Journal Club

Transcription factors make a turn into migration

Pietro Fazzari

Instituto de Neurociencias de Alicante, CSIC and Universidad Miguel Hernandez; Sant Joan d’Alacant, Spain

Key words: transcription factor, neural specification, neural migration, Neurogenin2, Nkx2-1, Rnd2, Semaphorin, Plexin

The formation of the brain depends on a tightly regulated process of proliferation, neuronal fate specification and migration which eventually leads to the final architecture of the cerebral cortex. The specification of different neuronal subtypes depends on a complex developmental program mastered by several transcription factors. Besides, it was shown that the same transcription factors can subsequently control neural migration. However, the mechanisms of this regulation are still unclear. Two papers recently published by Heng et al.\(^1\) and Nóbrega-Pereira et al.\(^2\) confirm that these transcription factors are involved in controlling neural migration. In addition, these studies show that these transcription factors can control neural migration via different molecular mechanisms: Heng and coworkers show that Neurogenin 2 controls neural migration by directly regulating the expression of the small GTPase Rnd2 (a modulator of cytoskeletal dynamics); whereas Nóbrega-Pereira and colleagues demonstrate that Nkx2-1 establishes the response to guidance cues, in migrating interneurons, by directly regulating the expression of the semaphorin receptor Neuropilin 2.

Taken together, these findings support the idea that transcription factors are reused during development to control neural migration and they shed light on the molecular mechanisms underlying this regulation.

Summary

In the development of mammalian cerebral cortex, neural progenitors undertake a process of progressive differentiation that will determine the cell fate of the different neuronal subtypes. Notoriously, transcription factors play a pivotal role in this process by controlling the gene expression profile of neural progenitors. Subsequently, postmitotic neurons migrate away from their sites of origin in order to finally give rise to the complex multilayered structure of cerebral cortex. Two new studies, published by Heng et al. and Nóbrega-Pereira et al., show that transcription factors that coordinate cell determination subsequently control neural migration via surprisingly straight forward mechanisms.

Neurogenin 2 Regulates the Migration of Cortical Pyramidal Neurons via Rnd2

Neurogenin 2 (Neurog2) is a proneural transcription factor that plays a major role in the specification of neuronal identity. Moreover, Neurog2 deficient mice display overt migration defects in the cortex.\(^3\) Heng et al. performed microarray analysis on Neurog2\(^{-/-}\) and Neurog2 overexpressing mice and found that the expression of Rnd2 is strongly downregulated in Neurog2\(^{-/-}\) mutant and upregulated in Neurog2 overexpressing mice. Rnd2 is a small GTPase that is involved in the migration of pyramidal neurons. By loss of function experiments using small interference RNAs, Heng et al. showed that Rnd2 silenced neurons fail to migrate properly to the upper layers of the cortex (Fig. 1A and B). Moreover, acute deletion of Neurog2 obtained by electroporating the Cre recombinase in embryonic brains of Neurog2 conditional mutants (Neurog2\(^{flox/flox}\)) resulted in a similar phenotype. Remarkably, this phenotype was rescued by co-electroporation of Rnd2 and Cre in the Neurog2\(^{flox/flox}\) mice, showing that Rnd2 is a major effector of Neurog2 in the regulation of neuronal migration. To complete the study, Heng et al. demonstrated that Neurog2 control the expression of Rnd2 by direct binding to a 3’ enhancer element of Rnd2 gene.

Rnd family proteins (formed by Rnd1, Rnd2 and Rnd3) are known regulators of cytoskeletal rearrangements and are required for axon guidance and branching. The molecular functions of Rnd proteins are still poorly understood, although they have been shown to function in Semaphorin/Plexin signalling pathway at different levels (e.g., via p190 RhoGAPs or Mgc RacGAP). Moreover, Rnd1 binds to Plexins and it is required for the activation of Plexin GAP activity (reviewed in Chardin P et al.).

