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Review

Stem cells of the adult mammalian brain and their niche

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Abstract. The mammalian brain is a paradox of evolution. Although the advance in complexity of the human brain has exceeded the development of other organs, it has practically lost the ability to regenerate, and damage is repaired mainly by functional plasticity. This disparity is, however, not due to the lack of progenitor cells in the adult mammalian brain, but to their diminished or repressed capacity to replace neurons in most brain regions. Here, we discuss the current literature describing the processes of neurogenesis in the adult mammalian brain, and the recent advances in adult neural stem cells (aNSCs) with a focus on their identity, cell cycle and niche signals. Understanding these processes may hopefully lead to therapies in the future to reinstate self-repair of the brain from endogenous progenitors.

Keywords. Neural stem cells, neurogenesis, stem cell niche, adult brain, subventricular zone.

The discovery of neurogenesis in the adult brain

NSCs are the foundations of the brain during development, and despite poor regenerative capacity, they persist in the mammalian brain throughout postnatal development and into adulthood and continue to generate neurons. aNSCs self-renew and retain multipotency in almost all mammalian species analyzed, including humans. NSCs reside in specialized germinal layers where multiple cell-types interact with them and contribute to generate niches that control their fate choices and permit neurogenesis. Genetic and functional analyses have revealed roles for several genes and signaling pathways in controlling adult neurogenesis. However, the identities of the stem cells in the brain remain elusive, which presents an elementary problem for the interpretation of these results. In attempts to identify aNSCs, several groups have defined populations that contain cells with stem cell features, although unambiguous markers are still missing. Given their potential as putative tools for cell-based therapies, elucidating the molecular pathways that identify aNSCs and govern their cell fate is essential.

Neurons in most regions of the adult mammalian brain are generated from NSCs and restricted progenitors during embryonic development before a switch to gliogenesis in peri- and postnatal development [1]. As early as the 1960s and 70s, newly generated neurons were identified by nucleotide analogue incorporation assays in adult rodents [2, 3]. These results, however, met with skepticism due to the poor regenerative capacity of the mammalian brain. Detailed studies went on to show extensive neurogenesis in the vocal control center in the brains of adult canaries, which correlates with seasonal song learning [4, 5]. After a brief re-visitation to the topic in the mid-1980s, it was the use of retroviral lineage tracing assays that identified newborn neurons in the adult mammalian brain. These findings were quickly followed by the identification of zones with neurogenic capacity in

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multiple mammalian species including humans [2, 3, 6–9]. Evidence of continued adult neurogenesis intrigued many who long believed that the adult mammalian brain had lost its neurogenic capacity compared to the avian and fish brain, and further provoked questions about the neural progenitors which retain proliferative capacity and are capable of giving-rise to more differentiated progeny including neurons. The phenomenon of NSC as a life-long source of neural progenitors and newly generated neurons in adults was proposed after the isolation of cells that can be propagated for an unlimited amount of time and generate all three lineages of the adult brain *in vitro* [6, 7, 10].

Cellular architecture of the neurogenic zones

Although multiple proliferative zones have now been identified in the adult central nervous system, neurogenesis is most prominent and best studied in two defined germinal centers, the subependymal layer of the lateral ventricle wall covering the striatum (SEZ) and the dentate gyrus of the hippocampal formation. The SEZ is the major source of adult neurogenesis generating at least 5 subtypes of interneuron of the olfactory bulb and, to a limited extent, oligodendrocytes of the corpus callosal white matter [2, 11, 12]. Estimations suggest that 30–60,000 new neurons may be generated per day in the adult rodent olfactory bulb [13, 14].

Morphologically, four major cell-types have been identified in the rodent SEZ. SEZ astrocytes are mitotically inactive and can be subdivided depending on chromatin structure [15, 16]. One undisputed role of the astrocytes is to form "glial tubes" that ensheath migrating neuroblasts, confining them to the rostral migratory stream (RMS) and separating them from the surrounding parenchyma. Neuroblasts are the principal product of the SEZ and migrate in chains to the olfactory bulb where they distribute radially to the granule and glomerular layers before undergoing terminal differentiation. Neuroblasts are generated from resident stem cells in the SEZ through a transient amplifying population (TAPs) [11, 13, 15]. The neurogenic zone is covered by a ventricular lining of mitotically-inactive ependymal cells with motor cilia extending into the ventricle that circulate cerebrospinal fluid generated by the choroids plexus. Evidence indicates that ependymal cell-mediated directed movement of factors, including Slit proteins in the cerebrospinal fluid, determines migration of neuroblasts to the olfactory bulb [17].

