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Neuron
Review

Communication, Cross Talk, and Signal Integration in the Adult Hippocampal Neurogenic Niche

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https://doi.org/10.1016/j.neuron.2019.11.029

Radial glia-like neural stem cells (RGLs) in the dentate gyrus subregion of the hippocampus give rise to dentate granule cells (DGCs) and astrocytes throughout life, a process referred to as adult hippocampal neurogenesis. Adult hippocampal neurogenesis is sensitive to experiences, suggesting that it may represent an adaptive mechanism by which hippocampal circuitry is modified in response to environmental demands. Experiential information is conveyed to RGLs, progenitors, and adult-born DGCs via the neurogenic niche that is composed of diverse cell types, extracellular matrix, and afferents. Understanding how the niche performs its functions may guide strategies to maintain its health span and provide a permissive milieu for neurogenesis. Here, we first discuss representative contributions of niche cell types to regulation of neural stem cell (NSC) homeostasis and maturation of adult-born DGCs. We then consider mechanisms by which the activity of multiple niche cell types may be coordinated to communicate signals to NSCs. Finally, we speculate how NSCs integrate niche-derived signals to govern their regulation.

Radial glia-like neural stem cells (RGLs) in the dentate gyrus subregion of the hippocampus give rise to dentate granule cells (DGCs) and astrocytes throughout life, a process referred to as adult hippocampal neurogenesis (Bonaguidi et al., 2012; Garcia et al., 2004; Gonçalves et al., 2016b; Pilz et al., 2018; Seri et al., 2001). Although much less is known about adult-born astrocytes, adult-born DGCs (abDGCs) integrate into hippocampal circuitry by remodeling the network and ultimately contribute to hippocampal-dependent learning and memory and regulation of emotion (Anacker and Hen, 2017; Gonçalves et al., 2016b; Miller and Sahay, 2019; Toni and Schinder, 2015; Tuncdemir et al., 2019). Levels of adult hippocampal neurogenesis are highly sensitive to experience (Cope and Gould, 2019; Gonçalves et al., 2016b; Kempermann et al., 1998; Mirescu and Gould, 2006; van Praag et al., 2000; Yun et al., 2016), suggesting that neurogenesis may represent an adaptive mechanism by which hippocampal circuit performance is optimized in response to demands of the environment. Experience is conveyed to RGLs, neuroblasts, and immature adult-born DGCs via signals sensed by the hippocampal neurogenic niche that is composed of diverse local cell types, including astrocytes, DGCs, inhibitory interneurons, endothelial cells, extracellular matrix (ECM), and subcortical neurons that project to the DG. Thus, the local and extended niche enables NSCs to listen and respond to changes in neural activity and systemic factors (Guo and Sahay, 2017). Understanding how the niche performs its functions may guide strategies to maintain its health throughout the lifespan and provide a permissive milieu for adult hippocampal neurogenesis.

A swath of evidence generated over several decades describes how different kinds of experiences affect neural stem cell and progenitor proliferation and differentiation and survival of adult-born DGCs (Cope and Gould, 2019; Dranovsky et al., 2011; Encinas et al., 2008; Gonçalves et al., 2016b; Song et al., 2016). However, much less is understood about how different cell types within the local and extended niche communicate to NSCs and adult-born DGCs to mediate the effects of experience on adult hippocampal neurogenesis. Experience modulates NSCs by governing quiescence (state of reversible growth arrest) or activation decisions and symmetric/asymmetric self- renewal. These fundamental decisions made by the NSC are essential for homeostasis: maintenance of reservoir of NSCs ready for mobilization in response to experiential demands. Not surprisingly, NSCs do not act autonomously but instead sense and integrate a plethora of niche-derived signals communicated by local, distal, and systemic actors. Transplantation studies exemplify the role of niche in instructing and respecifying fate of biased progenitors (Gage et al., 1995; Seidenfaden et al., 2006). Additionally, many of these local niche cell types also govern the maturation and synaptic integration of adult-born DGCs. Here, we first discuss *representative* contributions of distinct niche cell types to regulation of NSC homeostasis and maturation of adult-born DGCs, with each section conveying outstanding questions. We then consider mechanisms by which the activity of multiple niche cell types may be coordinated to communicate signals to NSCs. Finally, we speculate how NSCs integrate these multiple niche-derived signals to make decisions.

Anatomical Constraints of the Neurogenic Niche

Ultrastructural analysis and high-resolution imaging provide a ground truth for understanding how NSCs and immature adult-born DGCs may respond to local niche signals. The subgranular

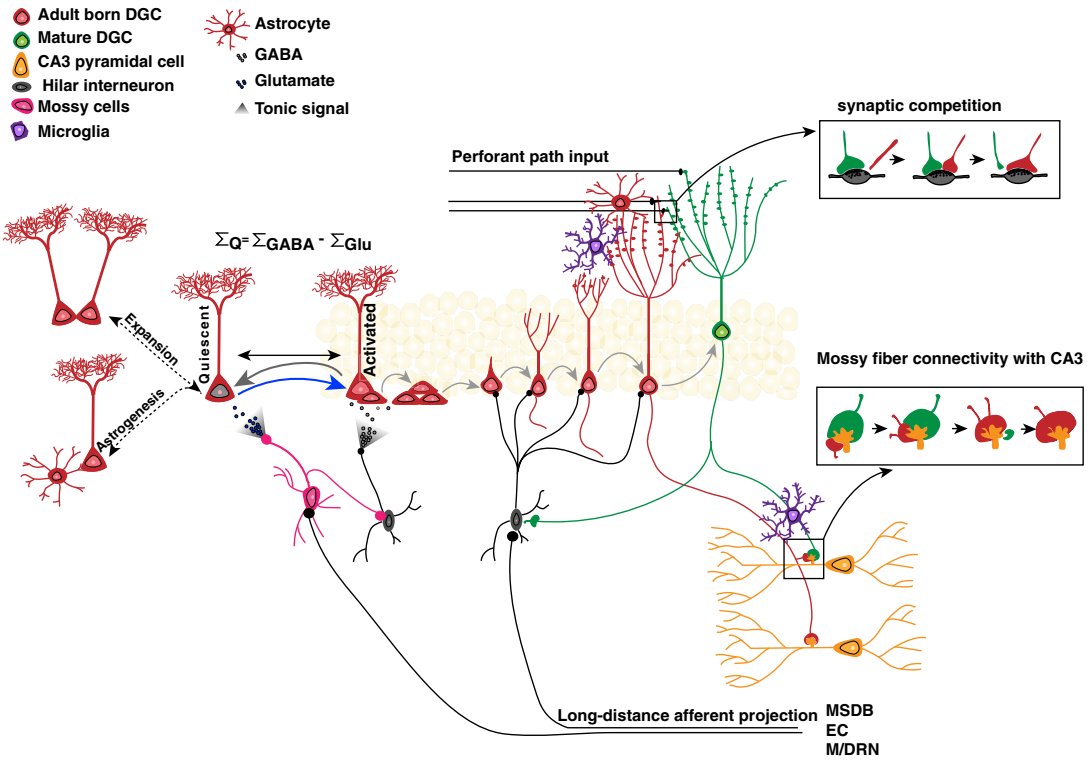

Figure 1. Local DG Circuits Regulate NSC Homeostasis and Integration of Adult-Born Neurons
Local hilar inhibitory interneurons, mossy cells, and, potentially, astrocytes relay local and distal inputs onto NSCs and differentiating adult-born DGCs. NSCs summate GABAergic and glutamatergic inputs to mediate quiescence-activation and self-renewal decisions. Tonic GABA release onto NSCs promotes quiescence (gray arrow), whereas mossy-cell-dependent glutamate release promotes activation of NSCs (blue arrow). Afferent and efferent synaptogenesis of adult-born DGCs occurs at pre-existing synapses, and astrocytes and microglia may modulate synaptic competition through vesicular release of D-serine and secreted synaptogenic factors and trogocytosis. EC, entorhinal cortex; M/DRN, median/dorsal raphe; MSDB, medial septum/diagonal band. See text for details.

zone of the DG, where neural stem cells differentiate into DGCs, is highly vascularized (Palmer et al., 2000). Electron microscopy (EM) analysis has revealed that RGL cell bodies have concave edges presumably reflecting the convex curvature of adjacent DGC bodies. The primary (apical) processes of RGLs navigate the granule cell layer to branch extensively in the inner molecular layer (Moss et al., 2016). Secondary and tertiary processes contact DGC dendritic spines and apposing axon terminals of entorhinal cortical and subcortical projections and mossy cells. RGL processes do not establish synaptic contacts but, much like astrocytes, wrap around or form tight appositions with axon terminals and spines (Moss et al., 2016). Larger diameter processes, like astrocytic endfeet, wrap local blood vessels, creating a blanket of coverage along with astrocytic processes. Basal processes project along the subgranular zone axis and into the hilus, where they are positioned to sense signals from hilar neurons (Moss et al., 2016).

