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Hippocampal Mossy Cells Provide a Fate Switch for Adult Neural Stem Cells

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The pathways that convert neural stem cells (NSCs) into functional neurons in the adult hippocampus are tightly regulated. In this issue of *Neuron*, Yeh et al. (2018) demonstrate that the activity of dentate mossy cells determines the balance between quiescence and activation of NSCs.

Neuronal plasticity is the ability of nervous system networks to adjust to the dynamic conditions in the environment. In most circuits, plasticity is expressed as changes in synaptic weight. In a few regions of the adult brain such as the dentate gyrus (DG) of the hippocampus, plasticity also includes neurogenesis: the generation of entire new sets of functional units, the dentate granule cells (GCs). Positive experiences such as enriched environment (EE), voluntary exercise, or spatial learning increase the rate of neurogenesis and accelerate neuronal integration in the existing circuits. In contrast, stress and several pathological conditions reduce this plasticity or render abnormal connectivity of new GCs. Interestingly, not only experience exerts an impact on neurogenesis; new GCs also modify behavior, contributing to cognitive flexibility and mood regulation (Toda and Gage, 2017). It is thus crucial to understand the mechanisms that control the generation and integration of adult-born GCs. The process starts from quiescent radial neural stem cells (NSCs) that—upon activation—divide, produce amplifying progenitor cells and, finally, produce the daughter cells that may became neuroblasts that will mature and integrate during several weeks into local and long-range dentate circuits (Toda and Gage, 2017). Several steps in the neurogenic pathway from NSCs to the final stages of maturation are modulated in response to mood and cognitive demand. While the parameters that rule these forms of network homeostasis remain largely unknown, it is becoming clear that network activity plays a fundamental role. What cells are the main activity sensors?

The DG is a sparse network in which principal neurons, the GCs, are mostly silent due to a strong GABAergic tone (Piatti et al., 2013). In contrast, mossy cells (MCs), glutamatergic dentate interneurons, are very active and have been proposed as sentinels of the DG network (Scharfman, 2017). Their major inputs arise from GCs, local GABAergic interneurons of the hilus and back-projections from CA3 pyramidal cells. Their output covers a long range of targets. The associational pathway, where axons extend ipsilaterally, covers about 60% of the longitudinal DG axis. The commissural pathway projects to the contralateral DG (Larimer and Strowbridge, 2008; Scharfman, 2017). Therefore, MCs have the capacity to integrate and adjust activity within the DG through excitatory feedback loops connecting GCs and local

