NEUROGENESIS

Determining fate is a local activity

Barton Stabler/Getty

“field stimulation of the dentate gyrus cell layer induced tonic GABA responses in RGLs ...”

Neuronal activity can regulate various stages of adult neurogenesis in the rodent brain, but it was unknown whether activity in local neural circuits directly affects adult neural stem cells. Now, Song *et al.* show that activity in parvalbumin-expressing (PV⁺) interneurons controls neural stem cell fate decisions in the adult mouse hippocampus, and that experience seems to exert its effects on adult neurogenesis through influencing such activity.

Quiescent adult neural stem cells termed radial glia-like neural stem cells (RGLs) have been identified in the subgranular zone (SGZ) of the hippocampal dentate gyrus in mice. These cells express nestin, which is a marker of neural precursors. First, the authors showed that such cells could be found in the SGZ of transgenic mice expressing green fluorescent protein (GFP)-tagged nestin.

To examine whether local interneurons regulate the quiescent state of adult neural stem cells, Song *et al.* prepared hippocampal slices from nestin-GFP mice and examined the responses of GFP-expressing (GFP⁺) RGLs to GABA in whole-cell voltage-clamp experiments. GABA and muscimol (a GABA_A receptor (GABA_AR) agonist) elicited strong responses in RGLs that could be blocked by bicuculline (a GABA_AR antagonist), indicating that these cells express GABA_ARs. Interestingly, field stimulation of the dentate gyrus cell layer induced tonic GABA responses in RGLs rather than spontaneous or synaptically evoked currents, indicating that synaptic spillover of GABA may affect these cells.

Next, the authors examined whether GABA signalling influences the proliferation of dentate gyrus RGLs *in vivo* by measuring the incorporation of 5-ethynyl-2'-deoxyuridine (EdU), a marker of DNA synthesis, and the expression of DNA replication licensing factor MCM2, which increases during DNA replication. Diazepam treatment, which potentiates GABA responses mediated by γ_2 subunit-containing GABA_ARs, greatly decreased the number of EdU-expressing RGLs and markedly reduced the number of MCM2-expressing RGLs. This suggests that GABA promotes quiescence in these cells by acting on γ_2 subunit-containing GABA_ARs.

The authors created a mouse line (cKO mice) in which γ_2 subunit expression could be conditionally knocked out in RGLs after administration of tamoxifen. These mice, unlike control mice, showed a marked increase in the number of RGLs that were able to proliferate at 7 days after tamoxifen treatment. Diazepam treatment promoted RGL quiescence in control animals, as expected, but had no such effect on cKO RGLs. Thus, these findings show that GABA release regulates fate choice in RGLs.

Which types of GABA-releasing interneurons in the adult dentate gyrus are responsible for regulating this fate choice? Immunohistological experiments showed that GFP⁺ RGLs were located in close proximity to the terminals of PV⁺ interneurons, and optogenetic studies showed that activation of PV⁺ interneurons in slices induced synaptic currents in dentate granule cells and tonic responses in GFP⁺ RGLs. In line with the other findings, light-induced activation and suppression of PV⁺ interneuron activity in the dentate gyrus for 5 days decreased and increased, respectively, EdU incorporation and MCM2 expression. Of note, optogenetic manipulation of activity in local somatostatin-positive or vasoactive intestinal polypeptide-positive interneurons had no effects on RGLs. Thus, local PV⁺ interneurons seem to regulate fate decisions in these cells.

Social isolation, like γ_2 subunit-deficiency, promotes the proliferation of RGLs in mice. The authors showed that social isolation had no additional effects to γ_2 subunit deletion on the proliferation of such cells. Moreover, optogenetic activation of local PV⁺ interneurons reversed the effects of such housing on control RGLs. Thus, experience might regulate adult neurogenesis in the SGZ through altering PV⁺ interneuron activity.

Taken together, these results reveal how a local neuronal signal from a specific population of interneurons can determine neural stem cell fate in an adult neurogenic niche and how experience can influence such signalling.

Darran Yates

ORIGINAL RESEARCH PAPER Song, J. *et al.* Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision. *Nature* 29 Jul 2012 (doi:10.1038/nature11306)

FURTHER READING Deng, W., Aimone, J. B. & Gage, F. H. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nature Rev. Neurosci.* **11**, 339–350 (2010)