EM analysis of retrovirally labeled adult-born DGCs has revealed that dendritic spines of adult-born DGCs establish contacts with perforant path boutons that have already formed synapses onto mature DGCs (Toni et al., 2007; Figure 1). Local inhibitory interneurons form synaptic contacts with early neuroblasts, maturing adult-born dentate granule cell (abDGCs), and DGCs (Catavero et al., 2018; Dieni et al., 2016; Espósito et al., 2005; Freund and Buzsáki, 1996; Ge et al., 2006; Heigele et al., 2016; Marín-Burgin et al., 2012; Miller and Sahay, 2019; Overstreet-Wadiche et al., 2006; Pelkey et al., 2017; Song et al., 2013, 2016). Serial section immune EM and electrophysiological recordings have demonstrated existence of astrocytic perisynaptic ensheathments of dendritic spines and mossy fiber terminals of adult-born DGCs (Krzisch et al., 2015; Sultan et al., 2015). 2-photon imaging has shown that dendrites of immature adult-born DGCs undergo pruning both at steady state and following enriched experience (Gonçalves et al., 2016a). Although the maturation of dendritic spines and mossy fiber terminals of adult-born DGCs continues for several months (Faulkner et al., 2008; Gonçalves et al., 2016a; Lemaire et al., 2012; Sun et al., 2013; Toni et al., 2007, 2008), the tempo of maturation is modifiable by experience (Alvarez et al., 2016; Piatti et al., 2011; Snyder et al., 2009; Vivar et al., 2013; Zhao et al., 2006), suggesting that different niche cell types relay experiential information to regulate the rate of neurogenesis. Imaging studies also identify microglia and oligodendrocytes as other local niche residents (Braun et al., 2015; Ribak et al., 2009; Shapiro et al., 2009; Sierra et al., 2010). The structural organization of DG neurogenic niche suggests extensive cross talk between niche cell types and positions NSCs and adult-born DGCs as integrators of diverse signals from the niche. We discuss examples of these dialogs in the next sections in the hope of shedding light on the logic underlying anatomical constraints of the niche. In each section, we begin

with the relationship between niche cell type and NSCs prior to transitioning to dialog between niche cell type and adult-born DGCs.

Local Neuronal Cell Types Coordinate Neurogenesis and Network Activity

DGCs are abundant niche cells and ensconce the cell bodies of NSCs located in the subgranular zone (Figure 1). DGCs receive excitatory inputs from diverse cortical and subcortical circuits and other hippocampal subregions and, as such, are well positioned to relay signals to NSCs and immature adult-born DGCs (Miller and Sahay, 2019). Growing evidence suggests that neuronal activity may recruit DGCs to modulate NSC homeostasis via secretion of factors. Several studies have identified activity-dependent production of pro-neurogenic secreted factors. A pioneering study found that electroconvulsive shock treatment induced a transient increase in GADD45b expression in DGCs (Ma et al., 2009). Gadd45b functions as a DNA demethylase and promotes expression of secreted factors, such as brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (FGF), to stimulate neural progenitor proliferation and dendritic maturation of adult-born DGCs. Neural activity and running were shown to decrease levels of sFRP3, secreted frizzled-related protein 3, an extracellular Wnt inhibitor, in DGCs (Jang et al., 2013). Reduction of sFRP3 levels promoted NSC activation without affecting lineage choice. Additionally, loss of sFRP3 also accelerated dendritic growth and spine formation, suggesting that it normally functions as a brake that calibrates the tempo of neuronal differentiation. DGCs also express other neurogenic ligands, such as vascular endothelial growth factor C (VEGF-C), which signals through VEGFR3 in NSCs to promote neurogenesis (Han et al., 2015). Exercise, enriched environment, and administration of selective serotonin reuptake inhibitors have been shown to decrease bone morphogenetic protein (BMP) signaling by either reducing BMP levels or increasing expression of noggin, an extracellular BMP inhibitor, in DGCs (Brooker et al., 2017; Gobeske et al., 2009). Viral overexpression of noggin in DGCs (Gobeske et al., 2009) or genetic ablation of BMP signaling in neural stem and progenitor cells (NSPCs) (when neither population is selectively targeted) promoted proliferation (Mira et al., 2010). Interestingly, inducible elimination of dendritic spines of mature DGCs is accompanied by robust activation of NSCs (McAvoy et al., 2016) and elevation in noggin expression in DGCs (K. McAvoy and A.S., unpublished data). These observations suggest that DGCs modulate NSC quiescence by regulation of BMP signaling in NSCs. Interestingly, the RNA-binding protein FXR2, which controls the stability of noggin mRNA, is expressed in mature DGCs. Loss-of-function experiments have shown that FXR2 deficiency results in increased expression of noggin and proliferation of NSCs (Guo et al., 2011). In addition to these ligands, many other ligand-receptor pairs that are expressed in complementary manner in NSCs and DGCs (Dong et al., 2019; Engler et al., 2018; Lie et al., 2005; Semerci et al., 2017) are also likely to mediate different kinds of experiential signals. Together, these examples illustrate how extrinsic signals induce expression of DGC-derived secreted factors to regulate NSCs and immature adult-born DGCs. However, many questions remain to be addressed regarding the mechanisms by which neural activity governs release of secreted factors from DGCs to modulate NSCs. Because most DGCs do not project into the inner molecular layer (except for semilunar granule cells [Williams et al., 2007] and a few adult-born DGCs [Luna et al., 2019]), where RGL's primary apical branches are located, it is unclear whether DGC-derived ligands signal to their receptors on NSCs via contact between cell bodies or mossy-fiber-dependent release into the hilus, where RGLs have basal branches (Figures 1 and 2A). Do specific patterns of neuronal activity in DGCs release different neurogenic factors? How are transcription factors that regulate NSC homeostasis and maturation of adult-born DGCs (Andersen et al., 2014; Beckervordersandforth et al., 2015; Hsieh, 2012; Hsieh and Zhao, 2016) recruited to govern expression of secreted factors?

DGCs also recruit circuit mechanisms mediated by local inhibitory interneurons (INs) and mossy cells to modulate NSC homeostasis and maturation of abDGCs (Figure 1). The DG is populated by distinct INs, such as parvalbumin (PV) basket cells and axo-axonic cells, somatostatin hilar perforant path, hilar commissural associational pathway, neurogliaform/Ivy cells, molecular perforant path (Deshpande et al., 2013; Li et al., 2013; McAvoy et al., 2016; Vivar et al., 2012), cholecystokinin (CCK), neuropeptide Y (NPY), calretinin, and vasoactive intestinal polypeptide (VIP) interneurons (Freund and Buzsáki, 1996; Pelkey et al., 2017). NSCs express $GABA_A$ receptors in both their cell bodies and processes, whereas glutamate transporters and AMPA receptors are found in the cell bodies and apical processes, respectively (Renzel et al., 2013). Activation of PV INs, but not somatostatin (SST) and VIP INs, promoted quiescence of NSCs and reversed social-isolation-induced increase in symmetric divisions (Song et al., 2012). Because NSCs appear to lack functional GABAergic synapses, PV INs are thought to regulate NSCs by tonic inhibition mediated by GABA spillover from PV-DGC synapses (Song et al., 2012; Tozuka et al., 2005; Wang et al., 2005). In contrast to NSCs, neural progenitors have functional GABAergic synapses (Tozuka et al., 2005) and PV INs (but not SST INs) inhibit their proliferation and survival (Song et al., 2013). DG interneurons receive inputs from different extra-hippocampal and subcortical circuits (Freund and Buzsáki, 1996; Pelkey et al., 2017). The medial septum/diagonal band (MSDB) GABAergic neurons constitute a major projection to DG INs and PV INs in particular (Freund and Antal, 1988; Salib et al., 2019). Consistent with this innervation pattern, optogenetic stimulation of MS GABAergic projections depolarized PV INs and promoted NSC quiescence (Bao et al., 2017).

