ChAT me up: how neurons control stem cells

Gregor-Alexander Pilz & Sebastian Jessberger

The proliferation of NSCs in the adult SVZ is controlled by a set of neurons expressing choline acetyltransferase, identifying a mechanism connecting brain activity to neurogenesis in the adult mammalian brain.

Most scientists enjoy forwarding papers and other newsworthy items to their laboratory members by e-mail. Doing so allows information to flow efficiently, connecting the group and propagating the message to elicit the appropriate response (new experiments or a frustration-filled coffee break). Our brain adopts a similar strategy for information processing: constantly updating various brain regions about what the rest of the brain and body is doing by using a complex neural network of forward and backward message-relay systems. However, our brains do not consist only of mature neural networks; NSCs continue to generate new neurons throughout life in discrete areas of the brain[1]. One of them is the subventricular zone (SVZ) lining the lateral ventricles, where NSCs divide and give rise to new neurons that migrate toward the olfactory bulb. There they differentiate into neurons and functionally integrate into olfactory bulb circuits (**Fig. 1**). Even though SVZ and olfactory bulb neurogenesis has been extensively characterized in rodents and other mammals, it may be absent in the human brain[2]. However, recent evidence suggests that NSCs in the human SVZ may retain their neurogenic potential to generate striatal interneurons throughout life that appears to be decreased in patients with Huntington's disease[3]. Thus, understanding the signals that regulate NSC activity and the mechanisms that connect neuronal activity with NSC proliferation is not only important for deciphering a basic feature of brain plasticity, but may also be relevant in the context of neurological disease.

In this issue of *Nature Neuroscience*, Paez-Gonzalez *et al.*[4] report an elegant series of experiments identifying a hitherto poorly characterized subset of choline acetyltransferase (ChAT)-expressing neurons in the SVZ that exert activity-dependent control over the proliferative activity and thus neurogenic response of NSCs in the SVZ. Their data pinpoint a new mechanism by which information from neuronal networks is translated into stem cell–associated structural plasticity of adult brain circuits (**Fig. 1**).

Spurred by their findings that acetylcholine (ACh) showed a powerful neurogenic effect on NSCs *in vitro*, Paez-Gonzalez *et al.*[4] first analyzed whether ACh-dependent neurotransmission is important for SVZ neurogenesis in the adult mouse brain by selectively deleting ankyrin 3, a large adaptor protein necessary for correct axonal function, in ACh-expressing neurons. Disruption of proper function of ACh-expressing neurons indeed resulted in a substantial decrease in NSC proliferation and subsequent generation of newborn neurons. In their next step, Paez-Gonzalez *et al.*[4] aimed to identify the cellular source of ACh release within the neurogenic niche of the SVZ. Using several immunohistochemical approaches combined with genetic lineage tracing, they identified a set of ChAT-expressing cells that lie in the subependymal space below the cell layer that covers the lateral ventricle and are therefore in close proximity to neurogenic NSCs in the SVZ.

Notably, Paez-Gonzalez *et al.*[4] found that ChAT$^+$ cells in the subependymal space were able to elicit action potentials in response to optogenetic stimulation (light-induced depolarization of the cells after expression of the light-sensitive ion channel channelrhodopsin). Moreover, the authors used a previously described reporter system for ACh release involving transplantation of cells from a human embryonic kidney cell line expressing a fluorescent reporter that becomes activated following stimulation of M1 muscarinic ACh receptors (M1-CNiFER). Optogenetic stimulation of ChAT$^+$ cells in the SVZ indeed led to activation of the fluorescent reporter system, indicating that these cells are competent to release ACh in an activity-dependent manner. Furthermore, direct electrophysiological or light-induced activation of ChAT$^+$ cells in the SVZ induced robust inward currents in SVZ NSCs. These results suggest that ChAT$^+$ cells in the subependymal space release ACh in response to activity and are functionally connected to SVZ NSCs. Thus, ChAT$^+$ cells talk to NSCs. But do they listen? And what are the consequences of activity-dependent release of ACh for neurogenesis?

Paez-Gonzalez *et al.*[4] next found that chronic optogenetic stimulation of ChAT$^+$ cells in the SVZ prompted increased proliferation of NSCs and enhanced neurogenesis in the SVZ, an effect that may be mediated in NSCs through the fibroblast growth factor pathway, which has been shown to be of pivotal importance for proper neurogenesis. Notably, inhibition of ACh release from ChAT$^+$ cells, again using an optogenetic approach, reduced neurogenesis. Thus, the data from Paez-Gonzalez *et al.*[4] describe a mechanism by which activity of neural networks is translated into NSC-dependent plasticity (**Fig. 1**).

Together with data showing that proliferation and/or differentiation of NSCs in the SVZ is influenced by GABAergic, dopaminergic and nitric oxide–releasing neurons[5], and a recently published study that identified a distinct set of serotonergic neurons in the raphe nucleus that controls NSC proliferation in the SVZ via direct synaptic contact with NSCs and ependymal cells[6], the findings presented by Paez-Gonzalez *et al.*[4] add an important piece to the puzzle depicting the mechanisms by which network activity controls NSCs.

As in the SVZ, it has been recently shown that local and remote neuronal networks control distinct steps during the neurogenic process in the second main neurogenic region of the adult brain, the hippocampal dentate gyrus. This region is critical for certain forms of learning and memory, and shows substantial amounts of neurogenesis in the human brain[7–10].

These data point toward a delicate cross-talk between the number of neurons generated and the activity in associated neuronal networks. Given these findings, the generation of new neurons is not a detached, singular process that is regulated independently of brain activity; rather, adult neurogenesis and the magnitude of neuron production appear to be part of the activity-dependent response to experience, adapting the structure of the brain to improve potential responses to future demands[11]. Along these lines, newborn, SVZ-derived neurons in the olfactory bulb and newborn granule cells in the dentate gyrus have been shown to be important for the proper function of these brain areas[12].

