

 STEM CELLS

A balancing act

“NPCs inhibit NSC proliferation through an EGFR–Notch 1 interaction.”

”

The subventricular zone (SVZ) of the lateral ventricle is a neurogenic niche of the adult brain that maintains pools of indefinitely self-renewing neural stem cells (NSCs) and more restricted neural progenitor cells (NPCs). The balance of these pools is crucial to supply the brain with specific neural populations. In the SVZ, Notch signalling regulates NSCs, and epidermal growth factor receptor (EGFR) signalling regulates NPCs. Aguirre *et al.* now show that these pathways interact to regulate the balance of the two cell populations.

The authors overexpressed human EGFR in mice and showed that it was present in NPCs but absent from NSCs. These mice, and mice infused with EGF in the lateral ventricle, have more NPCs but fewer NSCs in the SVZ. Enhanced EGFR signalling was also shown to upregulate genes involved in neurogenesis and to downregulate Notch signalling elements, indicating a potential interaction between Notch 1, which was mainly detected in the SVZ NSCs, and EGFR.

The NSCs in the SVZ of human-EGFR-expressing mice showed morphological defects that could be rescued by overexpressing constitutively active Notch 1. In addition, NPC depletion in the SVZ increased the numbers of NSCs in the SVZ of human-EGFR-expressing mice, and these NSCs expressed higher levels of Notch 1, suggesting an interaction between the two cell populations. Co-culture experiments confirmed that there is contact-mediated regulation between the cell types, as Notch signalling in SVZ NSCs and NSC proliferation were reduced in the presence of human-EGFR-expressing

NPCs. These data indicate that NPCs inhibit NSC proliferation through an EGFR–Notch 1 interaction.

EGFR signalling in NPCs was found to inhibit Notch 1 signalling in NSCs through Numb-mediated Notch 1 ubiquitylation. Specifically, the levels of Numb (which interacts with E3 ubiquitin ligases to mediate Notch degradation) and its association with Notch 1, as well as the amount of Notch 1 ubiquitylation, were upregulated in human-EGFR-expressing mice, and Notch 1 signalling was enhanced following Numb knockdown.

Therefore, two fundamental signalling pathways have a functional interplay in the maintenance of NSC and NPC pools in the SVZ and provide a homeostatic mechanism to balance the two populations. This study provides important information on the regulation of cell composition in a neurogenic niche.

Debbie Walker

ORIGINAL RESEARCH PAPER Aguirre, A., Rubio, M. E. & Gallo, V. Notch and EGFR pathway interaction regulates neural stem cell number and self-renewal. *Nature* **467**, 323–327 (2010)



Jacques Smit