Mossy cells project both ipsilaterally and contralaterally to form monosynaptic excitatory synapses onto DGCs and disynaptically inhibit DGCs via hilar INs (Scharfman and Myers, 2013). *Ex vivo* chemogenetic or optogenetic activation of mossy cells depolarized NSCs and hilar INs, including PV INs (Yeh et al., 2018; Figure 1). *In vivo* chemogenetic activation or inhibition of mossy cells promoted NSC quiescence and activation through recruitment of interneurons, respectively. The same study suggested that mossy cells may recruit hilar INs to exert their effects on quiescence, whereas direct release of glutamate from mossy cells depolarizes and activates NSCs.

Electrophysiological and viral synaptic tracing studies have demonstrated that adult-born DGCs progressively recruit

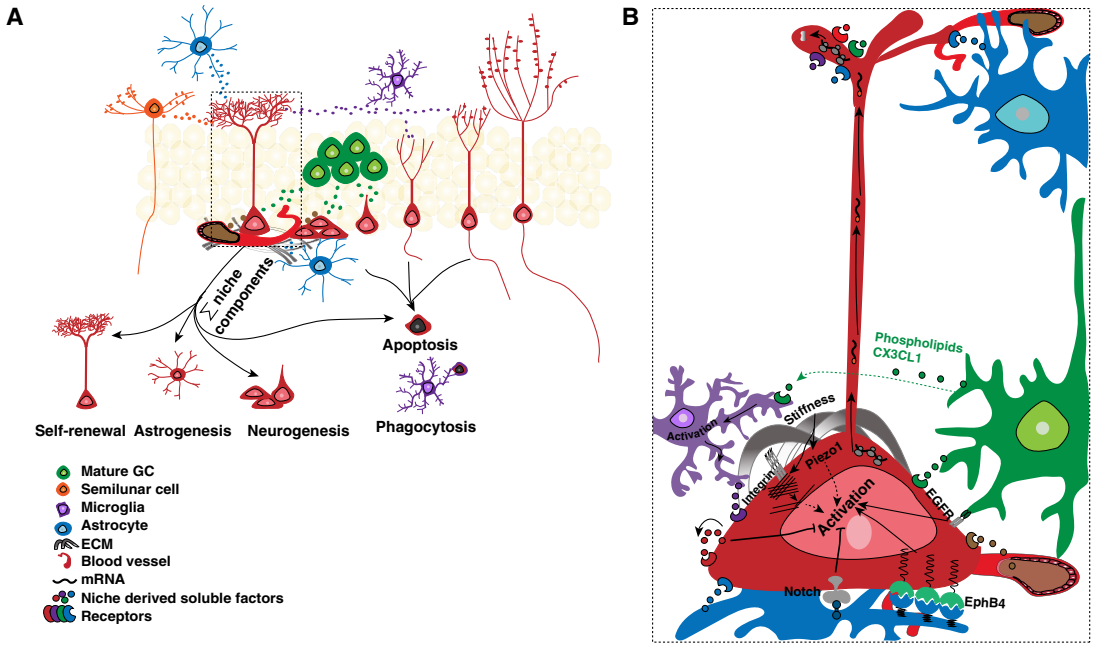

Figure 2. NSCs Integrate Secreted and Juxtacrine Signals from Diverse Niche Cell Types to Maintain Homeostasis

(A) NSCs integrate signals from astrocytes, DGCs, semilunar granule cells, inhibitory interneurons, blood vessels, extracellular matrix (ECM), and inhibitory interneurons to mediate quiescence-activation and self-renewal decisions. Different niche actors may release ligands onto discrete domains of NSCs. Receptors in the apical process of RGLs may sense ligands released by axon terminals of DG afferents or of semilunar granule cells in the inner molecular layer. Competition for niche-derived factors may trigger microglial-dependent pruning of NSC numbers to maintain homeostasis.

(B) Magnification of RGL in dashed line box in (A) conveying niche-derived secreted ligands (astrocyte-derived factors [blue]: IL-1b and Wnt3a; vasculature-derived factors [brown]: IGF; mature DGC-derived factors [green]: sFRP3, VEGF-C, noggin, BMP, and Fracktalkine; and microglia-derived factors [purple]) signal in paracrine or juxtacrine modes. DGCs may regulate NSC behavior through recruitment of microglia via release of phospholipids and fracktalkine. NSCs and progenitors may regulate their fate choices by autocrine signaling (red: VEGF and Mfge8). ECM regulates NSC behavior through ligands, such as laminin, reelin, and stiffness-dependent modulation of Piezo signaling in NSCs. Within NSCs, mRNAs encoding ligands may be transported along the radial apical process for local translation in response to physiological signals.

See text for details.

different INs during their differentiation to regulate synapse and dendritic maturation (Bergami et al., 2015; Dieni et al., 2016; Espósito et al., 2005; Ge et al., 2006; Marín-Burgin et al., 2012; McAvoy et al., 2016; Miller and Sahay, 2019; Overstreet-Wadiche et al., 2006; Vivar et al., 2012). Like that seen during embryonic and early brain development (Ben-Ari et al., 1997), dendritic depolarizing GABAergic synapses coupled with calcium signaling and cAMP response element-binding protein (CREB)-dependent transcription promotes the establishment of first glutamatergic synapses onto adult-born DGCs (Espósito et al., 2005; Ge et al., 2006; Jagasia et al., 2009; Markwardt et al., 2009; Overstreet-Wadiche et al., 2006). Ivy/neurogliaform (NGF) cells are among the earliest GABAergic presynaptic partners and are thought to couple newborn DGC depolarization with disinhibition of mature DGCs (Markwardt et al., 2011). During this window, hilar mossy cells are the first to establish glutamatergic synapses onto DGCs, thereby potentially coordinating NMDA-receptor-activation-dependent AMPA receptor insertion into silent synapses and disynaptic GABAergic depolarization (Chancey et al., 2013; Kumamoto et al., 2012). Dendritic elaboration and dendritic spine formation are modified by experience during the first few weeks of adult-born DGC maturation (Bergami et al., 2015; Gonçalves et al., 2016a; Sun et al., 2013). Mature DGCs recruit PV INs during this stage to depolarize immature DGCs and regulate these experience-sensitive developmental processes (Alvarez et al., 2016). Interestingly, pairing of glutamatergic subthreshold potentials with strong stimulation of GABAergic inputs suppressed firing of immature adult-born DGCs by shunting inhibition (Heigele et al., 2016). Thus, GABAergic INs can regulate immature DGC maturation by both excitation and shunting inhibition in response to network activity. Establishment of perisomatic inhibition and perforant path-DGC synapses is followed by an extended period of maturation, over several months, during which dendritic spine and dendritic complexity continue to be refined by experience (Figure 1).

