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## Cortical Development deNUDEd

**The development of the cerebral cortex is a highly orchestrated process of cell division and migration. In this issue of *Neuron*, Feng and Walsh and Shu et al. examine the roles of two related proteins, Nde1 (mNudE) and Ndel1 (NUDEL), in cortical development. These proteins play a crucial role in centrosome positioning, with Nde1 functioning mainly during progenitor cell divisions and Ndel1 functioning in neuronal migration.**

The cerebral cortex arises from a complex interplay of cell division, differentiation, and migration during embryogenesis. An error in one of these processes during development will impact brain function throughout the life of the organism. This is particularly evident in humans when cortical malformations cause mental retardation and epilepsy. An example of one such disorder is lissencephaly, where the normally convoluted cerebral cortex is smooth due to defects in neuronal cell migration (Gupta et al., 2002; Olson and Walsh, 2002). *LIS1*, which is mutated in an autosomal form of lissencephaly, is part of an evolutionarily conserved network of interacting proteins that regulates the function of the microtubule motor cytoplasmic dynein. In the filamentous fungus *A. nidulans*, the ortholog of *LIS1* is *nudF* (for nuclear distribution F)—one of several mutants isolated for their inability to move their nuclei into the tube-like mycelium (Xiang et al., 1995). This process is dependent upon the proper regulation of microtubules and cytoplasmic dynein. Further genetic screens in *A. nidulans* found that *nudE* overexpression could suppress the nuclear positioning defect due to a mutation in *nudF* (Efimov,

2003). Two highly related mammalian orthologs of *nudE*, *Nde1* and *Ndel1* (formerly *mNudE* and *NUDEL*), were isolated by their ability to bind to *LIS1*, suggesting that there is a functional relationship between *LIS1*, *Nde1*, and *Ndel1* in mammals (Feng et al., 2000; Niethammer et al., 2000; Sasaki et al., 2000). Somehow these proteins facilitate cytoplasmic dynein's motor activity or its ability to bind cargo. While it is gratifying to see conservation of the *nud* interactions across evolution, what role do these proteins play in brain development? Two papers in this issue of *Neuron* (Feng and Walsh [2004] and Shu et al. [2004]) address this question for both *Nde1* and *Ndel1*, respectively.

Feng and Walsh describe the consequences of inactivating *Nde1*, which is expressed by the proliferative progenitors that produce the neocortical neurons. During corticogenesis, a single layer of proliferative precursors that line the ventricle produces the six-layered cerebral cortex. Because neurons born in this ventricular zone will be unable to divide again, the precursor population has to balance the production of proliferative and postmitotic progeny: if too many neurons are produced ahead of schedule, there will be a shortage of progenitors to produce neurons later in development. Retrospective studies that date the birth of cortical neurons have shown that, early in development, progenitors produce more mitotic progenitors. Then, in midcorticogenesis, there is a switch (one that piques the interests of any developmental biologist) in which asymmetric divisions generate both proliferative and postmitotic progeny (Caviness et al., 1995). In *Nde1* mutant mice, Feng and Walsh found that this control system appears to break down, since depletion of *Nde1* resulted in a cortex that is smaller than that in wild-type animals. Subsequent analyses revealed that the later-born neurons that normally populate the superficial layers are missing, whereas earlier-born deep layer neurons are unaffected. If anything, slightly more neurons are born at earlier times. These results led Feng and Walsh to investigate asymmetric divisions in the *Nde1*<sup>-/-</sup> embryos.

Asymmetric division in a number of invertebrate organisms is accomplished by orienting the mitotic spindle so that developmental determinants are differentially inherited upon cleavage of the two daughter cells (Doe and Bowerman, 2001). This seems to hold true for the mammalian cerebral cortex, where time-lapse imaging has shown that the angle of mitotic cleavage can predict an asymmetric division (Chenn and McConnell, 1995; Haydar et al., 2003; Noctor et al., 2004). Feng and Walsh found defects in the cell division behavior of cortical progenitors of *Nde1*<sup>-/-</sup> mice. First, there was an accumulation of progenitor cells in mitosis along the ventricular surface, indicating a delay in mitosis. Normally in rodents, progenitors divide their chromosomes in a plane perpendicular to the ventricular surface. However, in the *Nde1*<sup>-/-</sup> mice, a larger portion of mitotic cells had division planes that varied from the normal 90°. The authors speculate that the absence of *Nde1* randomizes the division plane, causing more divisions to produce neurons rather than progenitors. A delay in the cell cycle may also affect the fate of the daughter cells: transplantation studies have shown that a cortical progenitor's fate is cell cycle dependent (McConnell and Kaz-

