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Neural Circuits Serve as Periscopes for NSCs

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Neural stem cells (NSCs) within the hippocampal niche integrate local cues, such as activity of inhibitory interneurons, into their homeostatic fate choices. Now in *Cell Stem Cell*, Bao et al. (2017) describe how these local interneurons relay signals from distal brain regions to govern NSC quiescence and activation.

The invention of the naval periscope in 1854 by Hippolyte Marie-Davy paved the way for submarines to sample information in the world above water and guide strategic decisions underwater. Neural stem cells (NSCs) residing in the subgranular zone of the dentate gyrus (DG) of the hippocampus generate new dentate granule cells (DGCs) throughout life, a process that is exquisitely sensitive to the animal's experience and external world. But, like submarines, NSCs must rely on periscopes to sense an external world. This is important as newly generated DGCs are thought to optimize hippocampal circuit functions in forming new memories of "what, when, and where" by keeping similar memories separate and ensuring that new memories do not overwrite those that have been previously stored (McAvoy and Sahay, 2017). As such, the decision of NSCs to activate or stay quiescent is an important one as it enables the hippocampus to anticipate new environments and consequently, confer adaptive benefits to the organism. It is therefore no surprise that NSC activation is tightly coupled to the animal's external environment. A fundamental challenge is to understand how external signals are communicated via niche elements or *periscopes* to the NSCs to guide these decisions.

NSCs are surrounded by different neuronal cell types, including DGCs, different classes of inhibitory interneurons, astrocytes, oligodendrocytes, and endothelial cells, and they are bathed in blood-borne factors, which all sense and relay changes in neural activity or physiological cues to NSCs. In a tour-de-force study, Bao and colleagues begin to illuminate circuitry-based mechanisms by which a local niche cell type, parvalbumin expressing inhibitory interneurons (PV INs), serves as a periscope for NSCs by linking activity of a distal brain region, the medial septum (MS), with NSC activation (Bao et al., 2017).

Inhibitory interneurons in the DG niche receive inputs from different brain regions and in turn coordinate network and ensemble activity within and across different hippocampal subregions (Hosp et al., 2014). Previous work by Song and colleagues found that PV INs dictate activation of NSCs (Song et al., 2012). Optogenetic activation of PV INs, but not other subtypes of INs such as SST or VIP, decreased activation of NSCs and was sufficient to reverse the enhancement in symmetric NSC divisions induced by social isolation. Conversely, optogenetic inhibition of PV INs or rendering NSCs insensitive to GABA, the inhibitory neurotransmitter released by INs, promoted activation of NSCs. Thus, PV INs may integrate and relay signals computed in extra-hippocampal circuits to NSCs to govern homeostasis (Song et al., 2012).

As a first step to begin to understand how PV INs serve as periscopes for NSCs, Bao and colleagues mapped the afferents onto PV INs. Using rabies-virus-based monosynaptic retrograde tracing, the authors identified GABAergic projection neurons in the MS as major afferents of PV INs, while the other major neuronal cell types in the MS were not labeled as potential afferents. The authors dexterously combined optogenetics, whole-cell recordings from genetically labeled DG PV INs, and FLP- and Cre-dependent viral expression systems to show that stimulation of MS GABAergic neurons elicited postsynaptic responses in DG PV INs at latencies consistent with monosynaptic connectivity, which were blocked by the GABAA receptor antagonist bicuculline. The authors extended this approach to determine connectivity between MS GABAergic neurons and mature DGCs, the largest niche constituent, as well as NSCs, but failed to detect monosynaptic responses in mature DGCs. Thus, MS GABAergic neurons directly synapse onto DG PV INs (henceforth referred to as $MS^{GABA\text{-}DG}$) and are potential regulators of NSC activation (Figure 1).

To directly interrogate the role of $MS^{GABA\text{-}DG}$ projections in regulating NSC homeostasis, the authors employed optogenetics and chemogenetics to stimulate or inhibit, respectively, $MS^{GABA\text{-}DG}$ projections *in vivo* and examined NSC activation. Stimulation of $MS^{GABA\text{-}DG}$ projections (at short or long timescales, 8 hours or 5 days) decreased NSC activation, whereas inhibiting $MS^{GABA\text{-}DG}$ projections increased NSC activation without affecting neural progenitors. The authors then marshaled an elegant dual chemogenetic strategy to demonstrate that activating DG PV INs occluded the effects of inhibiting $MS^{GABA\text{-}DG}$ projections on NSC activation. These experiments positioned PV INs as a bona fide relay of $MS^{GABA\text{-}DG}$ projections but also raised a paradox: how does GABA release from $MS^{GABA\text{-}DG}$ projections onto PV INs promote GABA release from these local niche periscopes if GABA inhibits PV IN activation? The authors again dug deeper, now using calcium imaging in slices and whole-cell recordings, and found that GABA depolarizes DG PV INs and raises their intracellular calcium levels, but does not evoke action potentials (Figure 1). Again and surprisingly, GABA exposure elicited the opposite response in another local niche