The study by Paez-Gonzalez *et al.*[4] represents a starting point by identifying a ChAT$^+$

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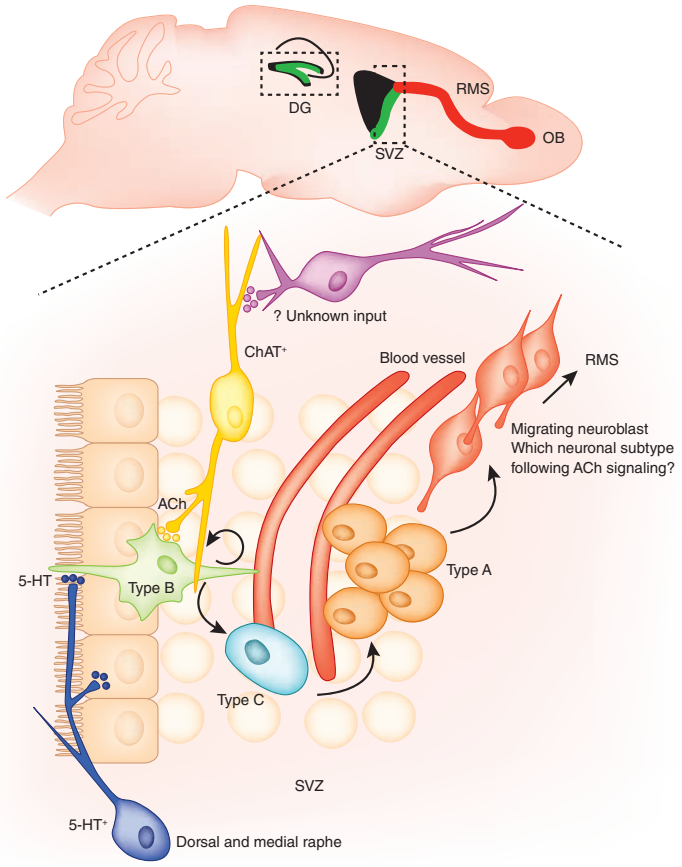

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Figure 1 ChAT+ neurons regulate the proliferative behavior of NSCs in the adult SVZ. The adult mouse brain contains two main neurogenic niches, in which NSCs continually divide to give rise to new neurons: the subgranular zone of the dentate gyrus (DG) and the SVZ lining the lateral ventricles (boxed areas)[1]. In the SVZ, astrocytic cells with stem cell properties, called type B cells, divide to give rise to fast-proliferating, transit-amplifying cells (type C cells) that in turn generate neuroblasts migrating along the rostral migratory stream (RMS) toward the olfactory bulb, where they integrate into the existing neural circuitry. The neurogenic process in the SVZ is controlled by numerous niche-dependent regulatory mechanisms (among others, cellular interactions with ependymal and endothelial cells and direct input from serotonergic cells originating in the raphe nucleus[6]). Paez-Gonzales *et al.*[4] report that ChAT+ neurons control NSC proliferation through the release of ACh onto type B cells[4]. Activation via ACh is necessary and sufficient to govern proliferation of type B cells in the SVZ, thereby representing a direct connection between neural network activity and the proliferative response in the neurogenic SVZ. Whether this newly identified ACh-dependent mechanism is associated with known regulators of SVZ neurogenesis in health and disease and whether distinct olfactory bulb neuron subtypes are preferentially generated following activation of NSCs via ChAT+ cells remains unknown.

cell population that releases ACh in an activity-dependent manner, subsequently affecting NSC proliferation. Notably, recent evidence has suggested that NSCs along the dorso-ventral axis represent heterogeneous populations with region-specific differentiation capacity: for example, NSCs in certain areas of the SVZ generate one neuronal subtype of olfactory bulb neurons, whereas NSCs in other regions preferentially differentiate into a different subtype[13]. Whether ChAT+ neurons affect all NSCs along the dorsoventral axis or preferentially regulate distinct subtypes of NSCs in the adult SVZ remains unknown.

Another obvious next step will be to analyze when this system is actually used to regulate neurogenesis. A number of physiological and pathologic regulators of SVZ neurogenesis have been described, among them pregnancy, pheromone-related mating preference, paternal offspring recognition and insults such as epileptic seizures, ischemic stroke and neurodegenerative diseases, including Huntington's disease[12]. It will be of interest to test whether the newly identified ChAT-mediated pathway modulates neurogenesis under any of those conditions. This is important not only because adult neurogenesis is a part of physiological brain function, but also because the neurogenic potential of NSCs in the SVZ may be harnessed for endogenous brain repair when neurons are lost. This has been shown in rodent models of diseases such as stroke[14], and, more recently, a provocative study showed, despite the virtual absence of neurogenesis in the human olfactory bulb, that substantial numbers of newborn neurons can be detected in the human striatum and that these are substantially depleted in patients who suffer from Huntington's disease[3]. At this time, the cellular source of those newborn neurons remains unclear; however, it is reasonable to speculate that newborn striatal neurons are generated by NSCs residing in the human SVZ. Nevertheless, the potential of human SVZ NSCs to generate neurons may be limited, as, for example, ischemic lesions in the human brain do not induce the generation of new neurons[15]. Thus, understanding the mechanisms by which activity of neuronal networks translates into stem cell–mediated structural changes in the adult mammalian brain may lead to the identification of targets with which to modulate the neurogenic response in the context of traumatic or degenerative brain damage. The findings reported by Paez-Gonzalez *et al.*[4] bring us one step closer to understanding neurogenesis in the adult brain and, ultimately, to using this knowledge to develop therapeutic strategies for neurological disease.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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