; Eriksson et al., 2009]. Vimentin can be transported as subunit to most likely play a signaling role, or as polymers of 10 nm fibers to provide structural stability to the cell [Fuchs and Cleveland, 1998; Julien, 1999; Goldman et al., 2008; Eriksson et al., 2009]. The implication of Ndel1 in vimentin-mediated signaling remains unclear but it may be linked to the retrograde ERK signaling pathway [Perlson et al., 2005]. These findings on Ndel1 in neurite outgrowth are in concordance with the results obtained with brain slices from Lis1 knockout mice showing defects in neurite extension [Youn et al., 2009] but contrast with the increased neurite length observed in brain slices from Ndel1 knockout mice [Youn et al., 2009]. Further studies are required to clarify these discrepancies.

Over the neuronal development processes, there is a switch in IF expression profile: vimentin expression decreases while NF protein (NF-Light, NF-Medium, and NF-Heavy chains) levels increase. A proper stoichiometry between the three subunits is required for proper NFs assembly [Julien, 1999]. The C-terminal domain of Ndel1 was found to bind directly to the rod coiled-coil domain of NF-L and to associate with other NF subunits in complex with dynein and kinesin motors [Nguyen et al., 2004]. These findings are reminiscent of the Ndel1-dependent interactions with the IF Lamin B and of the assembly of Lamin B-containing matrix on MTs in a dynein-dependent manner [Ma et al., 2009]. In vivo, neurons depleted of Ndel1 accumulate NF proteins in the cell body and neuronal processes, indicative of potential transport and/or assembly defects and, ultimately, show signs of degeneration (DNA fragmentation, deterioration of processes) [Nguyen et al., 2004]. Thus,
Ndel1 regulates IF homeostasis with potential impact on neuronal morphology and integrity.

**Beyond the Cytoskeleton: Emerging Roles for Nudel1 in Cell Signaling**

While the implication of Ndel1 in MTs and NFs functions has been investigated in depth, the contribution of the Ndel1-MFs interface is less understood. Nevertheless, studies have revealed that Ndel1 influences actin filaments organization through several signaling pathways [Shen et al., 2008; Shan et al., 2009]. The discovery of unexpected roles for Ndel1 in cAMP/protein kinase (PKA) and protein kinase B (AKT)/glycogen synthase kinase (GSK) signaling combined with the recent findings that Ndel1 regulates GTPases activity further suggest that Ndel1 acts as a hybrid cytoskeletal/signaling protein in cells (Fig. 1).

**The PDE4/cAMP/PKA Cascade**

A direct interaction between phosphodiesterase 4D (PDE4D) and DISC1, one of the best known interacting partners of Ndel1 has initiated elucidation of potential roles for Ndel1-DISC1 complex in the intracellular signaling mediated by cAMP [Millar et al., 2004; Murdoch et al., 2007; Collins et al., 2008]. PDEs hydrolyze cAMP to inactivate cAMP signaling and is activated by cAMP-dependent PKA-mediated phosphorylation [Houslay et al., 2007]. Later, Ndel1 itself was characterized as an interacting partner of PDE4s [Collins et al., 2008]. The binding of PDE4D3 can stabilize Ndel1 dimerization and Ndel1 is released from the complex by phosphorylation of PDE4D3 by PKA [Collins et al., 2008], which is reminiscent of the case of DISC1/PDE4B complex. In case of DISC1/PDE4B interaction, DISC1 binds to upstream conserved region (UCR) 2 of PDE4B to sequester it in a low activity form, which should increase the cAMP concentration and PKA activity [Millar et al., 2005b]. An activated PKA subsequently phosphorylates the UCR1 region of PDE4B, changes its conformation, and thus induces dissociation of DISC1 from UCR2 region to convert it to an active form [Millar et al., 2005b]. On the other hand, when PDE4B is dissociated from DISC1, the link between DISC1 and Ndel1/dynein/Lis1 complex appears to be potentiated, which possibly affects the related neuronal development pathways described above [see also Sawa and Snyder, 2005]. Similarly, Ndel1 can be phosphorylated by PKA at serine 306 residue, providing another route for the cAMP signaling to modulate the function of Ndel1/Lis1/dynein complex and thus to regulate normal MT dynamics [Bradhaw et al., 2008]. More recently, it has been shown that PKA phosphorylation of Ndel1, a paralog of Ndel1, at threonine 131 and serine 306, is DISC1- and PDE4-dependent and modulates its interaction with Lis1 and Ndel1. These results suggest an intertwined regulatory loop among Ndel1, Nde1, and DISC1 linked by cAMP-PKA signaling [Bradhaw et al., 2011]. Noteworthy is that a significant fraction of PDE4B/DISC1 complex seems to be associated with mitochondria, hinting at potential importance of the mitochondrion for Ndel1-linked cAMP signaling events [Millar et al., 2004, 2005a; Porteous et al., 2006].