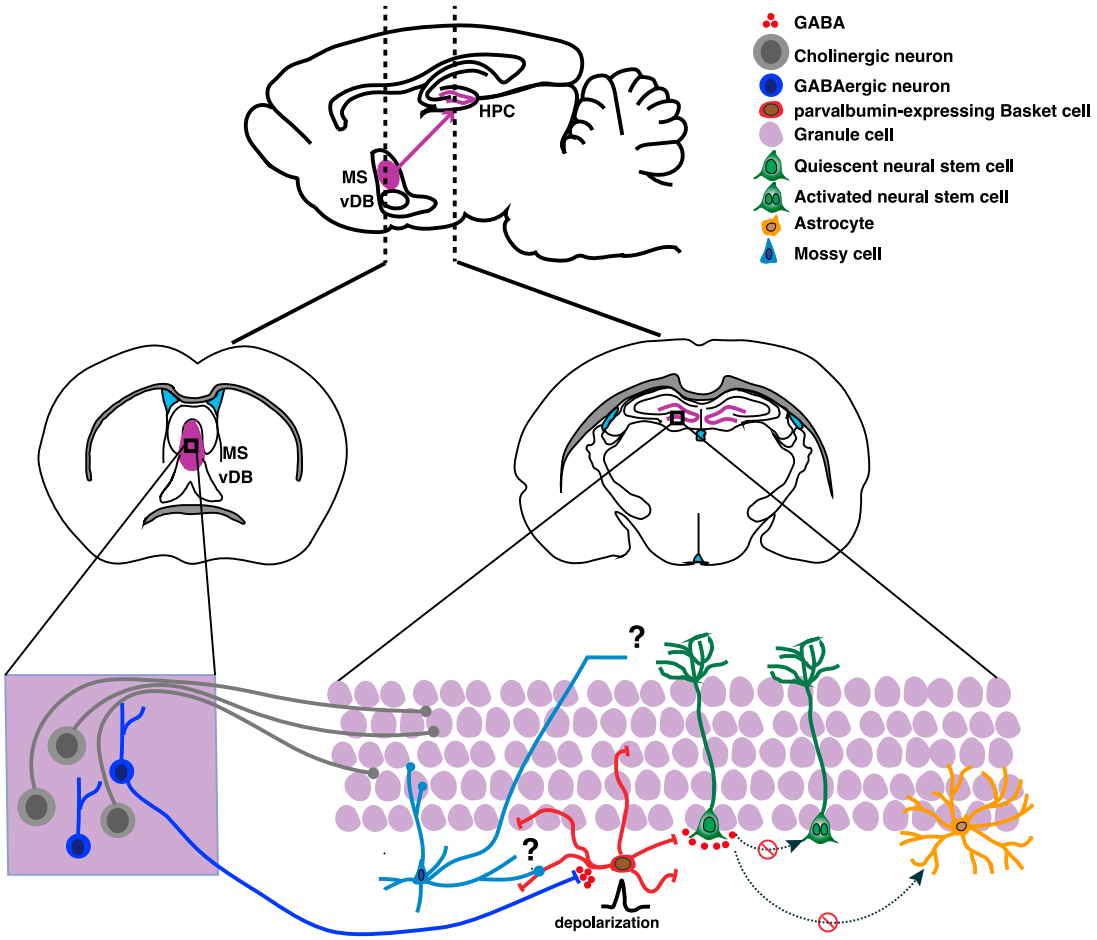

Figure 1. Schematic Delineating How Long-Range MS GABAergic Projections Govern NSC Activation via Local Niche Periscopes, DG PV INs
$MS^{GABA-DG}$ projections depolarize DG PV INs, which in turn release GABA onto NSCs and promote their quiescence.

IN, somatostatin neurons. Since it is generally accepted that GABAergic septohippocampal projections inhibit hippocampal INs to disinhibit pyramidal cells and promote theta rhythmic firing, it remains unclear how the finding that GABA depolarizes DG PV INs (and thereby potentially inhibits pyramidal cells) can be reconciled with this prevailing model (Colgin, 2016).