Together, these studies suggest that DGCs, local INs, and mossy cells regulate NSC homeostasis and maturation of adult-born DGCs (Figure 1). Growing evidence supports a role for extended inhibitory neuron networks that traverse brain regions and project across hippocampal subregions (Caputi et al., 2013; Freund, 2003; Klausberger and Somogyi, 2008; Salib et al., 2019; Szabo et al., 2017) to regulate and coordinate principal cell activity. However, more studies are needed to delineate the precise contributions of different local-DG INs and DG-projecting INs to NSC homeostasis and neurogenesis. It is likely that, just as in the case of PV INs, distinct DG INs are also regulated by different extra-hippocampal inputs to modulate NSCs and neurogenesis. Inhibitory neurons have distinct laminar

distributions of axonal and dendritic arborizations that influence dendritic, somatic, and distal compartments of principal cells to govern spiking, gate synaptic plasticity, and synchronize neuronal firing. Understanding how topographic organization and physiological patterns of IN activity relate to their roles in modulation of NSC homeostasis and neurogenesis will inform how hippocampal network activity calibrates levels of neurogenesis.

Glial Niche Actors: Astrocytes

Astrocytes are glial cell types abundantly present in the DG neurogenic niche that provide both functional and structural support for NSCs and maturing adult-born DGCs. A pioneering *in vitro* co-culture study demonstrated that mature astrocytes from adult hippocampus, but not adult spinal cord, promote proliferation and neuronal fate specification of adult neural progenitors (Song et al., 2002). Based on co-culturing of neural stem cells with astrocytes or astrocyte-conditioned media, the authors predicted roles for both astrocytic membrane-bound and diffusible factors in regulation of neurogenesis. Using cultured adult NSPCs, subsequent studies have identified pro-neurogenic (interleukin-1b [IL-1b] and IL-6, FGF-2) and inhibitory neurogenic-astrocytic-derived factors (decorin, IGFBP6; Barkho et al., 2006; Kirby et al., 2013). Astrocytes release gliotransmitters (Araque et al., 2014) that may modulate NSC activation. Preliminary evidence from an *in vitro* study suggested that ATP derived from astrocytes promotes proliferation of adult hippocampal neural stem and progenitor cells (Cao et al., 2013). Although hippocampal astrocytes express diverse repertoire of membrane-bound and secreted factors (Clarke et al., 2018; Hillen et al., 2018; Morel et al., 2017), many with potential roles in neurogenesis, a paucity of studies have examined their contributions to regulation of NSC homeostasis *in vivo*. One study showed that ephrin-B2 expression is enriched in hilar astrocytes and found that viral downregulation of ephrin-B2 in the DG decreased neuronal differentiation of progenitors without affecting progenitor and stem cell proliferation (Ashton et al., 2012). It is likely that transgenic lines (such as GLAST CreERT2; Mori et al., 2006) used to manipulate RGLs may also affect astrocytic contributions to RGL homeostasis.

Astrocytes, as part of tripartite synapses that involve presynaptic terminals and postsynaptic specializations, are thought to regulate excitatory synapse formation and synaptic functions in the developing and adult brain (Araque et al., 2014; Christopherson et al., 2005; Adamsky et al., 2018; Chung et al., 2015; Farhy-Tselnicker and Allen, 2018). Astrocytes secrete soluble factors, such as thrombospondins, glypicans, chordin-like 1, and hevin, that promote excitatory synapse formation, maturation, and refinement during development (Allen et al., 2012; Blanco-Suarez et al., 2018; Farhy-Tselnicker et al., 2017; Kucukdereli et al., 2011). Additionally, astrocytes also release factors that antagonize synapse formation, such as secreted protein acidic and rich in cysteine (SPARC) that inhibits Hevin (Kucukdereli et al., 2011). In addition to secreted factors, astrocytes also express fatty-acid-binding proteins that participate in uptake and transport of fatty acids and that may influence excitatory synapse formation (Ebrahimi et al., 2016). Interestingly, many of these factors, such as hevin and Fabp7, are expressed at high levels in DG astrocytes (Mongrédien et al., 2019), suggesting that they may continue to play a role in synapse maturation and refinement of adult-born DGCs. Direct evidence for a role of astrocytes in regulating maturation of adult-born DGCs comes from a study that deployed two conditional genetic approaches to block astrocytic vesicular release (Sultan et al., 2015). The authors found that inhibition of astrocytic vesicular release decreased extracellular levels of D-serine, but not glutamate, glycine, or GABA, and reduced dendritic arbor complexity and length and dendritic spine density of adult-born DGCs. These morphological changes were accompanied by reductions in functional excitatory synapses onto adult-born DGCs. Furthermore, exogenous D-serine administration rescued alterations in dendritic arbors, spine density, and excitatory synapse to different degrees. Interestingly, pre-existing spines of mature DGCs were not affected, suggesting that astrocytic vesicular release influences the formation rather than pruning of dendritic spines. Although the genetic manipulations used in this study affected astrocytic function and not astrocytic ensheathment of synapses, it is plausible that structural alterations of astrocytes may disrupt topographic control of dendritic spine formation and dendritic elaboration.

Astrocytes may also modulate DGC and IN activity to regulate NSC homeostasis and maturation of adult-born DGCs as described earlier (Figures 1 and 2A). Astrocytes sense neural activity and modulate synaptic transmission and plasticity via release of gliotransmitters (Adamsky et al., 2018; Araque et al., 2014; Haydon, 2001). In the adult DG, astrocytes release glutamate that transiently strengthens excitatory synaptic transmission by activating NMDA receptors (NMDARs) on their juxtaposed presynaptic partners (Jourdain et al., 2007). In addition, astrocytes may play a role in synchronizing network activity locally via spread of gliotransmitters (Araque et al., 2014) or distally through gap junction coupling with hundreds of other astrocytes to regulate neurogenesis (Chai et al., 2017). Whether astrocytes are coupled to their ancestral NSCs is not known.

Glial Niche Actors: Microglia, the Brain's Immune Cells

Microglia are the brain's macrophages that maintain neuronal homeostasis by scanning, surveillance, phagocytosis, and eradication of apoptotic cells and debris (Figure 2A). Microglia have highly motile processes that can contact different cell types and can respond to changes in the local environment (Davalos et al., 2005; Nimmerjahn et al., 2005; Paris et al., 2018). Fate-mapping studies have demonstrated that, in mice, microglia arise from the yolk sac progenitor cells that invade the brain during mid-gestation and then differentiate into microglia (Ginhoux et al., 2010). In the mouse hippocampus, the peak of microglia density is reached around postnatal day 15, when it is inferred that microglia show heightened synaptic pruning activity (Paolicelli et al., 2011). In the adult DG, EM in combination with Iba1 immunohistochemistry has revealed microglia in hilus and molecular layers tightly apposed to DGC bodies (Ribak et al., 2009; Shapiro et al., 2009). Confocal imaging shows microglia distributed across molecular layers and surrounding NSPCs and DGCs (Mosher et al., 2012; Sierra et al., 2010). Microglia that populate the hippocampal neurogenic niche are highly proliferative and undergo rapid turnover (Askew et al.,

2017). Single-cell transcriptomics has revealed that microglia barely express genes associated with the canonical activation state of microglia, suggesting that, in the adult DG, microglia exist in the M2 resting state and exert some of their functions in this state (Artegiani et al., 2017). Consistent with this idea, unchallenged ramified microglia were found to phagocytose late neural progenitors/early neuroblasts in the adult subgranular zone (SGZ), thereby potentially regulating survival of newborn neurons (Sierra et al., 2010). Indeed, EM analysis detected processes of microglial cells surrounding DGCs at the hilar-GC layer, suggestive of microglial-dependent phagocytosis of DGCs (Ribak et al., 2009). Furthermore, partial genetic ablation of microglia in adult mice decreased numbers of adult-born neuroblasts (Kreisel et al., 2019).

