Control of Adult Neurogenesis by Short-Range Morphogenic-Signaling Molecules

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Adult neurogenesis is dynamically regulated by a tangled web of local signals emanating from the neural stem cell (NSC) microenvironment. Both soluble and membrane-bound niche factors have been identified as determinants of adult neurogenesis, including morphogens. Here, we review our current understanding of the role and mechanisms of short-range morphogen ligands from the Wnt, Notch, Sonic hedgehog, and bone morphogenetic protein (BMP) families in the regulation of adult neurogenesis. These morphogens are ideally suited to fine-tune stem-cell behavior, progenitor expansion, and differentiation, thereby influencing all stages of the neurogenesis process. We discuss cross talk between their signaling pathways and highlight findings of embryonic development that provide a relevant context for understanding neurogenesis in the adult brain. We also review emerging examples showing that the web of morphogens is in fact tightly linked to the regulation of neurogenesis by diverse physiologic processes.

Neurogenesis in the adult mammalian brain is dynamically regulated by a number of genetic and epigenetic intrinsic factors as well as by extrinsic cues (Ninkovic and Götz 2007; Ma et al. 2010; Faigle and Song 2013). Among the latter, local signals emanating from the neural stem cell (NSC) microenvironment are thought to play a prominent modulatory role. This microenvironment, often referred to as the NSC or neurogenic “niche,” is viewed as a complex entity composed of stem and precursor cells, the surrounding mature cell types, cell-to-cell interactions, the extracellular matrix, the basal lamina, and secreted factors (Doetsch 2003). The principal mature cellular constituents of the adult NSC niches are parenchymal

astroglial cells, the vasculature, microglia, and ependymal cells, all of which secrete a variety of molecules that mainly control stem-cell behavior, but also influence other stages of the adult neurogenesis process (Basak and Taylor 2009; Mu et al. 2010; Ihrie and Alvarez-Buylla 2011).

As opposed to the majority of adult brain regions, the subventricular zone (SVZ) and the dentate gyrus (DG) subgranular zone (SGZ) niches are instructive milieus that allow NSC proliferation while promoting the specification and differentiation of new neurons. The relevance of the SVZ and SGZ microenvironments in adult neurogenesis was first evidenced by heterotopic transplantation experiments showing that precursor cells from a neurogenic niche,

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such as the SVZ, differentiate into glial cells and not into neurons when grafted to nonneurogenic areas of the brain (Seidenfaden et al. 2006). In contrast, SVZ or spinal cord precursor cells generated neurons when transplanted to a neurogenic region, such as the hippocampal DG (Suhonen et al. 1996; Shihabuddin et al. 2000). Although other *in vivo* studies have shown that SVZ-derived precursors maintain a certain degree of region-specific potential that is not respecified on transplantation to ectopic sites (Merkle et al. 2007), most studies suggest that local cues in the neurogenic brain niches are key for neuronal differentiation to occur. On the other hand, combined transplantation of both NSCs and niche cells to nonneurogenic areas, or expression of niche factors at the site where NSCs are grafted, promotes neuronal differentiation (Lim et al. 2000, Jiao and Chen 2008). Thus, it has progressively become apparent that extrinsic signals produced by niche cells enable the adult neurogenic program to proceed.

More recently, transgenic and virus-based approaches allowing cell type- and temporal-specific manipulation of gene expression in the niches have provided great insights into the identity of the extrinsic signals regulating neurogenesis *in vivo* and into the molecular mechanisms elicited by those signals. Several soluble and membrane-bound factors have been identified as determinants of SVZ and SGZ neurogenesis, including morphogens, growth factors, neurotrophins, and neurotransmitters. Among these determinants, morphogens are ideally suited to fine-tune the sophisticated processes of stem-cell activation, progenitor expansion, and differentiation required for proper adult neurogenesis. Morphogens are defined as signaling molecules that pattern developing tissues in a concentration-dependent manner (Ashe and Briscoe 2006; Rogers and Schier 2011). They mostly operate in long-range gradients created by synthesis and diffusion of the morphogen proteins from a source and clearance during their flux by diverse mechanisms, such as immobilization, degradation, or endocytosis. Additional molecules that act as anti- or pro-morphogens further refine their activity. It is

important to note that, although morphogens are graded signals, the response they elicit is not graded. Small differences in the concentration of a morphogen can trigger sharp thresholds in the expression of target genes. In addition, morphogens can also act at short range. Lipidation and low-affinity interactions with extracellular matrix components confine the movement of some morphogen proteins and promote effective morphogen–receptor interactions at the cell surface. Cells exposed locally to different morphogen doses respond by adopting different fates and, in this way, a morphogen can assign positional information to cells within a structure or territory, such as a stem-cell niche, and provoke different niche responses or outputs depending on the context (Ashe and Briscoe 2006; Rogers and Schier 2011).

Here, we review our current understanding of the role and mechanisms of short-range niche morphogens, including ligands from the Wnt, Notch, Sonic hedgehog, and bone morphogenetic protein (BMP) families, in the regulation of adult neurogenesis. We discuss cross talk between their signaling pathways and intersection with other signaling pathways operating in the niches. We also highlight findings and emerging principles of embryonic development that provide a relevant context for understanding the growing field of adult neurogenesis.