Notably, the migration of pyramidal neurons is driven by Semaphorins, and the phenotype described by Heng et al. is very similar to the phenotype observed when Semaphorin signalling is inhibited in these neurons. Therefore, it will be interesting to test whether the migratory defects of Neurog2 deficient neurons are due to an altered response to Semaphorins (Fig. 1B).

Nkx2-1 can Sort It Out

Nóbrega-Pereira et al. provided a demonstration of the function of transcription factors in regulating the response to guidance cues in migrating neurons.
Neurogenin 2 controls cortical neuron migration through regulation of Rnd2

Conclusions and Perspectives

During development, transcription factors are known to orchestrate the complex genetic program that leads to neuronal subtype specification. The works of Heng et al. and Nóbrega-Pereira et al. support the idea that these proteins can subsequently control neuronal migration. In principle, a transcription factor could regulate cell migration at several levels, for instance: (1) it could determine the cell repertoire of guidance receptors; (2) it could activate/repress the expression of factors that control cytoskeletal dynamics; (3) it could transcriptionally regulate proteins involved in cell detachment or adhesion. Surprisingly, Heng et al. and Nóbrega-Pereira et al. show that the function of Neurog2 and Nkx2-1 in migration relies, in good part at least, on the direct regulation of the expression of one gene. Future studies will tell if other cell determinants control cell migration in similar manner and if other downstream transcriptional targets of Neurog2 and Nkx2-1 finely tune the migration of postmitotic neurons. Notably, the mechanisms controlling the postmitotic expression of these transcription factors remain to be clarified.

Acknowledgements

I thank Ramon Pla Ferriz for his help on drawing the figure; Oscar Marín, Sandrina Nóbrega-Pereira and Luca Tamagnone for their useful comments on the manuscript. P.F. is supported by Marie Curie Fellowship (FP7-PEOPLE-2007-2-1-IEF-N° 220731).

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Figure 1. (A) Schema of a coronal section of an E13.5 mouse brain highlighting the major migratory routes of cortical neurons. Pyramidal neurons originate in the ventricle wall and migrate outward to the upper cortical layers. Striatal and cortical interneurons are born in the MGE. Next, striatal interneurons enter directly the striatum; conversely, cortical interneurons are repelled by the Semaphorin3A/3F expressed by the striatum and take their way to the cortex. (B) In pyramidal neurons, Neurog2 enhances the expression of Rnd2 which, in turn, regulates cell motility by impinging on cytoskeletal dynamics and, possibly, on Plexin signalling at different levels. (C) Striatal interneurons are insensitive to Semaphorins induced repulsion because Nkx2-1 represses the expression of the Semaphorin receptor Neuropilin2; therefore, these interneurons are sorted to the striatum.

The transcription factor Nkx2-1 is a cell fate determinant that controls the specification of striatal and cortical interneuron progenitors in the medial ganglionic eminence (MGE). Subsequently, postmitotic interneurons migrate out of the MGE to their final destination following two different routes (Fig. 1A): the interneurons lacking the semaphorin receptor Neuropilin 2 (Nrp2) are sorted to the striatum; conversely, the interneurons expressing Nrp2 are repelled by the Semaphorin3A/3F, expressed by the striatum, and funneled toward the cortex.8 Using an elegant series of in vivo and in vitro experimental approaches Nóbrega-Pereira et al. showed that this sorting is regulated by Nkx2-1. The authors found that striatal interneurons need the postmitotic expression of Nkx2-1 to repress the expression of Nrp2 and enter the striatum (Fig. 1C). On the other side, forced expression of Nkx2-1 in cortical interneurons, in which Nkx2-1 expression is normally downregulated, impairs their responsiveness to Semaphorins and, therefore, their migration to the cortex. Furthermore, Nóbrega-Pereira et al. showed that Nkx2-1 repress the expression of Nrp2 by direct binding to Nrp2 promoter.

In sum, this study demonstrates that transcription factors can control the migration of neurons by directly regulating the expression of guidance receptors.