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Exciting news from the adult mouse subventricular zone

Mila Komitova and Flora M. Vaccarino*

Yale University School of Medicine, New Haven, CT, USA
**Correspondence: flora.vaccarino@yale.edu*

A commentary on

Adult generation of glutamatergic olfactory bulb interneurons.
by M. S. Brill, J. Ninkovic, E. Winpenny, R. D. Hodge, I. Ozen, R. Yang, A. Lepier, S. Gascon, F. Erdelyi, G. Szabo, C. Parras, F. Guillemot, M. Frotscher, B. Berninger, R. F. Hevner, O. Raineteau and M. Gotz (2009). Nat. Neurosci. 12, 1524–1533.

In the adult mammalian brain the forebrain subventricular zone (SVZ) is a source of olfactory bulb (OB) GABAergic neurons. It is by now well established that astrocyte-like cells via fast-amplifying progenitor cells generate neuronal precursors that mature into functional neurons (Kriegstein and Alvarez-Buylla, 2009). The potential of the adult SVZ to generate neuronal progenitors that are recruited to lesioned brain regions in various injury models, has opened up new vistas in attempting to enhance neurologic recovery through neuronal replacement (Lindvall and Kokaia, 2006; Zhang et al., 2008).

Previous studies have established that the adult mouse SVZ contains heterogenous progenitor populations based on their embryonic origins and their potential to generate different subtypes of GABAergic interneurons (Merkle et al., 2007; Young et al., 2007). Brill and colleagues add a further level of complexity by demonstrating that some neural progenitors in the adult SVZ generate a subtype of glutamatergic neurons in the OB. The authors examined the transcription factors Neurogenin 2 (Neurog2), Tbr2 and Tbr1, known to be associated with acquisition of glutamatergic neuronal fate during cortical development. Using co-labeling with different transcription factors, 5-bromo-2′-deoxyuridine (BrdU) birth dating and transgenic mice with transcription factor-specific reporter expression, Brill et al. demonstrated lineage progression from Pax6$^+$/Mash1$^+$ cells, to intermediary progenitor cells expressing Neurog2 and Tbr2 and ultimately to Tbr1$^+$ postmitotic immature neurons. The Neurog2$^+$, Tbr2$^+$ and Tbr1$^+$ cells were only found in the dorsal region of the SVZ and proximal rostral migratory stream (RMS), as opposed to the progenitors of GABAergic interneurons, which were present over the entire SVZ. The authors next used their previously validated *GLASTCre::ERT2* mice, in which the promoter of the astrocyte-specific glutamate transporter (*GLAST*) drives tamoxifen-inducible Cre recombination in astroglial cells (Mori et al., 2006). Fate mapping using the *GLASTCre::ERT2; R26R-CFP* mice demonstrated that the Tbr2$^+$ progenitors observed in the SVZ and RMS originated from GLAST$^+$ astrocyte-like cells.

The authors showed that proliferating cells in the adult SVZ generated a subtype of glutamatergic neuron, which based on location and morphology was categorized as a short-axon juxtaglomerular OB interneuron. Glutamatergic fate of the adult-generated neurons was confirmed by demonstrating co-expression of vesicular glutamate transporter 2 (vGluT2). Only a small fraction of adult-generated BrdU$^+$ cells in the glomerular layer of the OB were found to co-express vGluT2 (2%). Brill et al. replicated the *in vivo* data by *in vitro* experiments where cultured SVZ cells were found to generate a small fraction of glutamatergic neurons which exhibited functional synaptic transmission. In order to further demonstrate that Neurog2$^+$ progenitors were indeed the source of the adult-born juxtaglomerular neurons, the authors also analyzed adult-generated Neurog2 lineage cells in the OB of *Neurog2::Cre* mice carrying a Z/EG reporter. A small fraction of BrdU$^+$ adult born cells in the glomerular layer of the OB were found to originate from the Neurog2 lineage (5%). It is unclear what is the number and proportion of Tbr-expressing excitatory neurons with respect to the overall number of adult-generated neurons in the SVZ, as well as what percentage of these cells reaches the OB. However, this may be hard to assess given the small number of BrdU$^+$ cells that acquires an excitatory fate. It seems that only a small proportion of the numerous cells that originally expressed Neurog2, Tbr2, Tbr1 in the SVZ reaches the periglomerular regions, raising the question what happens to the remaining cells.

The adult-generated glutamatergic neuronal progenitors down regulated Tbr2 and even Tbr1 before or just after reaching the OB despite acquiring glutamatergic fate, as assessed by vGluT2 expression. The authors did observe many vGluT$^+$ cells that co-expressed Tbr1 and Tbr2 in the glomerular layer. However, these glomerular layer Tbr2$^+$ cells were found to be generated embryonically. The significance of the difference in Tbr transcription factor expression between embryonically and adult-generated periglomerular glutamatergic neurons needs to be examined further. It is also possible that BrdU labeling of these cells somehow interferes with their normal transcription factor expression profile. Perhaps long term fate mapping of excitatory OB neurons generated in the adult using *GlastCre::ERT2;R26R-CFP* mice without using BrdU could answer this question.

Lastly, the authors showed recruitment of newly-generated Tbr2$^+$ neuroblasts from the SVZ toward the lesioned cerebral cortex after targeted callosal projection neuron degeneration. Some of the *Tbr2* lineage cells expressed the upper layer identity transcription factor *Cux1*. Even though the Brill et al. study does not provide any quantification of the Tbr2$^+$ neuronal progenitor recruitment, this seems to be a relatively rare phenomenon. The generation of new cortical pyramidal neurons in adulthood in response to apoptosis of resident neurons had already been shown (Magavi et al., 2000), however the source of these new neurons was unclear. The finding that new Tbr1$^+$ neurons can be generated in adulthood has important implications for pathological conditions of the cerebral cortex, as it implies that

SVZ cells can represent a source of cortical excitatory neurons. The idea that SVZ progenitors can generate pyramidal cortical neurons, as demonstrated by Brill et al., agrees with an earlier study which showed enhanced generation of $Tbr1^+$ neurons in the mouse neocortex after chronic postnatal hypoxia, a clinically relevant model for neuropathology in preterm infants (Fagel et al., 2009). Together, these papers suggest that new excitatory neurons can be integrated into the postnatal neocortex. The paper of Brill et al. lays important groundwork for future research avenues leading to an understanding of the molecular mechanisms by which progenitor cells migrate and integrate into the cerebral cortex.

The intriguing findings of Brill et al. emphasize that the plasticity of olfactory circuitry is not confined exclusively to inhibitory neurons. The major limitation of this study is the lack of understanding concerning the physiological role of adult-born olfactory and also cortical neurons for brain function. Despite this limitation, the study of Brill et al. is the first to extend the cellular repertoire of the SVZ to excitatory neuron progenitors, which was previously thought to occur only in embryogenesis. The maintenance of this large variety of cellular precursors in the adult SVZ niche raises our hope that the balanced replacement of different neuronal subtypes can be achieved in various lesion models, and that significant improvement of function in neurological or neuropsychiatric disorders can be attained.

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