BONE MORPHOGENETIC PROTEINS

BMPs are the largest subgroup of ligands of the transforming growth factor β (TGF- β) superfamily of cytokines and are versatile molecules that exert a plethora of effects in the nervous system. To date, more than 20 BMP members have been identified in vertebrates (Kingsley 1994; Bragdon et al. 2011). They signal through a tetrameric complex formed by two classes of serine–threonine kinase receptors: The BMP type II receptor (BMPRII) and the BMP type I receptors, namely, BMPRIA (ALK3), BMPRIb (ALK6), and the Activin receptor type I (ACVR1 or ALK2) (ten Dijke et al. 1996; Macías-Silva et al. 1998). Signaling downstream from BMPs is divided into Smad-mediated (canonical) and Smad-independent (noncanonical)

pathways. In the canonical pathway, activated type I receptors phosphorylate the DNA-binding proteins SMAD1/5/8. Phosphorylated SMADs then form a stable heterodimer with SMAD4 and translocate to the nucleus where, together with other cofactors, activate the transcription of Bmp-target genes (von Bubnoff and Cho 2001; Zeng et al. 2010). Although BMP ligands are secreted molecules, their actions are frequently local, because they avidly bind to extracellular matrix components that limit their spread while presenting the ligands in a biological active form (Hall and Miller 2004). Thus, BMPs can act as short-range morphogens in adult NSC niches.

The effect of BMP signaling changes throughout nervous system development and the precise cellular response elicited by BMPs depends both on the nature of the target cell and on the context, in which signaling occurs. The balance between BMPs and their natural antagonists Noggin, Chordin, and Follistatin plays a key role during the early organization and dorsoventral patterning of the embryonic neural tube. Later on, during embryogenesis, BMPs continue to regulate a wide variety of cellular processes, including proliferation, apoptosis, neurogenesis, and gliogenesis (Panchision and McKay 2002; Hall and Miller 2004; Chen and Panchision 2007). Elegant studies have shown for instance that fetal neural stem/precursor cells express BMPRIA and respond to BMPs by proliferating. At the same time, signaling through BMPRIA induces the expression of a different type I receptor, BMPRIB, so when BMPRIB protein levels exceed those of BMPRIA, precursor cells interpret BMPs as a termination signal that leads to cell-cycle exit and differentiation (Panchision and McKay 2002). Thus, the sequential induction of type I receptors has been proposed to underlie a switch in the precursor's response to a single BMP signal. As we shall see, although there are many differences in the regulation of embryonic and adult neurogenesis by BMPs, some principles may be conserved.

In the adult neurogenic niches, BMPs profoundly affect adult NSC proliferation and differentiation. In the SVZ-rostral migratory

stream (RMS)–olfactory bulb (OB) continuum, there is a marked segregation in the expression of BMP ligands and their receptors. At the level of the SVZ, NSCs (type B cells) and their direct descendants (transient amplifying progenitors, transient amplifying progenitors [TAPs], or type C cells) express BMP2/4, BMPRIA, and BMPRII. Instead, neuroblasts (type A cells) express BMPRIB and do not express BMP4 (Lim et al. 2000). The restriction of BMPRIB expression to late progenitors in the SVZ neurogenic niche is reminiscent of the receptor expression pattern described during embryonic development (Panchision and McKay 2002), pointing to an inductive role of BMPs in early precursors (NSCs/TAPs) and a terminating role in late precursors (neuroblasts). In vivo, the intracerebroventricular injection of BMP4 inhibits proliferation in the SVZ (Mercier and Douet 2014). The predominant cell types responding to BMPs are type B and type C cells, which show higher levels of phosphorylated Smad proteins (Colak et al. 2008; Gajera et al. 2010). This signaling pattern is consistent with the graded expression of the BMP target gene *Id1*, an antagonist of differentiation that is required for SVZ NSC self-renewal and for anchorage to the extracellular niche environment (Nam and Benezra 2009; Niola et al. 2012). Type B cells express very high levels of ID1 and give rise to more differentiated cells that progressively express lower levels of the protein. Thus, a threshold in ID1 dosage, possibly downstream from BMP signaling, may define the “stemness” of type B cells (Fig. 1A).

In vitro studies using SVZ-derived cells have shown that BMP4 can act as a potent gliogenic signal that inhibits the acquisition of the neuronal lineage while promoting the astroglial fate, thereby preventing type B/C cells from generating type A cells in a dose-dependent manner (Lim et al. 2000). This is in line with the role of BMPs during the embryonic and perinatal cortical gliogenesis period (Gross et al. 1996; Mehler et al. 2000). Intriguingly, other findings that apparently contradict this view have been reported in vivo. Blocking BMP signaling, specifically in type B cells, through conditional inactivation of *Smad4*, up-regulates the tran-

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Figure 1. Bone morphogenetic protein (BMP). (A) A local gradient of BMPs may be created in the subventricular zone (SVZ) niche caused by the release of antagonists by the ependyma lining the ventricle. The BMP target gene *Id1*, an inhibitor of differentiation, is highly expressed in type B neural stem cells (NSCs). (B) BMPs act on NSCs at the time fate is being established. BMPs promote an astroglial fate and/or block oligodendrocyte specification. (C) Signaling through BMPRIa maintains NSC quiescence (Q) in the subgranular zone (SGZ) niche. The antagonist noggin increases proliferation. A, astrocyte; NSC*, activated NSC; Nb, neuroblast; O, oligodendrocyte; TAP, transient amplifying progenitor.

scription factor OLIG2 and directs progenitors toward the oligodendrocyte lineage while severely impairing neurogenesis (Colak et al. 2008). This observation is concordant with the inhibitory role of BMPs on oligodendroglial differentiation observed throughout development (Mehler et al. 2000). Together, the available data indicate that BMPs act very early in the SVZ cellular hierarchy, most likely at the level of the stem cells at the time fate is being established. It is possible that subtle differences in BMP signaling may be critical, and depending on the degree of pathway activity achieved, the stem-cell progeny may either acquire an astroglial fate or undergo blockade of oligodendrocyte specification, favoring neurogenesis (Fig. 1B). Once entering the RMS–OB, the newly generated neuroblasts are again exposed to BMP4 and BMP7, because both proteins are highly ex-

pressed in the astroglial tubular meshwork surrounding migrating type A cells. This suggests a role for BMPs in survival or terminal differentiation of the newborn neurons (Coskun et al. 2001; Peretto et al. 2004), as it has been shown in cell culture (Lim et al. 2000; Liu et al. 2004).