**AKT/GSK3 Signaling**

Ndel1 may potentially be linked to AKT signaling and downstream GSK3 signaling pathways through DISC1 [Kim et al., 2009]. DISC1 interaction with KIAA1212 competitively interferes with its interaction with AKT, which appears important for normal brain development [Kim et al., 2009]. The developmental abnormalities caused by deficiency of DISC1 can be rescued by rapamycin, an inhibitor of the AKT-mTOR pathway [Kim et al., 2009]. As AKT activity is also known to be regulated by dopamine D2 receptor, a major target of antipsychotics, the findings suggest a tight connection between functionalities of DISC1 and AKT in the dopaminceptive neurons [Beaulieu et al., 2005]. Moreover, Mao et al. recently showed that DISC1 inhibits GSK3 to block the phosphorylation-dependent destabilization of β-catenin [Mao et al., 2009]. β-Catenin is then translocated into the nucleus and regulates transcription of various target genes that are related to neurogenesis [Mao et al., 2009]. GSK3 is normally inactivated by PKCζ in a cdc42-GTP-dependent manner at the leading edge of cellular processes [Etienne-Manneville and Hall, 2003; Etienne-Manneville et al., 2005; Shen et al., 2008]. Interestingly, Ndel1 stabilizes cdc42 by sequestering cdc42-GAP (guanine activated protein – a protein that inactivates the cdc42 GTPase) in this process, indicating important roles for Ndel1 in the associated signaling events [Shen et al., 2008; Shan et al., 2009]. Also noteworthy is that an N-terminal region of DISC1 is provided for both GSK3β and PDE4B interaction. Thus it is intriguing to see that Ndel1/DISC1 complex engages in GSK3 and cAMP signaling in a similar way through the direct interaction with core enzymes and signaling components. These phenomena may indicate that Ndel1/DISC1 complex interfaces multiple signaling pathways, including those regulated by GTPases.

**A Novel Regulator of GTPases?**

GTPases are key enzymes that are involved in a variety of biological processes, ranging from signal transduction to intracellular membrane trafficking. Despite a great heterogeneity in size and function, they all share the ability to bind GTP and hydrolyze it into guanosine diphosphate (GDP) and phosphatidylinositol. Interestingly, recent findings indicate that Ndel1 associates functionally with several GTPases. In particular, we have recently reported that
a pool of Ndel1 associates directly with Dyn2, a large cytosolic GTPase that severs membranes [Chansard et al., 2011]. In vitro, Ndel1 enhances Dyn2 GTPase activity in its unassembled and assembled forms, without promoting the oligomerization of the enzyme. This supports a role for Ndel1 on Dyn2 activity itself. Besides, gain and loss of function of Ndel1 in cells recapitulate the effects of overexpression of Dyn2 and Dyn2 dominant negative with reduced GTPase activity on the intracellular localization of the 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid [AMPA] receptor subunit GluR1, respectively. These results suggest that Ndel1 regulates Dyn2 GTPase activity and impacts GluR1-containing membranes distribution in a manner reminiscent of Dyn2. In this perspective, it is tempting to speculate that regulation of the Ndel1/Dyn2 interaction could impact membrane fission during trafficking by virtue of its interactions with Dyn2 [Chansard et al., 2011], the cytoskeleton, and kinesin and dynein motors [Niethammer et al., 2000; Sasaki et al., 2000; Ligon et al., 2004; Shu et al., 2004; Taya et al., 2007; Shim et al., 2008; Yamada et al., 2008] in the cytosol. On the one hand, by increasing the GTPase activity of Dyn2, Ndel1 could help cytosolic Dyn2 to constrict membranes and sever GluR1-containing vesicles from organelles. On the other hand, since Dyn2 has been mostly linked to actin, Ndel1 could also modulate actin organization and dynamics [Shen et al., 2008; Shan et al., 2009] to provide the longitudinal tension necessary to pull apart membranes during fission [Roux et al., 2006]. Such longitudinal force has already been suggested in yeast in the form of localized actin polymerization at the site of endocytosis at the plasma membrane [Engqvist-Goldstein and Drubin, 2003; Rodal et al., 2005; Kaksonen et al., 2006]. Alternatively, by
regulating dynein and kinesin activities (the two activities being linked together [Ligon et al., 2004]) through Lis1 [Taya et al., 2007; Yamada et al., 2008; Torisawa et al., 2011] and by activating the walking of soluble molecular motors on MTs, Ndel1 could generate a similar longitudinal force (Fig. 4). Further work is required to confirm this working model of dual forces involving Ndel1, MTs, and actin in mammalian cells during membrane morphogenesis and endocytosis.