Early studies suggested a role for activated microglia in regulation of neurogenesis *in vivo* (Ekdahl et al., 2003; Monje et al., 2003) and *ex vivo* (Butovsky et al., 2006) via secretion of inflammatory factors. Neuronally derived signals are thought to support resting and activated microglia states, each associated with distinct profiles of microglial-secreted chemokines and pro- and anti-inflammatory cytokines (Kierdorf and Prinz, 2017). Neuronally derived fracktalkine acting on its receptor, CX3CR1, expressed in microglia is thought to promote adult hippocampal neurogenesis. Mice lacking CX3CR1 exhibit reduced proliferation and numbers of adult-born DGCs (Vukovic et al., 2012). Intracerebroventricular infusion of CX3CR1-blocking antibodies into adult rats increased hippocampal IL-1Beta levels and decreased progenitor proliferation (Bachstetter et al., 2011). Conversely, fracktalkine infusions in aged, but not adult, rats increased progenitor proliferation (Bachstetter et al., 2011). *Ex vivo* studies also support a role for CX3CL1-CX3CR1 signaling in increasing proliferation (Vukovic et al., 2012). In addition to fracktalkine, hippocampal neurons secrete many other factors that may potentially modulate microglia. Overexpression of vascular endothelial growth factor A (VEGF-A) (referred to as VEGF), a neuronally secreted angiogenic factor that signals through VEGFR1 and VEGFR2, in hippocampal excitatory neurons increased microglial proliferation and adult hippocampal neurogenesis. Whether microglia, rather than endothelial cells or neurons, mediate these VEGF-dependent effects on neurogenesis is not clear (Kreisel et al., 2019). Although genetic targeting of pro-neurogenic factors within microglia has not been performed to date, an elegant study showed that conditional ablation of a core retromer transport protein (critical for endosomal membrane trafficking of transmembrane proteins) in microglia resulted in increased hippocampal microglial density (Appel et al., 2018). Interestingly, the number of immature DGCs was reduced because of increased NSPC proliferation and failure to exit cell cycle. It is plausible that deletion of the retromer protein impedes trafficking and secretion of specific transmembrane receptors in microglia that sense neurogenic signals. How is microglial activation correlated with both increased and decreased neurogenesis? One possibility is that distinct subpopulations of microglia are activated, each with opposing roles in promoting neurogenesis (Hammond et al., 2019; Masuda et al., 2019).

Neural progenitors may act as niche cells and directly modulate microglia independent of local neurons. Conditioned media obtained from early postnatal cortical neural progenitors increased microglial functions, such as phagocytosis, chemotaxis, and proliferation *ex vivo* and in the striatum (Mosher et al., 2012). The authors found that cortical-NPC-secreted VEGF was sufficient to regulate microglial functions in the striatum. Whether adult hippocampal NSPCs-derived VEGF regulates microglia is yet to be determined (Kirby et al., 2015). If so, NPCs may participate in a regulatory feedback loop that recruits microglia to control NSPC activation and phagocytosis of early NPCs and neuroblasts.

Studies in the developing brain suggest a role for microglia in regulation of synaptic pruning via engulfment of presynaptic terminals and dendritic spines (Schafer et al., 2012; Paolicelli et al., 2011; Tremblay et al., 2010; Weinhard et al., 2018). Neuronal activity appears to drive this process, and microglia preferentially engulf less active presynaptic inputs in the visual system (Schafer et al., 2012; Tremblay et al., 2010). Not surprisingly, and much like other niche actors, microglia also regulate maturation of adult-born DGCs. Cx3cr1-null mice exhibit an increase in activated microglia in DG and elevated levels of pro-inflammatory cytokines in the hippocampus (Bolós et al., 2018). In addition, there was increased deposition of extracellular matrix proteoglycans, some of which restrict IN plasticity and consequently may affect IN-NSC and adult-born DGC communication (Bolós et al., 2018; Fawcett et al., 2019). Adult-born DGCs had less complex dendritic arbors, fewer dendritic spines, and smaller mossy fiber terminals. Although the use of null mutants encumbers interpretation of these results, acute genetic deletion of retromer protein in microglia in adulthood also impaired dendritic arborization and decreased dendritic spine density of immature adult-born DGCs (Appel et al., 2018). Whether the dendritic spine alterations of adult-born DGCs are due to increased microglial-dependent phagocytosis is debated. This is because a recent study found no evidence for microglial-dependent phagocytosis of dendritic spines or functional synapses in CA1 (Paolicelli et al., 2011; Weinhard et al., 2018). Instead, the authors inferred that microglia participate in trogocytosis of axons and presynaptic terminals and generation of filopodia at pre-existing mature spines (Figures 1 and 2A).

The precise contributions of microglia to NSC homeostasis and maturation of adult-born DGCs necessitate more studies that acutely manipulate signaling pathways within these different cell types. Interestingly, DG microglia may differ from CA1 microglia in a limited set of genes, suggesting that they may preferentially exhibit a neurogenic program. Indeed, some of these genes, such as Axl and others that encode lipid binding, signaling, and transport proteins, have been previously implicated in neurogenesis (Kreisel et al., 2019). Do signals from NSPCs and adult-born DGCs regulate distinct aspects of microglial functions? Membrane phospholipids are thought to represent one such signal that promotes engulfment by macrophages (Weinhard et al., 2018). Do microglia regulate all or only specific inputs and output connectivity (inhibitory interneurons versus CA3) of adult-born DGCs? Given the prominent roles of inhibitory interneurons in governing adult hippocampal neurogenesis, it will be important to interrogate whether microglia regulate inhibitory synapse numbers.

ECM: Attachment, Signaling, and Stiffness

The ECM is a network of diverse glycoproteins (e.g., tenascin C), proteoglycans (bearing heparan sulfate, chondroitin sulfate, or dermatan sulfate side chains), and cell adhesion molecules that surrounds cells to provide a functional scaffold for maintaining signaling gradients and stiffness (Figure 2B). Key components of ECM, such as reelin, tenascins, laminins, and their receptors, integrins, have well-characterized roles in regulating progenitor proliferation, neurite extension, apical radial glial morphology, and neuronal differentiation during development (Long and Huttner, 2019). Consistently, ECM proteins, such as laminin, signal through integrins expressed in NSPCs to regulate NSPC homeostasis (Porcheri et al., 2014). Integrins are important for attachment of apical radial glial endfeet to basement membranes and maintenance of characteristic bipolar morphology of radial glial cells in the neocortex (Radakovits et al., 2009). Although cytoskeletal proteins, adhesion molecules, and ECM ligands that maintain RGL architecture in the adult DG have yet to be defined, their roles in regulating neurogenesis are emerging. The integrin-linked kinase is expressed throughout apical processes of NSCs and not in progenitors in the adult DG. Conditional deletion of integrin-linked kinase in adult NSPCs resulted in increased proliferation due to enhanced downstream c-Jun N-terminal protein kinase (JNK) activity (Porcheri et al., 2014). Conditional deletion of reelin signaling in adult DG NPCs enhanced gliogenesis and disrupted dendritic development of immature adult-born DGCs. Specifically, immature adult-born DGCs had reduced apical dendritic complexity and aberrant ramification of basal hilar dendrites (Teixeira et al., 2012).

Although a large number of secreted factors (Notch, FGFs, Wnts, BMPs, and Sonic hedgehog) have been identified as regulators of adult hippocampal neurogenesis, the precise distribution of these ligands within the niche is poorly understood. It is highly unlikely that ligands freely diffuse through the ECM but instead localize to discrete regions to facilitate communication between niche cell types and NSPCs (Figure 2B). Indeed, ultrastructural analysis of the subependymal layer in the anterior horn of the lateral ventricles has revealed extracellular matrix (ECM) projections called fractones because of their fractal structure that contact astrocytes, microglial cells, and NSPCs (Mercier, 2016; Mercier et al., 2002) Fractones are rich in *N* sulfate heparan sulfate proteoglycans that trap FGF2 to create pockets of NSPC proliferation (Kerever et al., 2007). Although structural fractone analogs are not observed in the DG, it is plausible that functional ECM analogs might exist in the DG niche to localize ligands.