It is interesting to highlight that at least two types of BMP inhibitors are naturally produced by the ependyma that faces the SVZ: Noggin and the low-density lipoprotein-related protein LRP2, a clearance receptor for BMP4 (Lim et al. 2000; Gajera et al. 2010). The astrocyte-derived protein Neurogenesis-1 may also participate as a BMP4 antagonist in the adult SVZ (Ueki et al. 2003). In addition, extracellular matrix structures, such as fractone-associated heparin sulfates capture BMP4 in the SVZ (Mercier and Douet 2014). These molecules locally counteract or adjust endogenous BMP signaling. Thus,

a local gradient of BMPs may be created in the SVZ niche thanks mainly to the presence of the ependymal wall and the extracellular matrix (Fig. 1A). It is plausible that active NSCs contacting the ventricular lumen are exposed to higher doses of Noggin and LRP2, and therefore, are not challenged with effective gliogenic BMP concentrations, allowing the formation of new neurons. In accordance with this model, overexpression of BMP7 in the SVZ niche using adenoviruses blocks SVZ regeneration and neurogenesis after antimitotic treatment, whereas forced expression of the antagonist Noggin in the striatum promotes neuronal differentiation of SVZ grafted cells, which form ectopic type A chain-like structures similar to those found in the SVZ–RMS (Lim et al. 2000).

In addition to the function of BMPs in fate determination of SVZ cells, recent studies established a major role for this family of morphogens in stem-cell maintenance in the hippocampus. Already, during embryogenesis, BMPs strongly influence DG development by regulating the formation of the stem-cell niche. Selective loss of BMP7, or conditional deletion of the *Acvr1* type I receptor gene or *Smad4* in embryonic DG NSCs results in marked postnatal SGZ defects and reduced neurogenesis (Choe et al. 2013). Instead, loss of function of *Bmpr1a* and *Bmpr1b* only leads to modest defects (Caronia et al. 2010). In the postnatal period and during adulthood, BMPs are essential in regulating the equilibrium between stem-cell proliferation and quiescence in the SGZ (Bonaguidi et al. 2008; Mira et al. 2010; Bond et al. 2014), preventing the premature depletion of hippocampal NSC activity (Fig. 1C).

As opposed to the embryonic DG, BMPRIA seems to be the most relevant transducer of BMP signaling in adult DG NSCs, whereas BMPRIIB appears to be associated with newly generated and mature granule neurons. Genetic deletion of *Bmpr1a* and *Smad4* in radial DG NSCs and infusion of the BMP antagonist Noggin have showed that canonical signaling downstream from the BMP type IA receptor maintains stem-cell quiescence (Mira et al. 2010). The physiological source of BMPs in the adult DG has not been fully tackled, although a recent

study suggests that a variety of niche cell types may be secreting BMP ligands (Yousef et al. 2014). For instance, although BMP4 colocalizes with the endothelium, BMP6 primarily colocalizes with microglial cells. In addition, adult hippocampal stem/progenitors in culture secrete BMPs, which may act to limit proliferation in an autocrine manner. Thus, it has been proposed that BMP antagonists expressed in the DG inhibit endogenously produced BMPs to allow proliferation of adult hippocampal NSCs in vivo (Bonaguidi et al. 2008).

In contrast to the SVZ, the antagonist LRP2 is not expressed in the hippocampus, because no ependymal-equivalent cell type is found in this region (Gajera et al. 2010). In neonates, in situ hybridization data show sparse and scattered expression of *Noggin* mRNA in the hippocampus, but by adulthood, a strong signal is clearly concentrated in the DG granule cell layer (Fan et al. 2003). Compared with the SVZ, neurons are much closer to NSCs in the DG, so high expression of Noggin by granule neurons may create a microenvironment that is sufficient to locally antagonize BMPs and thereby enable neurogenesis. Of note, the stability of *Noggin* mRNA in the DG is controlled by the RNA-binding protein FXR2, which is expressed in radial stem cells, immature neurons, and in most mature granule neurons. Loss-of-function experiments have shown that FXR2 deficiency results in increased expression of *Noggin* and reduced BMP signaling in the adult hippocampus, in turn leading to increased proliferation of radial NSCs and enhanced neurogenesis (Guo et al. 2011). Neurogenesis-1 is also expressed by hippocampal astrocytes and dentate granule cells adjacent to NSCs of the adult DG, counteracting astroglial specification by BMP4 (Ueki et al. 2003).

BMP signaling apparently plays a crucial role in regulating the physiological control of the adult hippocampal niche. For instance, it is a fundamental mechanism linking voluntary exercise with changes in neurogenesis. Running in mice increases *Noggin* expression and decreases *Bmp4* expression in hippocampal tissue, and the resulting blockade of the BMP pathway is necessary for the effects of exercise on neuro-

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genesis and cognition (Gobeske et al. 2009). It is tempting to speculate that other external stimuli that lead to enhanced neurogenesis, such as learning, enriched environment, or treatment with antidepressant drugs (Ming and Song 2005; Zhao et al. 2008), may converge on an increase in inhibitory factors that limit BMP signaling. On the contrary, the age-associated rise in BMP signaling may partly underlie the neurogenic decline in old animals, and what is more important, the inhibition of this pathway may allow rescuing the age-related drop in neurogenesis (Yousef et al. 2014).