In the same line, another study has implicated Ndel1 in the regulation of the small cdc42 GTPase during cell migration [Shen et al., 2008]. The study by Shen et al. suggests that Ndel1 competes with cdc42 GTPase for binding to cdc42-GAP. By sequestering cdc42-GAP at the cell leading edge, Ndel1 dose-dependently stabilizes active cdc42 in response to extracellular stimuli [Shen et al., 2008]. Excess of active cdc42 GTPase can in turn recruit cdc42-GAP from Ndel1 to temper the cdc42-mediated actin remodeling during migration [Shen et al., 2008].

Recently, our laboratory has explored the possibility that Ndel1 interacts with GTPases other than Dyn2 and cdc42. We have found that Rab5 GTPase and its modulator Rabaptin-5 are also binding partners for Ndel1, as detected by co-immunoprecipitations and yeast two-hybrid experiments (Fig. 2). Rab5 is part of the family of Rab GTPases, the largest family of small GTPases. Distributed throughout distinct intracellular compartments, they participate in cell organization and control intracellular transport between organelles [Zerial and McBride, 2001]. The most studied Rab GTPase, Rab5, regulates the intracellular trafficking of vesicles on MTs following endocytosis at the plasma membrane [McLauchlan et al., 1998; Nielsen et al., 1999]. Rab5 has been mostly studied for its role in initiating the homotypic fusion between early endosomes. The function of Rab5, which sits on the early endosomes membranes, is dependent upon a set of activators and effectors that are recruited at the early endosomes membrane. First, Rabex-5, a ubiquitously expressed guanine exchange factor (GEF) protein, has been identified as a highly selective activator of Rab5 [Horiuchi et al., 1997; Delprato et al., 2004]. The current model for Rabex-5-mediated activation of Rab5 suggests a bimodal dynamic [Zhu et al., 2007]. An initial activation of Rab5 occurs through direct targeting of Rabex-5 to the early endosomes membranes via its early endosomal targeting motif [EET; Zhu et al., 2007]. The active GTP-bound Rab22, which belongs to the Rab5 subfamily of RabGTPases, binds to the EET domain of Rabex-5 and targets the latter to the early endosomes membranes, bringing Rabex-5 in close proximity to inactive GDP-bound Rab5 [Zhu et al., 2009]. The activation of Rab5 then occurs through GDP/GTP exchange, mediated by the GEF domain of Rabex-5 [Delprato et al., 2004]. This initial activation creates a basal level of activated Rab5 on the membranes sufficient to recruit cytosolic complexes formed by the association of Rabex-5 and the Rab5 effector Rabaptin-5 [Horiuchi et al., 1997; Lippe et al., 2001]. By bringing additional Rabex-5, Rabaptin-5 is involved in the clustering of Rab5 activation at the docking site of endosomes, contributing to the formation of a