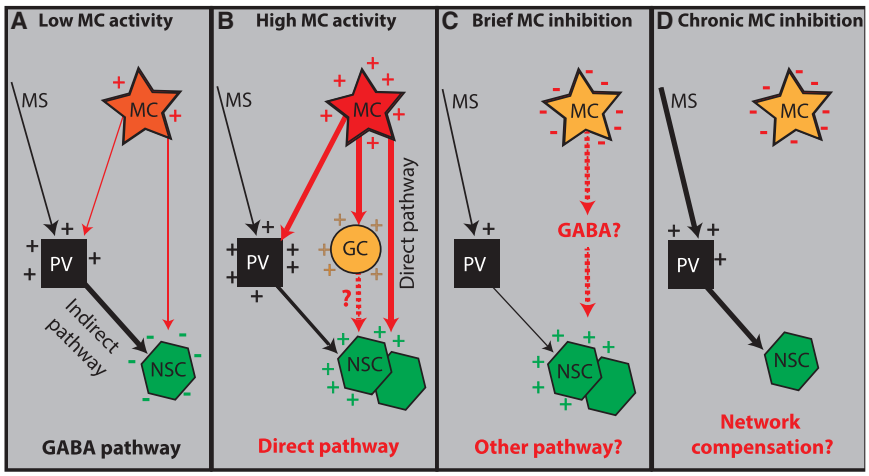

Figure 1. MCs Are the Local Master Modulators of the Neurogenic Niche
The schematic panels show different levels of activity of MCs and their outcome on fate decision of NSCs in the DG circuit, based on the findings by Yeh et al. (2018).
(A) Low firing rate of MCs could activate both direct and indirect pathways to determine NSC state. However, NSC fate decision (quiescence) is dominated by the indirect, GABA-mediated route (Bao et al., 2017).
(B) High MC activation may also recruit both pathways, yet NSC choice (proliferation) seems to respond mainly to the direct path. Recruitment of additional circuits involving GCs might also contribute to the NSC fate.
(C) MC silencing for short periods (4 to 5 days) leads to NSC activation. A local, indirect route mediated by GABA signaling might be involved.
(D) Chronic MC silencing (3 weeks) showed no change in NSC state. This lack of effect might be due to remodeling arising from long-range connections from the MS.
Arrows and their thickness denote synaptic connections and their level of activity (thicker = more active). (+) and (–) signs also illustrate the level of cell activity. Dotted arrows indicate hypothetical connections. MS: GABAergic long-range medial septum projections; PV: parvalbumin GABAergic interneuron; NSC: neural stem cell; MC: mossy cell; GC: dentate granule cell.

GABAergic networks. The work published by Yeh et al. (2018) in this issue shows that different states of activation of MCs control adult neurogenesis because they determine whether NSCs will enter quiescence or become activated to potentially generate neurons. Their findings reveal that MCs may switch between two parallel mechanisms existing in the neurogenic niche that modulate the fate of NSCs according to a demand imposed by the network.

Yeh and colleagues first combined confocal and electron microscopy to show that commissural MC projections establish physical contacts onto NSCs and hilar interneurons. To achieve this goal, all excitatory neurons in one hemisphere were labeled using AAVs carrying CaMKII-driven mCherry in Nestin-GFP mice, and contacts between NSCs and labeled axons were analyzed in the contralateral side. To assess functional connectivity, they used the same strategy to express excitatory DREADDs or channelrhodopsin in MCs and showed that activation of MCs depolarizes NSCs. MC activation also elicited depolarizing responses in GABAergic interneurons of the contralateral side, as visualized by calcium imaging measurements. The discovery of MC contacts onto NSCs and onto GABAergic interneurons suggested that parallel pathways might be recruited by MC activity. In fact, different concentrations of clozapine-N-oxide (CNO), the synthetic DREADD agonist, induced firing of MCs at different rates and, in turn, activated different pathways that converged onto NSCs. High CNO elicited firing of both MCs and contralateral GCs, assessed as an increase in cFOS expression, suggesting that strong MC activation recruited principal neurons of the DG. In contrast, low CNO only activated MCs, but not GCs, suggesting a weaker stimulation.

In vivo MC stimulation using low CNO induced quiescence in NSCs. This observation is in agreement with these authors' previous work demonstrating that parvalbumin-expressing (PV) GABAergic interneurons promote the quiescent state, and it therefore supports the notion that low MC activation acts through this "indirect" pathway (Bao et al., 2017; Figure 1A). By contrast, MC stimulation using high CNO elicited NSC proliferation through a GABA-independent pathway, which the authors called "direct" (Figure 1B). However, the lack of GABA-mediated effects under strong MC activation remains intriguing. Whether the direct pathway is indeed mediated by monosynaptic connections from MCs to NSCs remains to be investigated. As the authors showed, GCs were excited by strong MC stimulation; in essence, they might also contribute to the observed depolarizing effects onto NSCs. In fact, strong MC stimulation was shown to increase the excitability of GCs (Hashimotodani et al., 2017). Yet, whether GCs contact NSCs also remains to be determined. The authors then tested the effects of more natural stimuli on NSC activation. Nestin-GFP mice were exposed to an EE for two weeks. They observed an increase of cFOS in MCs, identified by the expression of the GluR2/3 subtypes of glutamate receptors; no change in cFOS levels on PV cells; and higher activation of NSCs compared to standard housing. These results suggested that EE activated the direct pathway. Future experiments using chemogenetic inhibition of MCs would contribute to an indisputable demonstration of the role of MCs as mediators of natural stimuli on NSCs.