Ultrastructural analysis reveals tight packing of different niche cell types and suggests a role for ECM in regulating mechanotransduction in NSCs. *In vivo*, atomic force microscopy measurements reveal a gradient of increasing stiffness from the SGZ upward through the granule cell layer (Luque et al., 2016). Additionally, cultured adult NSPCs increase their own intrinsic mechanical properties in response to increased ECM stiffness (Rammensee et al., 2017). The lineage sensitivity of adult NSPCs to ECM stiffness is manifest during the first 12–36 h *ex vivo*. Candidates for mechanosensors include the stretch-activated cation channel, Piezo 1, whose activity is modulated by ECM stiffness in cultured human fetal cortical NSPCs (Pathak et al., 2014). Importantly, Piezo 1 is necessary for mechanically induced currents in human neural stem and progenitor cells (hNSPCs) (Pathak et al., 2014). Several intracellular mechanisms have been invoked to convey ECM-stiffness-dependent signal transduction to bias lineage specification *ex vivo*. One group found a putative role for YAP (yes-associated protein)-beta-catenin interaction and mobilization of Rho guanosine triphosphatases (GTPases) (Keung et al., 2011; Rammensee et al., 2017), whereas another study showed that Piezo1 activity was necessary for nuclear localization of Yap1 (Pathak et al., 2014). Whether Yap's nuclear and cytoplasmic roles and Rho GTPases also mediate ECM-stiffness-dependent mechanotransduction in adult DG NSPCs *in vivo* is to be determined.

Neural Stem Cells: Masters of Their Own Destiny

Growing evidence suggests a role for stem cells as niche actors that regulate their own homeostasis and influence differentiation of their progeny (Figure 2B). In the subventricular zone, NSCs and progenitors produce an endozepine called diazepam-binding inhibitor that inhibits GABA-A receptors and whose proteolytic product blocks the differentiation-promoting effects of neuroblast-derived GABA (Alfonso et al., 2012). As such, NSCs and progenitors maintain a proliferative state by antagonizing signals from their descendants (Alfonso et al., 2012). In the adult hippocampus, NSPCs regulate their own activation and quiescence through distinct autocrine and paracrine mechanisms. One study showed using VEGF-GFP reporter mice and *ex vivo* cultures that NSPCs are an important source of VEGF in the SGZ. Conditional ablation of VEGF in Nestin+ cells led to a transient increase in NSC proliferation and subsequent partial depletion. This autocrine/paracrine effect was mediated by VEGFR2 expressed in NSPCs (Kirby et al., 2015). Quiescent NSCs also exhibit elevated levels of Mfge8 (milk-fat globule-epidermal growth factor EGF factor 8) that promotes quiescence through β1integrin receptors expressed on NSCs (Zhou et al., 2018). Thus, NSCs may regulate themselves via autocrine and paracrine mechanisms.

Because receptors for many NSC-derived ligands, such as VEGF, are also expressed in their progeny, neuroblasts and immature DGCs, and other niche actors (like microglia as discussed earlier), NSCs may regulate multiple stages of maturation of adult-born DGCs directly or indirectly through modulation of niche actors. For example, the NSC-secreted factor pleiotrophin was shown to act on anaplastic lymphoma kinase (ALK) receptors expressed on immature adult-born DGCs and influence their dendritic complexity, dendritic spine density, and afferent connectivity (Tang et al., 2019). NSCs may also modify their own ECM milieu by synthesizing and depositing proteoglycans around them, as suggested by *ex vivo* studies (Tham et al., 2010). How do NSCs secrete factors to self-regulate or modulate their niche? Embryonic cortical radial glial cells exhibit local translation of nuclear exported transcripts encoding signaling factors at their endfeet (Pilaz et al., 2016). NSCs may utilize a similar mechanism to secrete factors on demand via their endfeet-like processes (Figure 2B).

Systemic Niche Factors

RGLs sense and respond to blood-born circulatory factors through their apical processes that wrap around blood vessels.

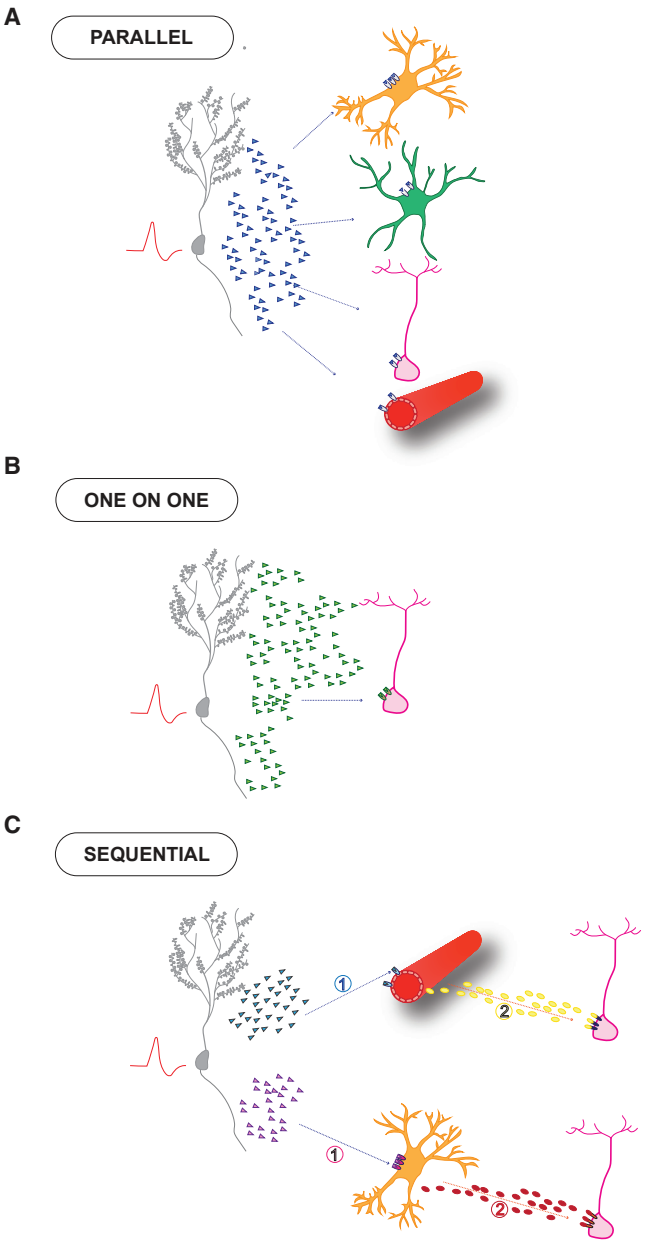

Figure 3. Inter-cellular Cross Talk in the Niche
Neuronal activity may recruit multiple modes of signaling to coordinate activity of diverse niche actors and NSCs.
(A) Parallel mode: a single niche-derived signal (light blue) may act simultaneously on cognate receptors present on astrocytes (green), microglia (orange), endothelial cells (red), and NSCs (pink).
(B) One-on-one mode: NSCs may receive a signal from only one cell type.
(C) Sequential mode: this mode invokes communication across a cascade of niche actors such that signals are sequentially transmitted to ultimately reach NSCs.
See text for details.

Heterochronic parabiosis studies that entail surgical joining of circulatory systems of young and aged mice have led to the identification of pro- and anti-neurogenic soluble factors (Villeda et al., 2011, 2014). Other studies have identified pro-neurogenic plasma factors, but it is not clear whether these factors traverse the blood brain barrier or are secreted by hippocampal neurons to exert their pro-neurogenic effects (Katsimpardi et al., 2014; Moon et al., 2016, 2019). Several immune system chemokines have been identified that negatively regulate NSPC proliferation in the adult DG (Lee et al., 2013; Smith et al., 2015). With aging, immune T cells are found to localize in the SGZ and may potentially impede proliferation akin to that seen in the SVZ (Dulken et al., 2019). NSCs also express steroid hormone receptors that enable responsiveness to circulating glucocorticoids that promote quiescence and constrain dendritic complexity and dendritic spine density (Fitzsimons et al., 2013; Schouten et al., 2019). Whether a reverse dialog between NSCs and peripheral tissues and blood exists remains largely unexplored. It is plausible that RGLs secrete factors that are taken up by blood to influence peripheral tissue homeostasis. Interestingly, patches of SGZ are thought to be hypoxic (Chatzi et al., 2016). However, it is not known whether the blood vessels that contact RGL processes are highly oxygenated. Further studies will inform how systemic factors and low oxygen act in concert to regulate activation-quiescence decisions of NSCs.