Similarly, the human SEZ is divided into four morphologically distinguishable layers with cell-types reminiscent of those found in rodents. Lining the ventricles, layer 1 is composed of ependymal cells extending basal processes into a hypocellular gap (layer 2). Layer 2 contains some neurons and neuronal fibers and occasional astrocytes [18]. Interestingly, neither rodents nor non-human primates have this hypocellular gap which, in addition to humans, has so far only been detected in bovine brains [18–20]. Layer 3 contains a ribbon of astrocytes that extend processes to layer 2 and might make contact with the ependymal cells [18]. Layer 3 contains cells morphologically similar to the TAPs in rodents and has been suggested to contain aNSCs [18, 21]. The SEZ is delineated from the brain parenchyma by the myelin rich layer 4 [20]. A migratory track reminiscent of the RMS in the other mammals is also present in humans and recent reports claimed to have identified β-tubulinIII+ (Tuj1) neuroblasts; however, evidence for chain migration is lacking [18, 20, 22].

Neurogenesis in the adult mammalian hippocampus involves similar steps to those of the SEZ, although unlike in the forebrain, the source (subgranule zone – SGZ) and target (granule cell layer) of the newborn neurons are juxtaposed [23, 24]. Astrocytes of the SGZ have two basic morphologies. Those with pyramidal cell-bodies and radial processes extending through the granule cell layer towards the surface of the dentate, similar to embryonic radial glia, include a population of stem cells [23, 24]. Recently, a second population of SGZ astrocytes with tangential rather than radial processes has been shown to express progenitor markers and behave like stem cells *in vivo* [25]. Interestingly, this finding questions the dogma of radial astrocytes as the sole stem cells of the dentate and indicates that tangential cells may make-up the predominant active stem cells of the hippocampus. In addition, retroviral labeling indicates that these non-radial cells undergo asymmetric cell division to generate neurons but can also produce daughters that adopt a radial morphology. As in the SEZ, dentate neurogenesis progresses through transient intermediates and mitotically active neuroblasts before newborn neurons migrate radially into the granule cell layer.

Neural progenitors in the adult brain

Endogenous NSCs are, according to the definition, capable of self-renewal throughout the life of the organism and multi-lineage differentiation (multipotency) into neurons, astrocytes and oligodendrocytes [26]. However, the exact identity of the aNSCs has yet to be determined. Due to the lack of unambiguous markers, single aNSCs in the adult neurogenic niches

cannot be identified [7]. As a consequence, marker gene expression, viral and genetic approaches can only be used to label populations of cells that include a variety of cell-types with different antigenic, cell cycle, self-renewal, and differentiation potentials. Thus, these experiments are inevitably a retrospective estimation of cell populations that may contain multi-potent or multiple lineage restricted stem cells. For instance, although both neurons and oligodendrocytes are generated in the adult mouse SEZ, there is no evidence that a single cell gives-rise to both lineages *in vivo*. Furthermore, although strictly speaking the stem cell should maintain self-replicating potential throughout the life of the organism, a more flexible and potentially more tangible scenario is that the stem cells have a limited life span. Thus, active stem cells may become exhausted with time, either resulting in a reduction in progenitors with age, which is observed in both adult neurogenic brain regions, or that the active NSCs are replaced by precursors that, under normal circumstances, do not contribute significantly to active neurogenesis. In reality, neurogenesis may use a combination of both strategies. It will be a central objective in the future to combine genetics and lineage tracing not only to identify the NSCs in the adult brain but also to elucidate the mechanisms that control their maintenance and fate *in vivo*.

Although it has not been possible to date to identify aNSCs *in situ*, cells with NSC-like character can be isolated from the adult brain and expanded *in vitro* using the neurosphere assay. Spherogenic cells self-renew *in vitro* in response to epidermal growth factor (EGF) or fibroblast growth factor 2 (FGF2) and clonally generate neurons, astrocytes and oligodendrocytes [6, 7, 27–29]. Spherogenic cells represent prospective NSCs, although the retrospective nature of the method evoked questions about their source and the relationship to the NSCs *in vivo*. In addition, expression analysis and differentiation experiments have cast doubt on the potential and validity of neurosphere-derived cells for cell therapy [29–32]. Furthermore, evidence suggests that not only NSCs but more differentiated progeny can also generate neurospheres *in vitro*. Ablation of rapidly dividing cells from the SEZ by treatment of mice with anti-mitotic drugs such as cytosine arabinoside (AraC) results in a reduction in neurosphere-forming cells isolated in EGF-containing medium [31]. This was interpreted to indicate that a significant proportion of the EGF-responsive spherogenic cells are TAPs. However, although there may be some foundation to this interpretation of the anti-mitotic paradigm, the experiments may also be biased. It has been suggested that a feedback mechanism to the NSC from its progeny may also regulate stem cell status (see later).

