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Moving Neurons back into place

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Abstract

Subcortical band heterotopia (SBH) is a neuron migration disorder characterized by an aberrant ‘band-like’ accumulation of neurons within the neocortical white matter, frequently leading to mental retardation and epilepsy. SBH can now be regressed by reactivating neuronal migration.

SBH is a developmental condition whose symptoms vary from normal IQ to severe mental retardation and intractable epilepsy¹. Current treatments for epileptic SBH patients are exclusively symptomatic, aimed at reducing seizure frequency and severity. Unfortunately, SBH seizures are mostly refractory to medication, and surgical resections of epileptic foci are ineffective in these particular cases². Therefore, when prenatal diagnostics show SBH, expectant parents facing the potential (and unpredictable) severity of the condition and the lack of effective treatments, often fatally choose to interrupt pregnancy. In this issue, Manent et al. describe a postnatal molecular intervention that partially rescues a rat model of SBH, morphologically and functionally. This very ingenious study is a landmark in translational research discoveries in neuron migration disorders and epilepsy.

Proper neocortical function requires appropriate neuronal positioning. During midembryonic development, cortical pyramidal neurons are generated adjacent to the lateral ventricle then migrate radially towards the surface of the brain to reach the cortical plate, and subsequently establish synaptic connections. In the past 50 years, several conditions displaying neuron migration disorders (NMD) have been described and many of the critical factors regulating this developmental step have been identified³. However, our capacity to manipulate migration *in vivo* to create new treatment options has not been realized. It has generally been accepted that, once a child is born with SBH or related condition, it is too late to consider curative treatments, since brain morphology is already set in place.

Doublecortin (DCX) plays a key role in neuronal migration by binding and stabilizing microtubules as cells migrate towards the brain surface. Mutations of DCX in human leads to SBH (aka “double cortex” syndrome) predominantly in females, and to the more severe lissencephaly (aka “smooth brain” syndrome) in males⁴. Joseph J. LoTurco's laboratory previously demonstrated that acute knockdown of *Dcx*, by way of *in utero* electroporation of *Dcx* short hairpin RNA (shRNA), induces dramatic cortical migration defects in rat and mouse⁵. Moreover, in rat only, *Dcx* knockdown induces the formation of a massive band of abnormally positioned neurons lying between the ventricular walls and the cortical plate, thus constituting a powerful rodent model to test potential SBH therapies⁶.

A few other animal models of cortical heterotopia have been described and are currently actively studied, such as the spontaneous mutant *tish* rats⁷, the *HeCo* mice⁸ or the antimetabolic methylazoxymethanol (MAM) prenatal injection model⁷. *In vitro* rescue experiments have been conducted showing that neurons of MAM treated ferret cortical slices were able to migrate more effectively into adjacent co-cultured normal cortical plate⁹. However, no *in vivo* rescue

of NMDs has been reported, leaving open the question of whether gene therapy or other such options might someday help treat these disorders.

In this paper, Manent et al. from the LoTurco's lab tested whether a delayed re-expression of *Dcx* could restimulate the migration of stalled neurons to result in regression of the SBH. This delay is a crucial feature that mimics the incompressible time period between the phenotype completion, the diagnostic and the treatment. This was enabled by co-electroporating the *Dcx* knockdown shRNA vector with a drug-inducible *Dcx* expression vector system. Very interestingly, the postnatal re-expression of *Dcx* was able to stimulate the migration of neurons already settled in the heterotopic band, leading to a significant reduction of the size of SBH. More surprisingly, rescued neurons migrated to their correct laminar position, and adopted a normal morphology. Indeed, they show here that their rat model of SBH displays an increased susceptibility to pentylenetetrazol-induced seizures and that neuronal migration reactivation also partially rescues this seizure phenotype.

Such a successful rescue only occurred in rat in a short postnatal time window between P0 and P5 which, if applicable to humans, would roughly correspond to late prenatal to early postnatal ages. This critical feature of the *Dcx* induced SBH rescue makes potential molecular intervention possible in patients. Indeed, *in utero* intraventricular cerebral injections might be possible in the future, as advances in foetal surgery continue, and even more safely after birth. It is exciting to consider potential treatments for these seemingly “incurable” neurodevelopmental disorders.

However, as stated by the authors, this specific experimental intervention is clearly not applicable to human. In this study, both the “problem” (the *Dcx* shRNA) and the “solution” (the inducible *Dcx* encoding vector) are introduced simultaneously in a population of neurons. Thus, only those cells in which *Dcx* is knocked down are later subject to forced re-expression of *Dcx*. Whereas the electroporation procedure could be replaced by a viral injection in humans with a *DCX* mutation, the precise targeting of the heterotopic neurons would remain problematic. On the other hand, one wonders if precise targeting of heterotopic neurons is necessary. *Dcx* over-expression in embryonic cortical neurons causes cells to adopt highly bipolar morphology¹⁰ but consequences on more mature neurons remains to be tested and would need to be balanced with any potential clinical improvement in patients with SBH.

Finally, if *Dcx* delayed re-expression can reactivate migration, could other actors of neuronal migration function similarly? Conversely, could *Dcx* re-expression rescue heterotopia caused by other gene mutations? In other word, is this recovery specific to compensation of *Dcx* deficiency or can *Dcx* re-expression generally reactivate or promote migration? Of note, *Dcx* can compensate *in vitro* migration defects induced by *Lis1* deficiency, another migration stimulating protein¹¹. Those questions are surely exciting to scientists thinking about ways to improve outcome for a host of NMDs as well as other neurodevelopmental disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Dcx delayed re-expression rescues the SBH phenotype induced by *Dcx* shRNA. *In utero* electroporation of *Dcx* shRNA in rat lateral ventricle wall disturbs the migration of neurons, which then accumulate in a heterotopic subcortical band (left panel). Simultaneous electroporation of a drug inducible *Dcx* encoding vector allows temporal and spatial-specific re-expression of *Dcx*. Without *Dcx* re-expression, these neurons would locate heterotopically and lowered seizure threshold. When *Dcx* re-expression is induced in these neurons between P0 and P5, many restart migration. Most of these neurons reach their correct target within the cortical plate, where they differentiate and integrate to the cortical networks (right panel).