Competition in the Niche

The signaling mechanisms described support a framework for thinking about how competition contributes to homeostasis in the adult hippocampal neurogenic lineage. Limitations in access to niche actors, such as endothelial cells, astrocytes, and microglia, may result in competition within NSCs by influencing activation-quiescence decisions (Figure 2A). NSCs may use on-demand translation mechanisms at their endfeet-like processes to signal in autocrine or paracrine mode and advance self-survival versus that of neighboring NSCs (Bonaguidi et al., 2012; Garcia et al., 2004; Gonçalves et al., 2016b; Pilz et al., 2018; Seri et al., 2001; Figure 2B). Unlike granule cells in the olfactory bulb (Platel et al., 2019), adult-born DGCs compete with pre-existing mature DGCs for perforant path inputs (McAvoy et al., 2016; Miller and Sahay, 2019; Tashiro et al., 2006; Toni et al., 2007; Krzisch et al., 2017). Partial genetic elimination of dendritic spines in mature DGCs or increasing dendritic spines in immature abDGCs enhanced neuronal integration of immature abDGCs. Neural activity may directly influence this competition or indirectly via regulation of niche actors, such as astrocytes and microglia. Astrocytes and microglia may promote formation of dendritic spines by inducing filopodia (Figure 1).

Cross Talk: Who Is Listening to Whom?

The rich repertoire of signaling mechanisms within the niche described in previous sections begins to edify how participation of different niche actors is coordinated or orchestrated to maintain NSC homeostasis and regulate adult hippocampal neurogenesis. Given evolution's parsimony, it is most likely that signaling mechanisms coordinate activity of multiple niche actors much like a conductor in an orchestra. Within this framework, DGCs or local inhibitory neurons may secrete ligands in response to neural activity that in turn act simultaneously on astrocytes, microglia, and endothelial cells to recruit their functions (Figure 3A). As discussed in previous sections, evidence from different studies suggests that a single secreted factor (such

as VEGF, Notch, Wnts, and BMPs) acts on cognate receptors in distinct niche cell types to mobilize their activities. An important next step is to concurrently evaluate within the same study how secreted factors coordinate mobilization of different niche cell types to regulate neurogenesis. An alternative mode of cross talk involves niche actors subscribing to privileged lines of communication such that NSCs or abDGCs receive signals solely from one cell type (Figure 3B). A third mode invokes communication across a cascade of niche actors such that signals are sequentially transmitted to ultimately reach NSCs or abDGCs (Figure 3C). For example, a DGC-PV-endothelial cell axis has been implicated in mediating experience-dependent regulation of neurogenesis. Specifically, activity levels of DGCs may regulate blood flow through secretion of neuronal nitric oxide synthase (NOS) from local PV interneurons in the DG. neuronal nitric oxide synthase (nNOS) elicits release of insulin growth factor (IGF) from blood vessels to promote neurogenesis (Shen et al., 2019). As we glean more insights from studies on different signaling mechanisms within the niche, the prevalence of each of these modes of cross talk will become clearer.

Signal Integration

The diversity of niche actors suggests that NSCs filter and integrate a wide range of signals to make activation and division decisions. However, signal integration in adult NSCs is poorly understood. The identification of master transcription factors (TFs) and epigenetic factors involved in NSC underlying activation-quiescence and lineage choice will permit inference of how niche signaling mechanisms are linked to regulation of gene expression (Andersen et al., 2014; Beckervordersandforth et al., 2015; Hsieh, 2012; Hsieh and Zhao, 2016; Urbán and Guillemot, 2014; Urbán et al., 2016; Sueda, 2019; Sueda and Kageyama, 2019). A small number of TFs have been identified that couple maintenance of NSC quiescence with repression of asymmetric stem cell renewal (Gao et al., 2011; Jones et al., 2015; Mukherjee et al., 2016; Zhang et al., 2019). Specifically, conditional loss of TFs, such as RE1-silencing transcription factor (REST), results in activation of NSCs and increased asymmetric stem cell divisions, thereby producing more neurons (Gao et al., 2011; Mukherjee et al., 2016). It is likely that other as yet unidentified TFs couple NSC quiescence with repression of asymmetric and symmetric stem cell renewal (Figure 4A). Expression of master TFs may require convergence of a range of inputs (BMP signaling, Wnt signaling, glucocorticoids, and calcium signaling effectors) onto *cis*-regulatory elements as suggested for regulation of key meristem regulatory genes in plant stem cells (Janocha and Lohmann, 2018; Figure 4B, top). Different signaling pathways may act co-operatively or antagonistically at the level of regulation of expression of master TFs. Alternatively, signaling pathways recruit distinct co-activators that bias master TF chromatin occupancy at different target gene promoters (Figure 4B, middle).

Signal integration may also occur sequentially across a multi-layered network where each successive layer integrates and transduces fewer signals to converge onto one or few regulatory factors. Ligand-receptor signaling (e.g., BMPs) duration and strength mediated by one niche actor may be modulated by antagonists (e.g., noggin) governing ligand availability produced by another niche cell type (Warmflash et al., 2012). Niche architecture may also dictate topography of ligand distribution in the milieu of NSCs such that some ligands may produce graded responses in NSCs (Figure 4C). Superficial layers may be populated by multi-signal integrators, such as the mammalian target of rapamycin (mTOR) (Amiri et al., 2012; Bonaguidi et al., 2011; Zhou et al., 2018; Yu and Cui, 2016), that recruit effectors in deeper layers to drive gene expression regulating stem cell state. Co-activators of gene expression, such as SMADs, may integrate multiple signaling pathways, such as BMP, WNT, and glycogen synthase kinase-3 (GSK3), to transcriptionally regulate gene expression in stem cells (Luo, 2017). Modulation of intracellular calcium dynamics in superficial layers may afford integration of different mitogenic signaling pathways, including Notch, to influence stem cell proliferation as shown in the intestine (Deng et al., 2015). Studies in the *Drosophila* wing imaginal disc elegantly convey how various morphogens affect spatiotemporal patterning of intracellular calcium and how variations in calcium signaling result in a range of distinct biological readouts (Brodskiy et al., 2019). Although adult DG NSCs also exhibit elevation in calcium transients in response to pro-proliferative signals (Itou et al., 2011), much less is known about how different signaling pathways affect calcium levels in NSCs (Figure 4B, bottom). Future studies should determine how a multi-layered architecture, such as that described here, supports signal integration in adult NSCs.

The induction of expression of master TFs is reflective of signal integration. Dynamic regulation of levels of master TFs may permit efficient coupling of re-entry into quiescence with symmetric and asymmetric stem cell renewal (Figure 4A). Prior signaling events may alter epigenetic landscape of regulatory elements of master TFs and, consequently, bias NSCs responses in the future. Finally, functional heterogeneity of NSCs may permit differential mobilization or recruitment to physiological signals (Bonaguidi et al., 2016; Gebara et al., 2016; Pilz et al., 2018; Figure 4D).