In conclusion, BMPs are widely expressed in the adult brain and this may partly explain why neurogenesis is restricted to regions expressing BMP antagonists, such as Noggin, LRP2, and Neurogenesis-1, that can adjust the level of BMP signaling. Nevertheless, there are significant differences in the roles exerted by BMPs/BMP antagonists in the two main neurogenic areas. The available data so far indicate that Noggin promotes proliferation of DG NSCs but not SVZ NSCs, although it promotes neurogenesis and decreases gliogenesis in both SVZ and DG NSCs. A certain level of BMP signaling may nevertheless be required to limit the acquisition of oligodendrocyte fates, at least in the SVZ. Moreover, some BMP signaling modulators appear to be specific for the SVZ (LRP2), whereas others act in the DG (FXR2), pointing to niche-related differences in the generation and interpretation of BMP gradients. More precise cellular localization of BMPs, their antagonists, and their receptors will provide a rich framework in which to interpret the role of this morphogen family in the regulation of adult neurogenesis.

WNT

Wnt ligands are a family of secreted glycoproteins implicated in a great variety of central nervous system developmental and adult processes (Ciani and Salinas 2005; Inestrosa and Arenas 2010). The vast number of Wnt-related genes illustrates the great complexity of this pathway (Gordon and Nusse 2006). In the mouse genome, there are 19 Wnt genes, 10 different Friz-

zled receptors, and several coreceptors, such as LRP5 and LRP6. Other transmembrane proteins that act as receptors for Wnt proteins have been recently identified, along with a number of secreted Wnt inhibitors that can sequester Wnts in the extracellular space, including secreted frizzled-related proteins (sFRPs). Moreover, signaling downstream from Wnt broadly branches into β -catenin-dependent (canonical) and β -catenin-independent (noncanonical) pathways. In the β -catenin-dependent pathway, Wnt triggers stabilization of β -catenin by the dissociation of a complex that normally phosphorylates and targets β -catenin for degradation by the proteasome. On stabilization, β -catenin enters the nucleus where it binds to T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors, activating Wnt-target gene expression (Angers and Moon 2009).

Lineage tracing experiments show the existence of Wnt/ β -catenin-responsive stem cells in both the SVZ and SGZ niches (Bowman et al. 2013), and several studies have implicated Wnt signaling in the regulation of adult neurogenesis (Varela-Nallar and Inestrosa 2013). In cell cultures, overexpression of *Wnt3a* and *Wnt5a* promotes proliferation and neuronal differentiation of SVZ neural progenitors (Yu et al. 2006; Zhu et al. 2014). In vivo, retrovirus-mediated expression of a stabilized form of β -catenin or inhibition of its degradation complex promotes proliferation of neural progenitor cells, increasing the number of new neurons in the OB, whereas expression of the Wnt antagonist Dickkopf-1 (DKK1) has the opposite effect (Adachi et al. 2007). Moreover, the nuclear orphan receptor TLX, an intrinsic regulator of adult NSC proliferation (Shi et al. 2004), induces the transcription of the *Wnt7a* gene and, through an autocrine signaling loop, the WNT7A ligand promotes proliferation of adult NSCs via the canonical β -catenin-dependent pathway (Qu et al. 2010). In addition, a paracrine contribution of SVZ niche cells to Wnt levels has been also described. SVZ niche astroglia secretes WNT7A, which enhances symmetric self-renewing divisions of adult NSCs, presumably through noncanonical signaling (Fig. 2) (More-

no-Estellés et al. 2012). In aged mice, up-regulation of DKK3 may partly underlie the attenuation of SVZ neurogenesis through the blockade of Wnt signaling (Zhu et al. 2014).

Canonical Wnt signaling also plays a central role in the adult and developing mammalian DG (Li and Pleasure 2005). Already, during embryogenesis, WNT3A/ β -catenin is required for the proper formation of the hippocampus. For instance, *Wnt3a* deletion leads to the absence of the DG (Lee et al. 2000) and the dominant-negative form of LEF1 or the conditional inactivation of β -catenin yield a similar phenotype (Galceran et al. 2000; Machon et al. 2003). In this same line, LRP6 Wnt coreceptor mutants display decreased production of dentate granule neurons and abnormalities in the radial glial scaffolding of the developing DG (Zhou et al. 2004). Signaling downstream from Wnt is also key in controlling NSCs and neurogenesis during adulthood. In young animals, hippocampal astrocyte-derived WNT3 promotes neuroblast proliferation and neuronal differentiation via the β -catenin pathway (Lie et al. 2005), although later on, decreased Wnt levels and the

increased expression of Wnt antagonists, such as DKK1, partly underlies the age-related decline in neurogenesis (Okamoto et al. 2011; Miranda et al. 2012; Seib et al. 2013). In addition to paracrine contribution of astrocyte-derived Wnts, adult hippocampal progenitors are also regulated by autocrine Wnt signaling. At least in cell cultures, progenitors secrete functional ligands that stimulate cell-autonomous baseline Wnt signaling required for the maintenance of proliferative activity and multipotency of the cells (Wexler et al. 2009). Furthermore, the TLX/WNT7A/ β -catenin autocrine-signaling loop that enhances proliferation of adult NSCs in the SVZ is also operative in the DG (Qu et al. 2010). Injection strategies in vivo further showed that blockade of the β -catenin degradation complex, via the inhibitor disrupted in Schizophrenia 1 (DISC1), represses cell-cycle exit, and neuronal differentiation (Mao et al. 2009).