**Fig. 2. Ndel1 interacts with Rabaptin-5 and Rab5 GTPase.** (A) HeLa cells were homogenized in Homogenization Buffer (HB; 250 mM sucrose, 20 mM Tris–HCl pH 7.4, 1 mM EGTA, 1 mM EDTA) supplemented with proteases and phosphatases inhibitors using a glass grinder, and a post-nuclear supernatant (PNS) was generated by centrifuging the lysates at 3000 rpm for 15 min. The PNS was loaded on a 5–25% iodixanol step gradient prepared in HB and centrifuged for 20 h at 27,000 rpm. 500 μL fractions were further carefully collected and odd fractions were analyzed by Western blot. Distribution pattern of the endosomal marker EEA1, Rab5, Rabaptin-5, and Ndel1 were examined. The distribution of the KDEL ER Marker was used as control. (B) Band intensities of EEA1, Rab5, Rabaptin-5, Ndel1, and KDEL ER Marker for each fraction were expressed as a percentage of the total intensity of all fractions. The results indicate that Ndel1 largely co-fractionates with Rab5 and Rabaptin-5 in the light membranes which include early endosomes, as confirmed with the presence of EEA1. (C) HeLa cells were co-transfected with expression vectors coding for Ndel1-flag and Rabaptin-5-EGFP. Using Ndel1 antibodies coupled to protein G sepharose, over-expressed Rabaptin-5-EGFP was co-immunoprecipitated with Ndel1 and detected by Rabaptin-5 antibodies. Similarly, using Rabaptin-5 antibodies coupled to protein G sepharose, Ndel1-flag co-immunoprecipitated with Rabaptin-5, as detected by flag antibodies. Co-immunoprecipitation with protein G sepharose only (noAb) and Myc antibodies coupled to protein G sepharose were used as negative controls. Five percent of cell lysate (5% input) was used as positive control. (D) and (E) Using Ndel1 antibodies coupled to protein G sepharose, Rabaptin-5 co-immunoprecipitated with Ndel1 in mouse whole brain (D) and spinal cord (E) lysates, as detected with Rabaptin-5 antibodies. Interestingly, Rab5 also co-immunoprecipitated with Ndel1, as detected with Rab5 antibodies, suggesting that Ndel1, Rabaptin-5, and Rab5 exist as a tripartite complex in the mouse CNS. Co-immunoprecipitation with protein G sepharose only (no Ab) and Myc antibodies coupled to protein G sepharose were used as negative controls. Five percent of cell lysate (5% input) was used as positive control. IgG, immunoglobulin. (F) Mapping of interaction interface between Ndel1 and Rabaptin-5 using the yeast two-hybrid assay. Deletion constructs of human Ndel1 and Rabaptin-5 containing various coding region (designated by the number of amino acid residues) for yeast two-hybrid assays were generated. MaV203 yeast cells were transformed with the constructs as indicated and applied to growth assay on HIS selective media containing 20 mM 3-amino-1,2,4-trizol (3-AT; Left) and colony-lifting assays for interaction-dependent β-galactosidase expression (Right). Schematic representation of Rabaptin-5 and Ndel1 domains. According to the yeast-two-hybrid data, the interaction domain with Ndel1 is located in the coiled-coil region CC2-1 of Rabaptin-5 (hatched rectangle), and the interaction domain with Rabaptin-5 localizes in the C-terminal segment of Ndel1 (hatched rectangle). BD, binding domain.
Ndel1 affects Rab5 functions and signaling (through docking, and McBride, 2001 for detailed references].

There are two microdomains of activated Rab5 at the endosomes membranes. Similarly, when complexed with Rabex-5, Rabaptin-5 promotes the stabilization of Rab5 activation by slowing down GTP hydrolysis [Rybin et al., 1996]. The activation of Rab5 further contributes to the recruitment of additional effectors, including the hVPS34–p150 phosphoinositide-3-OH kinase (PI3K), the early endosomal antigen 1 (EEA1), and Rabenosyn-5, which organize themselves into an activation cascade leading to SNARE (SNAP [soluble NSF attachment protein] receptor) activation, endosomes docking and membrane fusion [see Zerial and McBride, 2001 for detailed references].

