Nature Reviews Neuroscience | Published online 22 Sept 2016; doi:10.1038/nrn.2016.136

Brian Jackson/Alamy Stock Photo

ADULT NEUROGENESIS

Encouraging integration

> “mice with expanded cohorts of 5–8-week-old adult-born DGCs were able to discriminate between two similar contexts in a fear-learning task, unlike untreated mice”

The lifelong production of dentate granule cells (DGCs) is proposed to contribute to memory function. A study by Sahay and colleagues now provides insight into the underlying mechanisms and functional importance of adult neurogenesis, demonstrating the role of mature DGC connectivity in regulating the survival and integration of adult-born DGCs and showing that enhancing these processes can improve memory precision.

Previous work has suggested that the survival of adult-born DGCs and their integration into neuronal circuits require them to compete with mature DGCs for afferent inputs. To test this hypothesis, the authors devised a system to modulate the input connectivity of mature DGCs. They generated transgenic mice (known as $mDG^{K/K}$ mice) in which they could reversibly induce overexpression of Krüppel-like factor 9 (KLF9), a negative regulator of dendritic spines, in mature DGCs. *Klf9* induction in adult $mDG^{K/K}$ mice for 2 weeks resulted in a decrease in both dendritic spine density and activity in mature DGCs that was reversed when the animals were examined 2 weeks after the induction ended.

The authors showed that this transient modulation of mature DGC connectivity corresponded to an increase in the size of the adult-born DGC population, reflecting enhanced survival of the cohort of adult-born DGCs that were 1–3 weeks old at the time of *Klf9* induction. To investigate the effect of enhanced integration of adult-born DGCs on their afferent inputs, the authors labelled adult-born DGCs and their presynaptic partners in $mDG^{K/K}$ mice with a retrograde monosynaptic tracer. This revealed a transient reorganization of inputs onto 4-week-old adult-born DGCs that returned to normal (through the scaling up of DGC presynaptic connectivity) when the cells became 6 weeks old.

The authors next examined the effect of modulating adult neurogenesis on memory function. They found that mice in which transient *Klf9* induction was used to expand a cohort of 5–8-week-old adult DGCs exhibited enhanced ‘cognitive flexibility’ in a version of the Morris water-maze task as well as improved contextual discrimination in a fear-memory task.

Adult-born DGCs are thought to contribute to memory function by reducing interference between similar memories, a capacity that is typically impaired in aged animals (corresponding to a decrease in adult neurogenesis). The authors therefore examined the effects of boosting adult neurogenesis on memory precision in aged mice. They transiently induced *Klf9* in middle aged (11-month-old) or aged (17-month-old) $mDG^{K/K}$ mice and showed that mice with expanded cohorts of 5–8-week-old adult-born DGCs were able to discriminate between two similar contexts in a fear-learning task, unlike untreated mice.

The ability to discriminate between similar contexts may be mediated by ‘global remapping’ of activity patterns in the dentate gyrus. Here, the authors showed that, when exposed to two similar contexts, adult mice with an expanded population of 5–8-week-old adult-born DGCs exhibited more-distinct (less-overlapping) patterns of activation in the dentate gyrus than untreated mice, suggesting that adult-born DGCs act to suppress overlap of activity patterns (and thus to enhance global remapping).

This study uncovers connectivity-based mechanisms that govern the integration of adult-born DGCs, providing insight into the mechanisms by which experience might regulate adult neurogenesis, and demonstrates the functional importance of this process in memory processing.

Katherine Whalley

ORIGINAL ARTICLE McAvoy, K. M. *et al.* Modulating neuronal competition dynamics in the dentate gyrus to rejuvenate aging memory circuits. *Neuron* http://dx.doi.org/10.1016/j.neuron.2016.08.009 (2016)