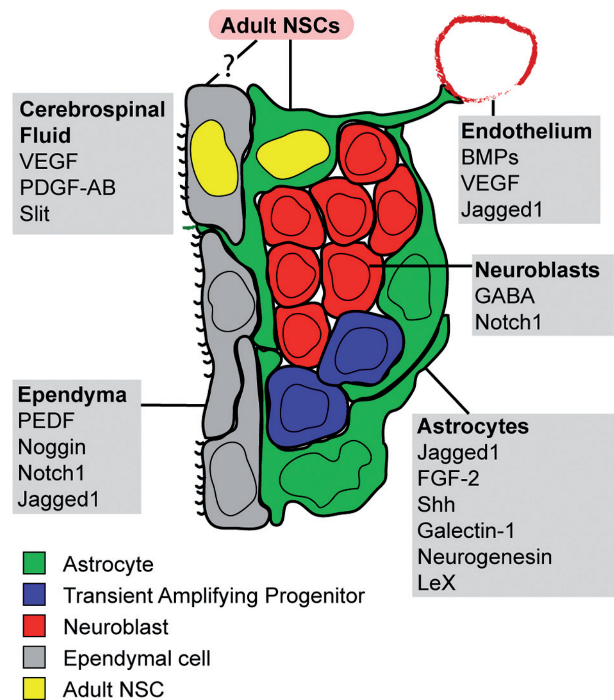

Figure 1. The adult neurogenic niche. The adult mammalian subependymal zone is composed of four principle cell types: Astrocytes (green cells) are resident support cells and accumulating evidence indicates that they include aNSCs. Ependymal cells (grey) line the wall of the ventricles and some might have NSC-like features. aNSCs rarely divide and give-rise to transient amplifying progenitors (blue) which, following a definite number of divisions, generate neuroblasts (red) that are destined for the olfactory bulb. Some of the astrocytes contact the endothelial cells, suggesting that aNSCs might be in direct contact with the circulatory system. The factors implicated in the control of the aNSC fate choices are listed in the grey boxes together with the cell type that presents them.

Thus, in the situation where the SEZ degenerates and the progeny of the NSC, TAPs and neuroblasts, are reduced due to anti-mitotic drug treatment, NSCs may be promoted to enter the cell cycle precociously to compensate, thus rendering them more susceptible to AraC than would have been predicted. Hence, NSCs could also be killed by the anti-mitotic treatment which would also result in a reduction in spherogenic cells. The lack of definitive markers again prevents the conclusive dissemination of the results. More detailed analysis is required to establish if neural progenitors that have a short cell cycle (TAPs) are able to form neurospheres from a non-lesioned forebrain. Clearly, the estimated number of non-NSC derived neurospheres indicates that very few TAPs (the major mitotic population in the SEZ) are spherogenic. In the future, it will be interesting to establish if these putative non-NSC spherogenic cells may be an intermediate between committed TAPs and NSC. Alternatively, spherogenic TAPs may belong to the relatively minor oligodendroglia progenitor population in the SEZ. Although the source