Data discussed so far indicate that strong MC stimulation promotes NSC activation via the direct path, while weak MC stimulation promotes NSC quiescence via GABA signaling. Interestingly, Yeh et al. (2018) found that chemogenetic silencing of MCs for 4 days resulted in NSC activation, which is consistent with a scenario of decreased GABAergic signaling (Figure 1C). By contrast, acute silencing of MCs in slice electrophysiology experiments rendered an increase in GABA-mediated signaling on NSCs. This apparent contradiction between acute and short-term actions of MC silencing remains puzzling. It is possible that other indirect pathways controlled by MCs through diverse GABAergic interneurons or immature GCs (Chancey et al., 2014; Larimer and Strowbridge, 2008) could also mediate this effect (Figure 1C).

The authors then tested the effects of chronic manipulations of MC activity. Prolonged chemogenetic silencing of MCs rendered no change in NSC states

(Figure 1D). It might be speculated that this condition may be compensated by long-range medial septum (MS) connections, which depolarize dentate PV interneurons (Bao et al., 2017). If NSCs would be active by default, this form of plasticity might be exhausted by reduction of the NSC pool (Ray et al., 2018). In this context, MS projections might play a protective role for the neurogenic niche. MCs may play critical roles in the regulation of the neurogenic niche not only under normal conditions but also under pathological insults. For instance, MC loss has been described in chronic temporal lobe epilepsy, in which hippocampal neurogenesis is largely impaired (Scharfman, 2017; Zhong et al., 2016). Yeh et al. (2018) have also investigated this issue. They showed that chronic ablation of MCs by expression of caspase 3 in 5htr2A-Cre mice decreased both the size of the NSC pool and the rate of neuronal differentiation. These new data support the idea that MC loss might be crucial for the loss of neuronal plasticity in pathological conditions.

In summary, the work by Yeh et al. (2018) shows that MCs could be master players modulating neurogenic potential of NSCs, acting through different local circuits. At present, many questions remain to be answered. It is unclear whether MCs are indeed indispensable or whether the NSC pool can be recovered after prolonged MC ablation. Future studies will shed light on how different players in the neurogenic niche work in concert to produce more new neurons while preserving the NSC pool.

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And the Band Keeps Marching On

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Before the onset of hearing, activity in the developing auditory system is dominated by periodic bursts of action potentials that originate in the cochlea from where they propagate up the central auditory pathway. In this issue of *Neuron*, Babola et al. (2018) provide new insight into the spatiotemporal organization of prehearing activity *in vivo* and its homeostatic control.

Burst-like patterns of spontaneous activity are a common phenomenon of developing sensory systems. This activity is present before external stimuli can activate sensory cells and thus arises endogenously, or spontaneously, in the immature sensory organ from where it is propagated to the brain. Spontaneous bursts of action potentials are also present in the auditory system before hearing onset, which begins around time of the opening of the ear canal (approximately postnatal day 12 in mice). This prehearing activity originates within the immature cochlea, which contains a transient group of epithelia cells, the inner supporting cells (ISCs) that form the Kolliker's organ located adjacent to inner hair cells (IHCs), the primary sensory cells in the auditory system. ISCs periodically release ATP, which, through the activation of purinergic receptors and TMEM16A chloride channels, leads to an efflux of potassium from ISCs into the extracellular space (reviewed by Wang et al., 2015) (Figure 1). This increase in extracellular potassium depolarizes nearby IHCs, triggering a barrage of synaptic glutamate release, which leads to trains of action potentials in postsynaptic ganglion cells (spiral ganglion neurons, SGNs) that are