nature neuroscience gateway

FEATURED ARTICLES

The direct road to migration

Neuroscience Gateway (August 2008) | doi:10.1038/ngw1815

The transcription factor Neurogenin 2 promotes the radial migration of newly born neurons by directly activating the small RhoGTPase Rnd2.

A key step in nervous system development is the migration of neurons from their birthplace to a final permanent location. Proneural transcription factors are known to control the differentiation of neural stem cells into neurons, as well as promoting neuronal radial migration in the embryonic cerebral cortex. However, the mechanisms underlying this migration-promoting activity have remained unclear. Reporting in *Nature*, François Guillemot and colleagues have identified the small Rho GTPase Rnd2 as a direct target of the transcription factor Neurogenin 2 (Neurog2), which is involved in neuronal migration.

The authors used microarray expression analysis to identify *Rnd2* as a gene that is downregulated in *Neurog2*-mutant mice embryos, and upregulated when *Neurog2* is overexpressed. Expression studies revealed that *Rnd2* is restricted to migrating cortical neurons and their immediate precursors, and confirmed that this expression was dependent on *Neurog2*.

Rnd2 silencing resulted in the disruption of all stages of migration through the cortex and the alteration of neuronal morphology. Conversely, other features such as progenitor proliferation and cortical neuron specification, as well as the organization of radial glia along which neurons migrate, were unaffected. These findings indicate that Rnd2 functions cell-autonomously to regulate both the shape and migration of cortical neurons.

Expression of *Rnd2* via the *NeuroD1* promoter, which is transiently and moderately active in newborn cortical neurons, rescued the early radial migration defects seen in *Neurog2* mutant neurons, but did not rescue the final migration phase for correct neuronal positioning in the cortical plate. Thus, *Rnd2* appears to be the main downstream effector of *Neurog2* that promotes radial migration, whereas other factors might regulate later stages of these processes.

But is *Rnd2* a direct target of Neurog2 or is it possible that its expression is induced via a transcriptional cascade? Using a luciferase reporter assay, the authors showed that *Neurog2* was able to efficiently activate transcription from an *Rnd2* 3' enhancer containing conserved E-boxes specific to *Neurog2*. Furthermore, Neurog2 bound to the *Rnd2* 3' enhancer in cortical cells *in vivo*. Together these results show that Neurog2 directly induces *Rnd2* expression in the embryonic cortex.

This work reports for the first time the spatio-temporal regulation of a small GTPase at the transcriptional level. Unlike other Rho family members, Rnd proteins are not regulated by guanine nucleotide exchange factors (GEFs) or GTPase-activated proteins (GAPs), and their expression is thought to have an important regulatory role. Interestingly, whereas *Neurog2* is downregulated when neuronal progenitors stop dividing, *Rnd2* continues to be expressed. This suggests that other factors might be responsible for the maintenance of *Rnd2* expression.

Kim Baumann

ORIGINAL RESEARCH PAPER

1. Heng, J. I-T. *et al.* Neurogenin 2 controls cortical neuron migration through regulation of *Rnd2*. *Nature*, 6 August 2008. doi:10.1038/nature07198 | Article |