NeuroD1, a proneurogenic basic helix–loop–helix (bHLH) transcription factor, and Prox1, the prospero-related homeobox 1 gene, act as downstream mediators from Wnt-induced hippocampal neurogenesis, participating in the initial stages of granule cell differentiation (Kuwabara et al. 2009; Karalay et al. 2011). NeuroD1 is required for both adult and embryonic granule cell genesis (Liu et al. 2000; Pleasure et al. 2000; Gao et al. 2009) and a molecular mechanism links *Neurod1* gene expression to canonical Wnt signaling. In NSCs, the *Neurod1* promoter is repressed by the transcription factor SOX2 and histone deacetylase 1 (HDAC1), yet, in the presence of Wnt, β -catenin forms an activator complex with TCF/LEF that results in *Neurod1* transcription and subsequent neuronal differentiation (Kuwabara et al. 2009). Furthermore, Wnt signaling is also important for the terminal differentiation and maturation of the newborn neurons, because loss of *Wnt7a* dramatically impairs dendritic arborization of dentate granule neurons in vivo (Qu et al. 2013). Using in vitro assays, on differentiating adult NSCs, a recent study identified a remarkable transition of Wnt-signaling responsiveness from the canonical branch (β -catenin-dependent pathway) to the noncanonical branch

Figure 2. Wnt. WNT7A promotes proliferation of adult neural stem cells (NSCs) via the canonical β -catenin-dependent pathway. TLX induces the transcription of *Wnt7a* gene and regulates NSCs through an autocrine-signaling loop. In addition, niche astroglia secretes WNT7A, which enhances symmetric self-renewing divisions of adult NSCs through noncanonical signaling. A, Niche astrocyte; NSC*, activated NSC; TAP, transient amplifying progenitor.

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(planar cell polarity or PCP pathway). Knock-down of PCP core proteins *in vivo* revealed severe maturational defects in newborn granule cells, demonstrating that Wnt/PCP is required for controlling late aspects of adult neurogenesis, such as dendrite initiation, radial migration, and dendritic patterning (Schafer et al. 2015).

In accordance with the central role of the canonical Wnt pathway in adult hippocampal neurogenesis, alterations in Wnt signaling influence some types of hippocampal-dependent learning and memory tasks. Mice injected with a lentivirus expressing a dominant-negative Wnt in the adult DG show reduced neurogenesis and impaired spatial and object recognition memory (Jessberger et al. 2009), whereas mice deficient in the Wnt antagonist DKK1 show enhanced generation of new neurons and increased spatial working memory and memory consolidation (Seib et al. 2013). Complementary studies also showed that the Wnt pathway links adult neurogenesis to changes in neuronal circuit activity. In this regard, the Wnt inhibitor sFRP3 is expressed by mature DG granule neurons, and its reduction is required for activity-induced proliferation of progenitor cells and for maturation of newborn neurons (Jang et al. 2013).

NOTCH

Notch was first described in the mid 1980s by Artavanis-Tsakonas and Young (Wharton et al. 1985; Kidd et al. 1986). The core components of Notch signaling include four Notch receptors, Notch1-4, which are single-pass transmembrane heterodimers, and five Notch ligands, Jag1, Jag2, Dll1, Dll3, and Dll4, and a DNA-binding transcription factor, Rbpjk. The various Notch receptors and ligands have overlapping tissue expression and cellular functions and may have many interchangeable molecular functions (Ables et al. 2011; Guruharsha et al. 2012). Notch ligands are presented by neighboring cells (*trans* interaction), Notch receptor-expressing cells (*cis* interaction) or extracellularly as soluble forms. In *trans* interaction situations, Notch receptors are subcellularly localized to the cell membranes adjacent to ligand-present-

ing cells. In response to ligand binding, followed by ectodomain shedding, the aspartyl protease γ -secretase (with a core catalytic subunit called presenilins) cleaves the Notch receptors. The cleaved Notch intracellular domain (NICD) is then released from the cell membrane and translocates to the nucleus to regulate target gene expression. In the absence of nuclear NICD activity, RBPJk is an active repressor engaging in signaling known as “default repression” (Barolo et al. 2002), via interaction with corepressors, such as SHARP (also known as MINT and SPEN), CIR1, BEND6, KyoT2, NcoR/SMRT, and histone deacetylases (HDAC) (Dai et al. 2013). The nuclear NICD binds RBPJk and recruits coactivators, such as MAML1 to regulate Notch-inducible gene expression (and relieve default repression). The canonical Notch target genes of the nervous system are basic helix-loop-helix-type (bHLH) nuclear factor Hes transcription factors, which repress the expression of proneural (also bHLH proteins including Neurogenins and Mash) transcription factors, and thus, maintain neuronal progenitor cells in an undifferentiated state.

The prominent neurogenic fate changes in the ectoderm of fly Notch mutants (Mohr 1919) became a guideline for many later studies of Notch function in mammals during development. Components of Notch signaling are expressed in the neuroepithelium during embryogenesis and also in the adult neurogenic niches. Expression analysis of Notch receptors and ligands indicates that at least Notch1, Notch2, Notch3, Dll1, and Dll3 are associated with cells in the embryonic ventricular zone (VZ) and SVZ; and expression of Notch1, Notch2, and Dll1 persists into adulthood in the neurogenic niches of the SVZ and the DG (Higuchi et al. 1995; Irvin et al. 2001; Hitoshi et al. 2002). Newly generated neurons recruit vascular and perivascular cells expressing Notch3, Dll4, or Jag1 and the circulatory system becomes one of the sources of Notch ligand-presenting cells in the adult neurogenic niche (Krebs et al. 2000; Shen et al. 2004; Hellstrom et al. 2007). Consistent with the expression of Notch receptors and ligands in the neurogenic niches, Notch signaling is active in NSCs as revealed by Notch-signaling

reporter mice (using transgenic mice either with the Hes5 promoter or tandem repeats of RBPJk-binding sites driving reporters) (Souilhol et al. 2006; Imayoshi et al. 2010; Lugert et al. 2010). Fluorescence reporter mice identified glial fibrillary acidic protein (GFAP) positive type-B cells of the SVZ and type 1 (radial glia-like) cells of the SGZ as highly activated by Notch signaling. Recent real-time imaging studies showed that interaction of Notch receptors and ligands maintains high levels of Notch signaling in NSCs in development (Kawaguchi et al. 2013) and a similar mechanism is likely operative in adults.