It remains unclear where in the cell and how Ndel1 affects Rab5 functions and signaling (through docking, activation, stabilization, clustering, transport, localization, etc.) but the phenotype generated by loss of Ndel1 on endosomes size argues for an implication of Ndel1 in Rab GTPases biology. Indeed, Ndel1 depletion by siRNA significantly increases the size of early endosomes, especially for endosomes with an area ranging from 0.05 to 0.2 \( \mu m^2 \) (Fig. 3). Considering that Rab5 over-activation increases significantly early endosomes size [Bucci et al., 1992; Stenmark et al., 1994], Ndel1 may alter early endosomes fusion by down-regulating Rab5 activity in cells through a direct interaction with Rab5. An alternative explanation for Ndel1’s effect on early endosomes size might involve other members of the Rab family of GTPases. In particular, Rabaptin-5, which associates with both Rab5 and Ndel1 (Fig. 2), is also known to interact with Rab4, a GTPase implicated in the sorting of endocytosed cargo and the genesis of recycling endosomes from early endosomes [Vitale et al., 1998; Deneka et al., 2003; Pagano et al., 2004]. Through its interaction with Rab5, Rab4, and Ndel1, Rabaptin-5 could therefore act as an organizing platform for the genesis of recycling vesicles. In this context, one can conceptualize that loss of Ndel1 function impedes the formation of recycling vesicles, thus increasing the size of early endosomes from which they are generated (Fig. 3). This idea is particularly attractive considering that the molecular motor dynein, a well-described Ndel1-binding protein, also interacts with Rab4 [McCaffrey et al., 2001] and could be involved, together with Ndel1, in pulling recycling endosomes apart from early endosomes in a MT-dependent manner (Fig. 4).

Studies on Rab5 in the past decade have aimed to understand the role that Rab5 GTPase plays in the biogenesis of signaling endosomes (the early endosomes that retrogradely transport ligand–receptor complexes to the soma [Delcroix et al., 2003]), and Ndel1 might be an important player in this signaling process (Fig. 4). Liu et al. have recently suggested that Rab5 may play a central role in the phenomenon [Liu et al., 2007]. They showed that an increase in Rab5 activation significantly decreases the nerve growth factor (NGF)-induced differentiation (i.e., neurite outgrowth) of PC12 cells into neuron-like cells. They observed that this was correlated to an impaired NGF-induced phosphorylation of tyrosine kinase receptor A (TrkA). Thus, they proposed that the blockade of Rab5 activity prevents the access of phosphorylated TrkA to phosphatases contained in mature endosomes because of an impaired early endosomes fusion. Based on the association between Ndel1 and Rab5 (Fig. 2) and the finding of increased early endosomes size following Ndel1 knockdown (Fig. 3), one can speculate that Ndel1 plays a dual role in regulating intracellular signaling (Fig. 4): Ndel1 could (1) reduce Rab5 activity to generate signaling endosomes and (2) promote the retrograde transport of signaling endosomes on MTs towards the soma in a dynein-dependent fashion. In sum, through synergism of its cytoskeletal functions and regulation of GTPases, Ndel1...
could be involved in a wide variety of cellular processes, including endocytosis, early endosomes fusion, endosomes signaling, endosomes sorting, and MTs-dependent fission and transport of vesicles and endosomes (Fig. 4).

**Of Humans, Mice, and Diseases**

Ndel1 functionally binds to several proteins mutated in human neurodevelopmental, neuropsychiatric or neurodegenerative disorders. Also, cells and animal models devoid of Ndel1 recapitulate some aspects of these diseases. Collectively, these results suggest that loss of Ndel1 interactions with disease-causing proteins may contribute to the etiology of these human pathologies.

**Lissencephaly**

The N-terminus of Ndel1 binds to Lis1. Heterozygous Lis1 mutations constitute the most common cause of human lissencephaly, a neural disorder characterized by mispositioning of cortical neurons and disarrayed cerebral lamination [Reiner, 2000; Reiner et al., 2002, 2006; Chae and Walsh, 2007; Wynshaw-Boris et al., 2011]. Patients with lissencephaly are often severely retarded, epileptic, and die at a young age. The most striking feature of the brains of affected individuals is their “smoothness,” i.e., their brains mostly lack the convolutions (sulci and gyri) typical of the normal brain [Reiner, 2000; Reiner et al., 2002, 2006; Chae and Walsh, 2007; Wynshaw-Boris et al., 2011]. In mouse embryos, depletion of Ndel1 or Lis1 in early-born migrating neurons by gene targeting or RNAi trigger alterations in the cytoskeletal and signaling pathways described above, and recapitulate the migration and positioning defects observed in human patients [Shu et al., 2004; Sasaki et al., 2005]. Overexpression of Ndel1 rescues the migratory defects of neurons lacking Lis1 [Shu et al., 2004], indicating that Ndel1 can compensate partly for the loss of Lis1. Thus, strategies boosting Ndel1 levels and/or stabilizing Lis1 could promote the generation of signaling endosomes and favor their transportation towards the cell soma in a dynein-dependent manner.
protein may be therapeutically used to attenuate the migratory defects in Lissencephaly. Indeed, inhibition of calpain increases LIS1 expression and rescues in part the deficits of a mouse model of lissencephaly [Yamada et al., 2009].