Following this fine dissection of the functional connectivity between $MS^{GABA-DG}$ neurons and DG PV INs in regulating NSC activation, the authors tested the impact of genetically ablating MS GABAergic neurons on adult hippocampal neurogenesis. Loss of MS GABAergic neurons resulted in sustained activation of NSCs, increased neuronal differentiation, and ultimately, a depleted NSC pool. Interestingly, the authors observed increased production of astrocytes consistent with previous reports suggesting conversion of NSCs to astrocytes with multiple divisions (Encinas et al., 2011). Furthermore, newly generated DGCs exhibited altered maturation, suggesting that projections of MS GABAergic neurons to the hippocampus are generally important for guiding maturation of adult-born DGCs.

These exciting advances raise important new questions to be addressed. Given the pivotal role of the GABAergic septohippocampal pathway in generating theta rhythms, it is curious that NSC quiescence, rather than activation, is the default state during generation of hippocampal theta rhythms. Fine dissection of the niche as exemplified by this study begs the question of how inputs onto the different niche periscopes are summated to govern NSC homeostasis. MS GABAergic neurons synapse onto several niche cell types, including potentially other DG INs. DG INs, by virtue of high interconnectivity, permit extensive summation of inputs prior to modulating NSC and network activity. Under what physiological conditions are these different niche periscopes recruited? Additionally, mature DGCs receive inputs from the entorhinal cortex and influence NSC activation by the production of secreted factors and, potentially, the recruitment of PV INs and mossy cells (Ma et al., 2009; McAvoy et al., 2016; Sun et al., 2017) (Figure 1). Mossy cells may modulate NSCs indirectly via DG PV INs or directly through release of glutamate in the inner molecular layer and onto apical tufts of NSCs (Figure 1).

Future studies integrating the contributions of local periscopes with non-neuronal niche cell types will shed light on the increasing complexity of

niche-stem cell communication (Schofield, 1978). These efforts will inform circuit-based approaches to modulate adult hippocampal neurogenesis and optimize memory processing in brain disorders characterized by cognitive and mood impairments.

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Location, Location, Location: Spatio-Temporal Cues That Define the Cell of Origin in Melanoma

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It is unclear whether melanoma initiates from mature melanocytes or stem cell precursors. In this issue of *Cell Stem Cell*, Moon et al. (2017) and Köhler et al. (2017) use *in vivo* lineage tracing to demonstrate that these two possibilities may occur downstream of the same pro-tumorigenic lesions, depending on environmental factors or the anatomical location.

Adult stem cells have been reported as the cell of origin in various cancer types (White and Lowry, 2015), but whether this is the case in cutaneous melanomas, the most aggressive form of skin cancer, is unknown. In this issue of *Cell Stem Cell,* two studies by Moon et al. (2017) and Köhler et al. (2017) report new lineage-tracing mouse models that provide insight into spatio-temporal cues defining melanoma initiation *in vivo*.

The need for functional analyses of melanocytic cells in their physiological niches has emerged from previous animal models. For example, live imaging in zebrafish has revealed melanomas resulting from de-differentiation to an early neural crest precursor, a feature conditioned by microenvironmental factors (Kaufman et al., 2016). A phenotypic switch involving loss of lineage specifiers has also been observed in genetically engineered mice that exploit promoters of melanocytic genes, such as tyrosinase (Tyr) or dopachrome tautomerase (Dct), to recapitulate the disease's characteristic genetic alterations in oncogenes or tumor suppressors (i.e., Braf or Pten) (Pérez-Guijarro et al., 2017). While this de-differentiation reflects epithelial-to-mesenchymal transitions in human melanoma cells (Caramel et al., 2013), the precise nature of the cells of origin is unclear. Moreover, an acknowledged limitation of these mouse models is that the induction protocols to activate Braf and delete Pten (typically at neonatal stages) result in dermal lesions instead of the interfollicular epidermal-dermal presentation seen in most human cutaneous melanomas (Pérez-Guijarro et al., 2017). Another method, neonatal UVB irradiation, has also been reported to mobilize melanocytes to drive epidermal melanoma with a marked inflammatory component (Zaidi et al., 2011). However, whether mature melanocytes and stem cells play differential roles in adult mice is still not well understood.

Moon et al. (2017) exploit tamoxifen-inducible Tyr (Tyr::CreERT2) and doxycyline-regulated Dct (Dct-rtta) mouse strains to drive fluorescent reporters (*LSL-tdTomato* or *TreH2B-GFP*, respectively) for *in vivo* tracing of the melanocytic lineage. These animals were further used to generate *Tyr::CreERT2; Braf^{V600E}* derivatives in the absence or presence of Pten (to monitor nevi or melanoma, respectively). Different protocols for depilation, or hair removal, and topical administration of tamoxifen were tested to assess the transformation potential of hair-follicle-associated melanoma cancer stem cells (MCSCs). With this approach, *Braf^{V600E}; Pten$^{-/-}$* were found to induce dermal