When NSCs are activated to asymmetrically divide, Dll1 protein is induced and asymmetrically segregated to one daughter cell during cell division. The Dll1-expressing daughter cells signal via Notch back to the NSCs to help maintain them in their undifferentiated state (Mizutani et al. 2007; Yoon et al. 2008). It is also believed that during the successive generation of deep layer neurons in the embryonic cortex, lateral inhibition by Notch signaling inhibits neighboring cells from becoming cells of the same type. Live multiphoton imaging showed that DLL1 particle-containing cellular processes of intermediate progenitor cells in E14.5 embryo cortex may be responsible for this feedback on

the stem cells (Fig. 3) (Nelson et al. 2013). Thus, radial glia cells cycling in the VZ during interkinetic nuclear migration transiently contact Notch ligands from intermediate progenitor cells through these cellular extensions, and this Notch signaling governs cell fate decisions in the stem cells. Interestingly, recent studies showed that embryonic neural progenitors express Hes1 and Dll1 in an oscillating fashion with a period of 2 to 3 h in mice during embryonic days 9.5 to 14.5 (Kageyama et al. 2008). This implies that the Notch ligand-presenting processes are dynamically regulated among the progenitors and that this oscillatory behavior is likely to generally control the onset of neurogenesis. Whether similar temporally specific and spatially precise mechanisms are operative under the control of Notch signaling in the adult niches still remains to be explored, but it seems likely that similar interactions will be found.

The activation of Notch signaling works largely through the genomic targets of RBPJk. Genome-wide profiling of RBPJk-binding targets has helped to understand the diverse functions of Notch activation. In vivo analysis of genomic binding sites for NICD/Rbpjk using mouse embryonic cortex revealed Sox2, Pax6, Tlx, Id4, Gli2, and Gli3, among others (Li et al. 2012). Consistent with the high Notch

Figure 3. Notch. The lateral inhibition of neuronal progenitors in the pseudostratified neuroepithelial cells becomes lateral inhibition of grouped neuronal progenitors between the subventricular zone (SVZ) and the ventricular zone (VZ).

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activation state seen in VZ radial glial cells, NICD/Rbpjk target genes help explain the specific role for Notch signaling in stem-cell maintenance. The consensus RBPJk-binding motifs and its variant sequences were determined in another more refined study using myogenic cells under active or inhibitory Notch-signaling conditions (Castel et al. 2013). This study clearly showed that there are two distinctive sets of RBPJk-binding genes, which are Notch dependent and Notch independent. NICD is only recruited to RBPJk and acts on the Notch-dependent genomic regions in activated Notch-signaling conditions. Notch-independent RBPJk-binding sites are not regulated by Notch activation. In the zebrafish neurogenic niche and the pancreatic stem-cell niche, quiescent and active NSCs are dependent on the levels of Notch activation (Chapouton et al. 2010; Ninov et al. 2012). Induction of Notch signaling drives activated NSCs to quiescence. In the mouse dentate SGZ, a Hes5-GFP reporter revealed subpopulations of adult NSCs that transit back and forth between quiescent and active states (Lugert et al. 2010). Notch-signaling reporters expressing fluorescent proteins will be the next vital tool for the analysis of Notch target genes in heterogeneous stem-cell pools to shed light on mechanisms maintaining quiescence in the adult neurogenic niches.

Inactivation of Rbpjk in the embryonic brain promoted actively dividing stem cells to differentiate into neurons. In the adult brain, Rbpjk inhibition induced quiescent NSCs to divide transiently, in addition to driving generation of postmitotic neurons from transit amplifying neural progenitors. Thus, in the adult neurogenic niche, transient initial proliferation was observed by inhibition of Rbpjk (Imayoshi et al. 2010). Despite the clear differences in the adult NSC niche, with different environmental influences, Notch signaling recapitulates its roles from embryonic neurogenesis in the adult with, so far, only minor modifications found. When adult quiescent NSCs are activated during regeneration, they become dependent on Notch1 (Basak et al. 2012). In the absence of Notch1, activated NSCs are depleted as in Rbpjk conditional knockouts. Inactivation

of Rbpjk in quiescent NSCs caused temporary cell proliferation through activation of these cells (Basak et al. 2012). Depletion of quiescent NSCs in the absence of Rbpjk could involve loss of expression of direct targets, such as Tlx (Nr2e1) (expressed exclusively in NSCs in the postnatal SVZ and SGZ and hindering exit of cell cycle by inhibiting p21^{cip1/waf}) or Sox2 (an essential SoxB1 transcription factor necessary for maintaining progenitor cells) (Niu et al. 2011). Tamoxifen-inducible human GFAP promoter-driven inhibition or activation of Notch1 showed mechanistic regulation of neurogenesis by Notch1 levels. Activation of Notch1 induced reentry of cell cycle and inactivation of Notch1 promoted cell-cycle exit (Breunig et al. 2007). Neurogenesis is also induced by Notch inhibition regulated by cell-type-specific transcription factors, such as Sox21, expressed in the SGZ stem cells. Sox21 mediates Hes5 inhibition and generation of neurogenic transit amplifying cells from the stem-cell pool (Matsuda et al. 2012).

Depending on which neurogenic niche is considered, mutation of Hes genes (the canonical Notch transcription targets) showed distinct neurogenic defects. Combined conditional mutants of Notch receptors (Notch1 and Notch3) or Hes transcription factors (Hes1, Hes3, and Hes5) was not able to recapitulate the neurogenic defects of Rbpjk conditional knockouts in the cortex (Hatakeyama et al. 2004; Mason et al. 2005; Imayoshi et al. 2008; Imayoshi et al. 2010) indicating redundancy of Notch receptors or RBPJk targets in the developing neocortex. However, neurogenic defects observed in the Dll1 or Mib1 conditional mutant embryos, did recapitulate the Rbpjk mutant phenotypes, suggesting that Dll1 is a critical Notch ligand during embryonic cortical neurogenesis (Kawaguchi et al. 2008; Yoon et al. 2008). In adult neurogenic niches, such as the SVZ and the SGZ, tamoxifen-inducible inactivation of Rbpjk using the Nestin promoter showed that activation of RG stem cells generated transient cell proliferation and led to long-term depletion of radial glial stem cells with repression of neurogenesis. Conditional deletion of Jagged1 had a similar effect (Lavado and Oliver 2014). Along with these

effects, Sox2 was shown to be a direct target of RBPJk, acting as a likely direct regulatory target of neurogenesis controlled by Notch-signaling interaction (Ehm et al. 2010). In contrast to direct manipulation of RBPJk, inactivation of Notch1 using Nestin-CreERT showed reduced neurogenesis without transient cell proliferation. However, activation of NSCs by exercise rescued the number of newly generated neurons even with persistent defects of type 1 RG cells and transit amplifying cells. This indicates that other Notch receptors or signaling-pathway components likely compensate for Notch1 deficiency in the postnatal SGZ (Ables et al. 2010).