Outlook

Studies in rodents, non-human primates, and humans suggest that adult hippocampal neurogenesis is conserved across mammals (Boldrini et al., 2018; Eriksson et al., 1998; Gould et al., 1999; Knoth et al., 2010; Moreno-Jiménez et al., 2019; Spalding et al., 2013), and this unique form of circuit plasticity may be altered in different disease states (Boldrini et al., 2012; Moreno-Jiménez et al., 2019; Tobin et al., 2019; Yun et al., 2016). However, a recent study (Sorrells et al., 2018) has warranted further investigation into quantification of adult-born DGCs generated in the human hippocampus across the lifespan. As new efforts continue to address this challenge, insights gleaned from systematic analysis and comparison of the DG and SVZ niches in adulthood and during development in multiple species (Bjornsson et al., 2015; Götz et al., 2016; Obernier and Alvarez-Buylla, 2019; Paul et al., 2017; Kalamakis, 2019) may guide strategies to boost neurogenesis, reactivate dormant NSCs, or expand the NSC pool to optimize DG functions in memory and regulation of emotion (Anacker and Hen, 2017; McAvoy and Sahay, 2017; Miller and Sahay, 2019; Snyder, 2019; Toda et al., 2019; Tuncdemir et al., 2019). Targeting cell-autonomous

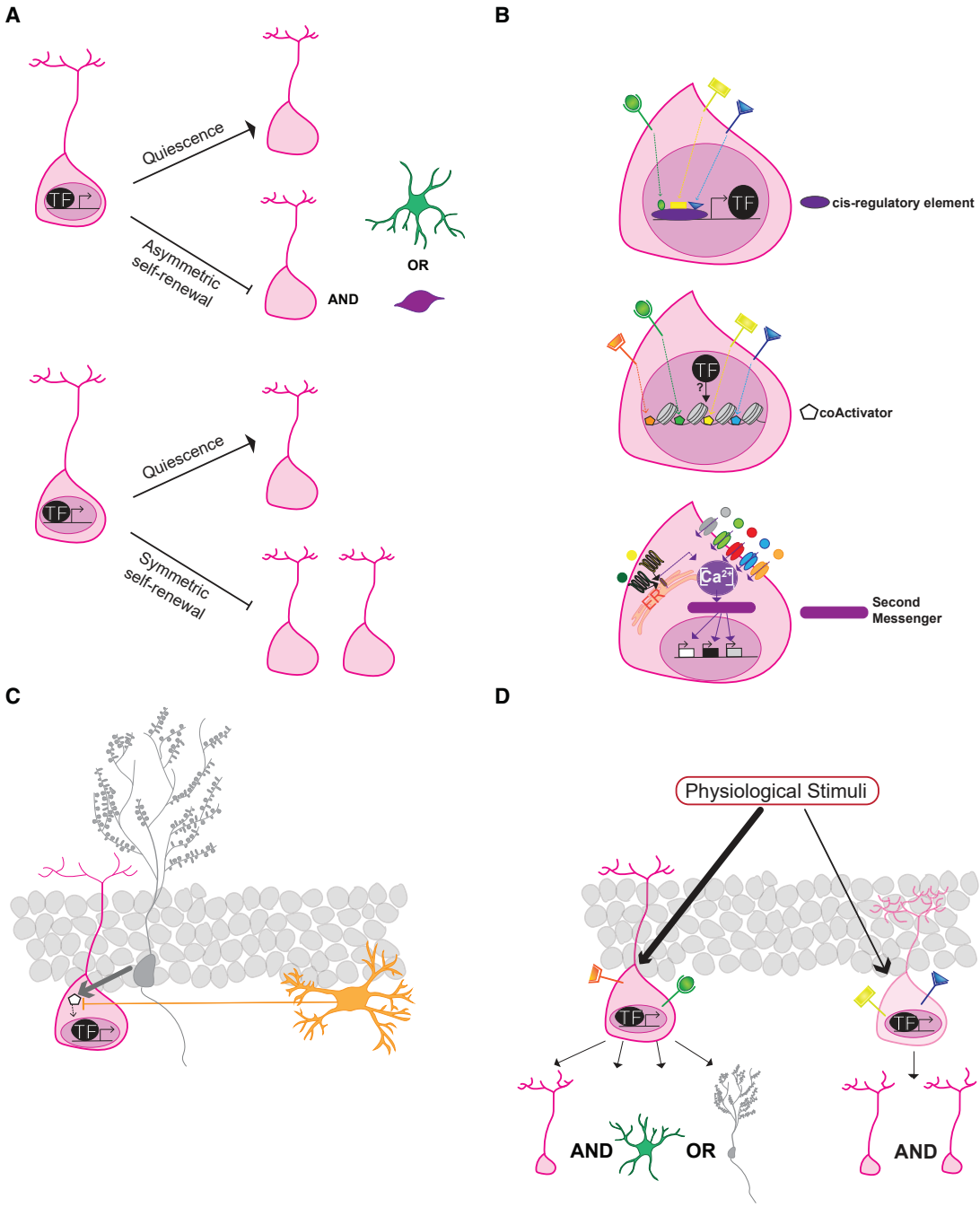

Figure 4. Signal Integration in NSCs

NSCs filter and integrate a wide range of signals to make activation and division decisions.

(A) Master TFs may couple maintenance of NSC quiescence with repression of asymmetric stem cell renewal or symmetric stem cell renewal.

(B) Distinct physiological signals may converge onto the same *cis*-regulatory element (purple) to regulate expression of master transcription factors (black) and influence the expression of target genes involved in NSC quiescence-activation, fate choice, and self-renewal (top). Distinct signals may recruit different co-activators (orange, green, yellow, and blue) that bias master TF occupancy (black circle) at target gene promoters, resulting in differential expression of genes (middle). Levels of intracellular calcium may mediate different biological responses in NSCs. Ca^{2+} influx into the cytoplasm from the extracellular environment (gray, green, red, blue, and orange receptors) and from the endoplasmic reticulum (G-protein-coupled receptors [dark green and yellow] and endoplasmic reticulum (ER) [light orange]) contributes to intracellular levels of calcium that, through the activation of second messengers, can mediate distinct cellular behaviors (bottom).

(C) The spatial organization of the niche can influence signal integration in NSCs. For example, a signal released by a DGC (gray) proximal to the NSC (pink) outcompetes an antagonistic signal released by distally located microglia (orange).

(D) Phenotypic and functional diversity of NSCs in the niche may support distinct fate choices, i.e., bias toward asymmetric neurogenic or astrogenic stem cell renewal or symmetric stem cell renewal.

See text for details.

mechanisms within NSCs or abDGCs are unlikely to prove effective on their own in promoting integration of abDGCs into an unhealthy niche. Instead, multipronged efforts that repair disease-associated alterations in the niche are necessary to promote neurogenesis (Choi et al., 2018). For example, targeting reactive astrocytes and inflammatory microglia and maintaining healthy vasculature in Alzheimer's disease and aging is critical to support integration and maturation of abDGCs. Because transcriptional and epigenetic-dependent maturation of abDGCs is intimately dependent on signals from the milieu, it is plausible that targeting non-cell-autonomous mechanisms (niche actors and input connectivity) may partially compensate the impact of disease mutations on physiology and function of abDGCs. Parabiosis studies support this idea of restoring vitality to adult hippocampal neurogenesis in aged rodents (Fan et al., 2017). Additionally, the use of tissue scaffolds that mimic stiffness of neonatal environments to revert mechanical and chemical signaling may restore NSPC plasticity, as shown recently for adult oligodendrocyte progenitor cells (OPCs) (Segel et al., 2019). Ultimately, a deeper understanding of communication, cross talk, and signal integration in the niche will inspire novel approaches to stimulate neurogenesis to restore cognitive functions in diseases characterized by impaired hippocampal functions.

ACKNOWLEDGMENTS

We thank members of Sahay lab for discussions. C.V. is supported by a NARSAD Young Investigator Award. A.S. acknowledges support from the NIH-R01MH104175, NIH-R01AG048908, NIH-1R01MH111729, James and Audrey Foster MGH Research Scholar Award, the Ellison Medical Foundation New Scholar in Aging, the Whitehall Foundation, an Inscopix Decode award, a NARSAD Independent Investigator Award, Ellison Family Philanthropic support, the Blue Guitar Fund, a Harvard Neurodiscovery Center–MADRC Center Pilot Grant award, Alzheimer's Association research grant, a Harvard Stem Cell Institute development grant, and HSCI seed grant.

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