By virtue of its critical role in mitotic cells, mice null for Ndel1 are embryonic lethal at peri-implantation stage (~E4.5–E5) [Sasaki et al., 2005], precluding to a clear modeling of the lissencephaly phenotype. Compound heterozygote knockout for Ndel1 and Lis1, or compound mice hypomorph for Ndel1 and heterozygote for Lis1, show synergistic defects in neuronal migration [Sasaki et al., 2005]. These provide compelling evidence that Ndel1 and Lis1 functionally interact to control normal neuronal migration defective in lissencephaly. However, none of these mice die post-natally at young age in a manner reminiscent of lissencephalic patients. These results suggest that other factors or pathways may be involved to fully reproduce the lissencephalic phenotype. In this regard, it is noteworthy that Lis1 is a subunit of the platelet-activating factor acetylhydrolase 1B, which functions have been linked to membrane tubule formation, functional organization of Golgi complex, etc. [Bechler et al., 2010, 2011]. These diverse Lis1 functions may further support the cytoskeletal, membrane trafficking and signaling roles of Ndel1. In any case, the design of the current mouse models for lissencephaly is apparently not optimal to unravel all the pathological features of the disease. Mouse models with peri-natal or early-post natal cell type-specific depletion of Ndel1 and/or Lis1 may reveal new insights into the roles of Ndel1 in lissencephaly.

**Schizophrenia**

The identification of Nde1 as one of the most robust interacting partners of DISC1 has led Nde1 to the cellular pathways related to the pathogenesis of major psychiatric disorders, including schizophrenia, bipolar disorder and major depressions [Ozeki et al., 2003]. DISC1 was first characterized as a gene disrupted by a balanced translocation between chromosomes 1 and 11, t(1;11)(q42;q14) that co-segregates with symptoms of schizophrenia and bipolar disorders. The mutant DISC1 protein with C-terminal truncation caused by the chromosomal translocation loses Nde1 binding motif and, when overexpressed, proper localization of Nde1/Lis1/dynein complex is disrupted [Ozeki et al., 2003; Kamiya et al., 2006].

The functional deficiency of DISC1 has been linked to multiple abnormalities in the neurodevelopmental processes including neurogenesis, neuronal migration, neurite outgrowth, and synaptogenesis [Miyoshi et al., 2003; Ozeki et al., 2003; Kamiya et al., 2006; Mao et al., 2009]. As these neurodevelopmental abnormalities have been regarded as pathological hallmarks of schizophrenia and related psychiatric disorders in many clinical studies [Rapoport et al., 2005; Ayhan et al., 2009], it has been thought that DISC1 may provide critical insight into many aspects of schizophrenia and related mood disorders [Hennah et al., 2003; Palo et al., 2007]. Nde1 and its paralog Nde1 shows complementary expression profile in the developing brain; Nde1 expression peaks at E12 and Nde1 expression increases as Nde1 expression becomes lower [Niethammer et al., 2000; Sasaki et al., 2000; Feng and Walsh, 2004]. Accordingly, Nde1/DISC1 complex in the early embryogenesis is gradually replaced by Nde1/DISC1 complex [Brandon, 2007; Burdick et al., 2008] indicating that Nde1 and Nde1 regulate DISC1-mediated processes in a complementary manner throughout the brain development, which maybe partially defective in schizophrenia pathogenesis.

Nde1 is the same protein as the endo-oligopeptidase A, a thiol-activated peptidase converting and inactivating numerous bioactive peptides [Hayashi et al., 2005, 2010]. The oligopeptidase activity of Nde1 is conferred by catalysis-associated cysteine 273 that once mutated cannot compensate for the loss of Nde1 function (by RNAi) in neurite outgrowth and differentiation of PC12 into neurons [Hayashi et al., 2005, 2010]. These results suggest that the peptidase activity of Nde1 is important for neurite outgrowth though it remains unclear how this activity is related to the cytoskeletal and signaling functions of Nde1 during neurite extension. Of note, DISC1 inhibits Nde1 peptidase activity. As DISC1 mutations have been associated with neuropsychiatric diseases, these results highlight a potential implication of cysteine 273 and the peptidase activity of Nde1 in neuropsychiatric disorders.

