Nature Reviews Neuroscience | AOP, published online 15 october 2008; doi:10.1038/nrn2519

DEVELOPMENT

The many faces of NKX2-1

The diversity of neuronal subtypes in the brain belies the fact that many of these neuronal populations arise from the same precursor pools. How the fate specification, differentiation and migration of these precursors are coordinated to generate this diversity is largely unknown. Two recent papers enhance our understanding of these mechanisms, demonstrating multiple roles for the transcription factor NKX2-1 in interneuron development.

The medial ganglionic eminence (MGE) gives rise to striatal and cortical interneuron populations that are distinct from those that arise from its neighbours, the caudal and lateral ganglionic eminences (CGE and LGE). NKX2-1 is highly expressed in the MGE and has been implicated in fate specification; however, the death of *Nkx2-1*$^{-/-}$ mice at birth has hampered work in this area. To circumvent this problem, Fishell and colleagues used mice in which *Nkx2-1* could be conditionally deleted from MGE cells at particular developmental time points. The mutant cells were genetically labelled with a fluorescent marker, allowing their immunohistochemical, electrophysiological and morphological characteristics to be examined.

Eliminating *Nkx2-1* at embryonic day (E) 10.5 resulted in the absence of MGE-derived striatal interneurons and caused cells that are normally fated to become cortical interneurons to differentiate into striatal medium spiny projection neurons (which are normally derived from the LGE). When *Nkx2-1* was deleted at E12.5 the cells became cortical interneurons but adopted profiles typical of CGE-derived cells. Thus, it seems that the presence or absence of *Nkx2-1* in MGE progenitors determines the genetic differentiation programme that the interneuron will execute.

Marín and colleagues investigated NKX2-1's postmitotic functions. They showed that as cells migrate from the MGE, those heading for the cortex downregulate NKX2-1 whereas those migrating towards the striatum continue to express it. This suggested that NKX2-1 might regulate the direction of migration of MGE-derived cells. Indeed, when NKX2-1 was overexpressed in MGE progenitors in brain slices, most of the transfected cells migrated to the striatum. Furthermore, postmitotic deletion of *Nkx2-1* in mice resulted in a complementary loss of MGE-derived striatal interneurons.

How does NKX2-1 mediate its effects on cell migration? MGE-derived cells that are destined to become cortical interneurons are prevented from entering the striatum by striatal expression of semaphorins 3A and 3F. Marín and colleagues showed that overexpression of NKX2-1 suppressed the repulsive effect of these semaphorins on MGE-cell migration *in vitro*. This coincided with reduced expression of the semaphorin receptor neuropilin 2 in the migrating cells, indicating that NKX2-1's effect is mediated by the regulation of guidance receptor levels.

These studies illustrate the multifaceted role of NKX2-1 in interneuron development. To fully understand the underlying mechanisms, it will be important to determine which factors regulate the spatiotemporal changes in the expression of NKX2-1.

Katherine Whalley

ORIGINAL RESEARCH PAPERS Butt, S. J. B. *et al.* The requirement of *Nkx2-1* in the temporal specification of cortical interneuron subtypes. *Neuron* **59**, 722–732 (2008) | Nóbrega-Pereira, S. *et al.* Postmitotic Nkx2-1 controls the migration of telencephalic interneurons by direct repression of guidance receptors. *Neuron* **59**, 733–745 (2008)