DEVELOPMENT

Directing neuronal destiny

The capacity of the adult brain to generate new and functional neurons raises some interesting questions about the mechanisms that guide adult neural stem cells towards a specific neuronal fate. Hack *et al.* shed light on these mechanisms through studies of the adult olfactory system, in which interneurons are continuously regenerated.

The adult olfactory bulb contains two types of interneuron that undergo neurogenesis: granule cell layer interneurons (granule neurons) inside the olfactory bulb, which are exclusively GABA (γ -aminobutyric acid)-expressing, and glomerular layer interneurons (so-called periglomerular cells) in the outer regions of the olfactory bulb, which release several neurotransmitters, including dopamine.

In adulthood, these cells are specified during their migration along the pathway from the subependymal zone (SEZ), which lines the brain ventricles, via a rostral migratory stream (RMS) to the olfactory bulb. Hack *et al.* set out to unravel the molecular mechanisms that determine how and when the fate of these neurons is specified along this pathway. The transcription factors PAX6 and OLIG2 are both expressed in the SEZ in adulthood but not during development, which prompted the authors to investigate their expression patterns.

Immunostaining showed that OLIG2 was expressed exclusively in the adult SEZ in transit-amplifying precursor cells — the progeny of

stem cells. Moreover, viral vector-mediated overexpression of mouse OLIG2 in the SEZ, but not the RMS, facilitated oligodendrocyte development, thereby repressing neuronal development.

By contrast, PAX6 was scarce in the SEZ but more abundant in neuroblasts for both periglomerular and granular neuronal types that migrate along the RMS, which signifies that PAX6 influences the extent of adult neurogenesis in the SEZ–RMS system. Furthermore, in the RMS, PAX6 was highly expressed in dopaminergic periglomerular cells that had differentiated into postmitotic neurons, but not in other types of differentiating neuron. Viral vector-mediated repression and genetic deletion of PAX6 in the SEZ led to a reduction in the proportion of neuronal precursors, with none reaching the olfactory bulb and differentiating into neurons. These results point to an important role for PAX6 in the specification of neuronal fate.

Maintenance of PAX6 expression through retroviral transduction converted all RMS precursor neurons, including those that would otherwise have become granular cells, to a periglomerular neuron fate. This shows that the neuronal lineage is irreversible, but that the neuronal subtype is still flexible at this stage.

Using targeted retroviral labelling, Hack *et al.* also showed that periglomerular neurons most frequently originated from the RMS, whereas granular cells were generated further

away from the olfactory bulb, which indicates that cells from different layers are specified at different stages in their migration along the SEZ–RMS pathway.

These findings support the idea of a gradient of fate specification along the SEZ–RMS system, in which a cell can acquire either a neuronal or a glial fate in the SEZ, depending on the expression levels of OLIG2. As the precursors progress more rostrally, their fate as neurons becomes more fixed in response to the upregulation of PAX6. Depending on neuronal subtype, they are specified at different stages in this system, and periglomerular neurons are specifically promoted by a second wave of expression of PAX6 later in their migration and, therefore, closer to the olfactory bulb.

This comprehensive study emphasizes important roles for PAX6 and OLIG2 in adult neuronal regeneration in the olfactory system. Moreover, PAX6 specifically promotes the neurogenesis of periglomerular dopaminergic neurons, which are abnormally regulated in Parkinson's disease. These results take us a step closer to understanding the mechanisms of adult neurogenesis, which could be exploited in the development of therapeutics for neurodegenerative disorders.

Alison Rowan

References and links

ORIGINAL RESEARCH PAPER Hack, M. A. *et al.* Neuronal fate determinants of adult olfactory bulb neurogenesis. *Nature Neurosci.* 12 June 2005 (doi:10.1038/nn1479)