nowski, 1991). However, a spindle defect is likely the primary cause since Feng and Walsh show that interference with Nde1 function in 293T and COS-7 cell lines impairs spindle orientation, possibly through a defect in the integrity of the centrosomes which anchor the mitotic spindle through microtubule connections to the cell cortex.

Centrosomes also figure prominently in the study of the Nde1 homolog Ndel1 by Shu et al. In contrast to Nde1, Ndel1 is highly expressed by migrating neurons. Although there have been studies on the role of dynein in the orientation of the centrosome as fibroblasts migrate in vitro, most studies have focused on the microtubule connections from the centrosome to the leading edge of the cell (Etienne-Manneville and Hall, 2001; Palazzo et al., 2001). A migrating neuron translocates its nucleus/cell soma after its leading process has extended in a manner similar to an axonal growth cone. Very little is understood about how the nucleus of a migrating neuron is translocated. The haploinsufficiency of LIS1 in a human neuronal migration defect indicates that dynein and its associated proteins must play a crucial role at some stage of somal translocation.

Shu et al. first connect Lis1 and Ndel1 biochemically by examining the protein complexes that are formed in the presence and absence (via RNAi) of Ndel1 in tissue culture cells. Depletion of Ndel1 causes a slight decrease in the association between Lis1 and cytoplasmic dynein. Since Lis1 is postulated to be an activator of dynein, a deficiency in Ndel1 should have a similar effect as a Lis1 deficiency. Shu et al. find that individually inactivating Ndel1, Lis1, and the heavy chain of cytoplasmic dynein (DHC) using RNAi produces similar effects: migration is perturbed. Close examination of the transfected cells reveals a common anomaly, that the distance between the nucleus and the centrosome is increased. Based on these observations, Shu et al. propose a model that places Ndel1, Lis1, and DHC function at the nucleus, where the centrosome-directed DHC motor activity is anchored on the nuclear envelope and maintains a microtubule-based link between the nucleus and the centrosome. The centrosome acts as a hub for microtubules that are directed toward the nucleus and dynein motors its nuclear cargo along microtubules toward the centrosome.

When taken together, the findings reported by Feng and Walsh and Shu et al. are remarkable in that inactivation of two separate but highly homologous genes disrupts two distinct phases of the life of a cortical neuron: cell division and migration. This is likely due to the complementary expression patterns of Nde1 and Ndel1. By studying dynein regulators that are differentially expressed, we are able to gain insight to specific functions in different milieus. A bountiful future awaits researchers at this border of cell biology and developmental neurobiology with further questions: How does Nde1 regulate spindle orientation, and what developmental cues trigger this regulation? What anchors dynein to the nucleus, enabling dynein to move the nucleus toward the centrosome? Finally, what is the mechanism for dynein's "activation" by LIS1? Dynein is a highly cosmopolitan mechanoenzyme, appearing in diverse cellular functions, and LIS1 is proving to be a Rosetta stone for understanding

the cellular roles of dynein that underlie the development of the cerebral cortex.

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## Peering into the Birth Canal during Ion Channel Parturition

**Recent studies have provided detailed structures of the N-terminal T1 domain of Kv channel  $\alpha$  subunits that mediates contranlational subunit assembly. In this issue of *Neuron*, Kosolapov et al. probe T1 domain structure within the ribosomal tunnel. They find that the T1 domain forms secondary structure within the tunnel, in preparation for its immediate role in governing channel assembly upon exit.**

Voltage-gated potassium or Kv channels are key determinants of intrinsic electrical activity in excitable cells, and of crucial signaling events (insulin release, response to antigen, etc.) in a variety of nonexcitable cells. Kv channels are oligomeric membrane proteins, composed of four polytopic transmembrane  $\alpha$  subunits, which are the voltage-sensing and pore-forming constituents of