In human genetics, an association study in American population has confirmed the link between Nde1 gene and schizophrenia [Burdick et al., 2008]. Nde1, the paralog of Nde1, has also been designated as a schizophrenia-associated locus in a genome-wide linkage study of the Finnish family with DISC1 risk variant [Hennah et al., 2007]. Moreover, there is a report showing the level of Nde1 transcript is reduced in schizophrenic patients [Lipska et al., 2006]. Nde1 or Nde1 loss of function shows reduced number of neurons in cerebral cortex and thinner cortical layering defects, which are consistent with the phenotypes caused by Lis1 loss-of-function such as cortical and hippocampal disorganization and associated defects in cognitive behaviors [Cahana et al., 2001; Feng and Walsh, 2004; Sasaki et al., 2005]. Considering the fact that Nde1/Lis1 complex is known to be a downstream component of Reelin [Wynshaw-Boris et al., 2011], another schizophrenia susceptibility factor, the developmental defects associated with Nde1 may have strong implications in the neuroanatomical abnormalities in schizophrenia.

**Neurodegenerative and Motor Neuron Diseases**

Although neurodegenerative diseases are slow progressive disorders with selective vulnerability for populations of
neurons, the cell deterioration, and death processes are remarkably similar among the diseases. For instance, intracellular transport defects, membrane trafficking dysfunctions, and disruption of the cytoskeleton are common signatures of dying neurons. Genetic and biochemical alterations in cytoskeletal proteins, molecular motors, and membranes-associated proteins can be a primary cause for several neurodegenerative disorders such as Alzheimer’s disease (AD), Frontal temporal dementia [Lee et al., 2001], and amyotrophic lateral sclerosis (ALS), the most common form of human motor neuron diseases [Ilieva et al., 2009]. These facts raise the question as to whether deregulation of Ndel1 could promote neurodegeneration. Several findings suggest an active role for Ndel1 in neuronal survival and thus, in neurodegeneration upon loss of function. First, in vivo differentiated cortical neurons depleted of Ndel1 show accumulation of NFs in cell bodies, reminiscent of the NF inclusions in AD and ALS, collapse of neuronal processes, and DNA fragmentation [Nguyen et al., 2004]. Second, in a mouse model expressing a mutant form of superoxide dismutase 1-linked to familial ALS, a decrease in levels of Ndel1 has been associated with transport defects, prior to motor neuron degeneration and paralysis [Nguyen et al., 2004]. The generation of mutant SOD1 mice in a conditional knock-out background for Ndel1 in motor neurons would clearly define the role of Ndel1 in motor neuron survival. Third, mice with a mutation in dynein heavy chain also develop motor dysfunction [Hafezparast et al., 2003], suggesting that loss of Ndel1’s regulation on dynein function may contribute to motor neuron demise. Finally, autosomal recessive mutations in the Alsin gene linked to the juvenile form of ALS, affects endosomes trafficking through Rab5 [Devon et al., 2006; Chandran et al., 2007], probably because Alsin is an activator of Rab5. As Ndel1 functionally associates with Rab5 and affects endosomes size (see Figs. 2 and 3), this further highlights a potential implication for Ndel1 in motor neuron dysfunction.

Charcot–Marie–Tooth (CMT) Diseases is a group of inherited disorders that affect peripheral motor and sensory nerves [Niemann et al., 2006]. CMT neuropathies constitute one of the most common inherited neurological disorders, with 36 in 100,000 affected. They are divided into primary demyelinating neuropathies that involve destruction of the myelin sheath wrapping the axon (CMT1, CMT3, and CMT4) and primary axonal neuropathies (CMT2) which targets the axon first [Niemann et al., 2006]. Mutations in NF-L and Dyn2 cause CMT2 [De Jonghe et al., 2001; Zuchner et al., 2005]. Both proteins bind to Ndel1 [Nguyen et al., 2004; Chansard et al., 2011], suggesting that Ndel1 may be a pivotal molecule in organizing cytoskeletal dynamics and membrane trafficking in axons of motor and sensory neurons. It is unknown how the interactions between Ndel1 and the mutated proteins are mediated, whether they form bi-par-
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Institute post-doctoral scholarship.

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**CYTOSKELETON**

**Nuclear Distribution Element-Like 1**


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