Dentate neurogenesis ultimately requires integration of newly generated neurons into the hippocampal circuit. Notch also plays a role in neuronal survival, maturation, and plasticity in the DG. During the maturation of granule neurons, inhibition of Notch1 simplified dendritic trees, whereas ectopic expression of NICD increased dendritic complexity, indicating a role for Notch signaling in neuronal differentiation (Breunig et al. 2007). Physical activity increases Notch1 expression in the doublecortin-positive immature neurons further indicating involvement of Notch signaling in the survival of young dentate granule neurons (Brandt et al. 2010). Thus, neuronal arborization regulated by Notch signaling likely plays a role in the integration of new neurons, which adds to the roles of Notch in regulating stem-cell quiescence.

HEDGEHOG

Hedgehog was identified among 15 loci affecting the anterior–posterior segmented body plan of flies (Nusslein-Volhard and Wieschaus 1980). Mouse homologs were sequenced in 1993; Desert hedgehog (Dhh) was found using *Drosophila* hedgehog cDNA as a probe and Sonic hedgehog (Shh) and Indian hedgehog (Ihh) were obtained by hybridization with chicken Shh cDNA as a probe (Echelard et al. 1993). Expression of Shh was strong in signaling centers, such as the notochord and floor plate in ventral domains along the rostrocaudal axis of the neural tube, consistent with Shh function in

ventral patterning throughout the neural tube, including the forebrain. Hedgehog is synthesized and released through multiple enzymatic modifications and a few molecules involved in this process were identified, such as Skinny hedgehog, an acyltransferase mediating palmitoylation (Chamoun et al. 2001), Dispatched and Scube, cholesterol-interacting proteins mediating the release of hedgehog (Tukachinsky et al. 2012). In the developing wing epithelium of *Drosophila*, solubilized lipoprotein particles mediated long distance spreading of Hedgehog (Panakova et al. 2005). Within the chick limb bud, Shh travels up to 300 μ m and a recent finding showed delivery of Shh particles via specialized filopodia (Sanders et al. 2013). These suggest that Hedgehog signaling uses diverse cellular modes of delivery. Released Hedgehog binds Patched (Ptch1), reversing the repression of Smoothened (Smo), a G-protein-coupled receptor. Downstream signaling from Smo receptors results in the activation of the Gli zinc-finger transcription factors. GLIs contain a carboxy-terminal activation domain, whereas GLI2 and GLI3 contain an additional repressor domain in the amino terminus. In the absence of Hedgehog activation, phosphorylation of GLI2 and GLI3 on multiple sites involving PKA, GSK-3 β , and CKI kinases (Methot and Basler 2000; Price and Kalderon 2002), recruits a bTrCP containing SCF E3 ubiquitin ligase complex, and releases amino-terminal repressor forms of GLIs (Pan et al. 2006; Wang and Li 2006). After activation of Hedgehog signaling, GLIs bypass the proteasome, are enriched at basal bodies and form a full-length transcription activator in the nucleus. Thus, the gradient of Hedgehog ligand generates a transcriptional gradient of activator and repressor forms of GLIs across Hedgehog-responding tissues. Hedgehog pathway modulates composition and polarization of signaling molecules in the apically projected cilia. Activation of Hedgehog signaling increases levels of GLI2 and GLI3 in the cilia before transcriptional activation in the nucleus (Haycraft et al. 2005). Several human diseases, also known as ciliopathies, show symptoms characteristic of Hedgehog-signaling mutation (Oh and Katsanis 2012).

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During forebrain development, Shh is necessary for proliferation of progenitors, ventral patterning, segmentation of progenitor zones, and later for the maintenance of NSCs in the SGZ and SVZ throughout life. Interestingly, persistent activation of Shh signaling in these niches contributes to the development of brain tumors that are likely transformed versions of NSCs (Ng and Curran 2011). FoxG1-Cre-mediated inactivation of Smo by E9.5 in the forebrain led to the failure of ventral forebrain formation (Fuccillo et al. 2004). In the mutant, cortical development was not severely affected. By comparison, Nestin-Cre-mediated inactivation of Smo by E12.5 did not show failure of patterning in the ventral forebrain. In the ventral forebrain, the developmental time period between E9.5 and E12.5 is, thus, critical for Shh-mediated ventral progenitor specification (Machold et al. 2003). In the developing dorsal pallium, Shh mRNA expression was too weak and only very sensitive methods (such as RT-PCR) were able to detect Shh gene expression until after postnatal day 3 (Dahmane et al. 2001). Consistent with Shh expression at only low levels in the developing cortex, inactivation of Smo using conditional transgenic mice, such as Emx1-Cre showed only mild defect. However, the defect became prominent when postnatal NSCs emerge in persistent neurogenic niches; at this time, Shh expression could be easily detected close to the adult NSC niches, such as in the septum and the hilus (Machold et al. 2003; Komada et al. 2008; Li et al. 2013).

Gli3 functions as a repressor in the absence of Hedgehog signals and the extra-toes (Xt) Gli3 mutant mice showed defects in the patterning of dorsal forebrain structures not observed in the Smo mutants (Theil et al. 1999; Tole et al. 2000). Inactivation of Gli3 during cortical neurogenesis revealed that the repressor form of Gli3 is critical for the control of upper layer, late-born cortical neuronal fate (Wang et al. 2011). The ratio of GliA to GliR in the ventral forebrain is, however, more crucial for the specification of GABAergic interneurons through a gradient of Gli3 repressor, which is opposed by Shh signaling and Gli activators. Within the medial ganglionic eminence, the dorsal area has

expression of the Hedgehog-signaling effector Gli1 and produces somatostatin-expressing interneurons and the ventral medial ganglionic eminence produces parvalbumin-expressing interneurons (Wonders et al. 2008). The local gradient of GLIs in the medial ganglionic eminence specifies these two different interneuron subgroups and ectopic Shh in the medial ganglionic progenitors directed generation of somatostatin-expressing interneurons at the expense of parvalbumin-expressing interneurons (Xu et al. 2010). This suggests that the ratio of GliA to GliR is critical for the determination of neuronal progenitor cell fate during embryonic brain development.

Shh signaling is highly active in the juvenile SGZ (Choe and Pleasure 2012) and persists in quiescent adult NSCs in the SVZ and SGZ (Ahn and Joyner 2005). In addition, studies using ectopic expression showed that Shh strongly regulates neural precursor proliferation both in the SGZ and in isolated hippocampal precursors in vitro (Lai et al. 2003). Consistently, activation of Shh signaling in adult NSCs leads to a marked expansion of the stem-cell pool (Feret et al. 2014). In vitro, this phenotype is associated with a Notch-dependent increase in NSC symmetric divisions. A recent study also showed that the fate of adult NSCs in the SVZ is determined by the GliA to GliR ratio determined by dorsoventral position (Ihrle et al. 2011). The SVZ is the largest neurogenic area in the adult brain and generates thousands of new neurons each day. Deep granule olfactory interneurons are generated from the ventral SVZ where the Hedgehog-signaling effector Gli1 is enriched, whereas the superficial granule interneurons arise from the dorsal SVZ. Ectopic Shh activation directs dorsal SVZ progenitors to produce deep granule interneurons. This shows that the ratio of GliA to GliR plays a similarly crucial role for the determination of the fate of adult NSCs as in the developing brain. Another recent study (Petrova et al. 2013) further amplifies this message. In this study, the investigators showed that the behavior of quiescent NSCs in the SVZ is largely under the control of the Gli3R-signaling tone and that precise titration of Gli3R (and to a lesser degree the somewhat redundant Gli2R)

by Shh signaling is critical for establishing the balance between quiescence and proliferation in adult NSCs.

Shh signaling appears to mediate the emergence of distinct progenitor types. Coincident with the decline of Gli3 expression, Gli1 is increased in adult NSCs. Inactivation of Smo in the Nestin-Cre lineage hindered the formation of the adult NSCs (Machold et al. 2003). This effect was later confirmed by inactivating Smo using human GFAP-Cre transgenic mice. These mice showed a hypoplastic adult SGZ with failure of the emergence of adult dentate stem cells (Han et al. 2008). The perinatal induction of Shh-responding adult dentate stem cells initiates ventrally from the temporal pole of the embryonic dentate and the Shh-responding adult stem cells contribute stem cells along the septo-temporal axis (Li et al. 2013). Thus, Shh signaling plays critical roles for induction, distribution, and also maintenance of the adult stem cells (Balordi and Fishell 2007).

Cell-intrinsic mechanisms, such as transcriptional factors, have recently been shown to be critical to interpret Shh activity and modulation of neurogenesis (Balaskas et al. 2012). Twenty different Sox genes share HMG domains and consensus DNA-binding sites with high sequence homology, and homo- or heterodimerization among Sox proteins selectively achieve affinity for *cis*-regulatory sequences (Sarkar and Hochedlinger 2013). Transcriptional networks driven by the SoxB1 family of these genes underlie the interpretation of Shh activity by neuronal progenitors (Oosterveen et al. 2013). Sox2, a member of SoxB1 superfamily, is required for development of the ventral forebrain and adult hippocampal NSCs, and the effect of Sox2 was mediated by regulating Shh activity and a Shh-dependent gene regulatory network (Favaro et al. 2009; Ferri et al. 2013). Sox2 proteins directly regulate Shh expression and later become essential cofactors that cooperate with GLIs by occupying *cis*-regulatory modules on target genes. This integration of Sox2 proteins and nuclear effectors of Shh at the genomic level provides instruction for the fate specification of neuronal progenitors (Fig. 4) (Favaro et al. 2009; Ferri et al. 2013; Oosterveen et al. 2013).

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Figure 4. Shh. The ratio of GliA and GliR together with SOX, *cis* regulatory transcription factors, instructs the fate of neuronal progenitors.

CONCLUDING REMARKS

In this review, we have discussed in detail the diverse but overlapping roles of the four main morphogenic-signaling molecule families in regulating events in the two adult neurogenic niches. Although there are still molecular details that need to be filled in and much needs to be learned about the roles of particular target molecules of these pathways, the overall role of each of these families is quite securely established. Where the next big steps will be taken is in gaining further understanding of the interactions between these signaling pathways. Two notable examples inferred from our synthesis include (1) the role of Notch in regulating expression of Sox2, which interacts with intracellular Shh signaling; and (2) Bmp signaling regulates the expression of Lef1 in embryonic dentate granule precursors, thereby modulating Wnt-signaling output. Undoubtedly, further examples will emerge to establish that these morphogenic signaling act in some ways, more as a web of influences controlling neurogenesis, and that this tangled web is tightly linked to the regulation of neurogenesis by diverse physiologic processes linked to stress and environmental interactions.

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