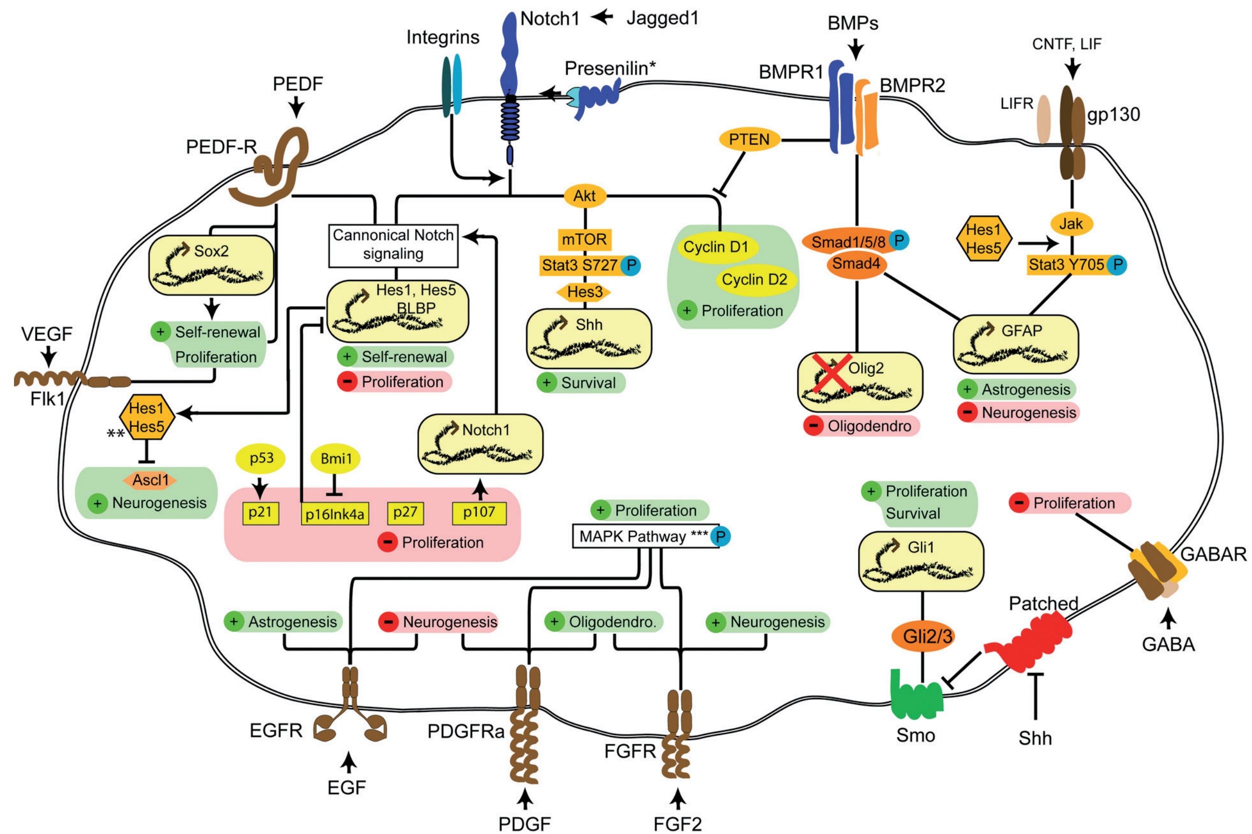

Figure 2. Interplay between multiple signaling pathways controls the fate of aNSCs. A complex net of signaling pathways influences the fate of aNSCs by affecting their proliferation, self-renewal, choice of lineage differentiation and survival. The interplay between the pathways and intrinsic regulator is complex, and among the vast intracellular interactions only those suggested to play a role in the control of the aNSC fate are shown. Cell extrinsic cues and the receptors they activate, intracellular components (connected with lines), the signal is either positive (+, green background) or negative (-, red background) for the given fate. Arrows indicate induction and discontinued lines indicate inhibition of the respective process. Oligodendro. : Oligodendrogenesis. Smo: Smoothened. *: Presenilins are the enzymatic subunit of the gamma-secretase complex. **: The roles of Hes1 and Hes5 as effectors of Notch signaling are well studied during embryonic neurogenesis; however, these are not conclusively shown in adult neurogenesis. ***: MAPK signaling is activated by multiple growth factor receptors, but not necessarily the means through which all the pleiotrophic effects are exerted. Further analysis is required for correct annotation of the downstream elements of receptor tyrosine kinases in aNSCs.

of spherogenic cells isolated from the adult brain and their relationship to NSCs *in vivo* remains unclear, they may still be of clinical use. However, there is also an obvious lack of *in vivo* models to address the full differentiation potential of *in vitro* expanded spherogenic cells in a stem cell assay comparable to the reconstitution and serial transplantation assay that has been used so successfully in the hematopoietic system [29].

Adult neural stem cells

The identification and isolation of adult human NSCs that generate neurons *in vitro* were milestones in regenerative medicine [9, 33–37]. Explant cultures established from epileptic patients provided the first data that the adult human brain, like that of rodents, contains neural progenitors that generate neurons *in vitro* [33, 34]. Analysis of post-mortem brains of carcinoma patients treated with bromodeoxyuridine (BrdU), which is incorporated into the genome of the proliferating cells, provided the first evidence of newborn neurons in the human brain [9]. Self-renewing and multipotent human NSCs were cultured soon after [36, 37]. Due to the inability to genetically manipulate human NSCs *in vivo*, the majority of the data remains descriptive but provocative, and whether there is indeed continuous neurogenesis in humans is still under debate [38, 39]. Thus, the majority of the information relating to human aNSCs stems from rodents. Hence, although amenable for genetic and experimental manipulation to address function and potential, the relationship of rodent cells to putative human aNSCs that may be useful for therapy remains vague and must be viewed critically.

Table 1. Identifying adult NSCs. The list of markers used to identify NSCs in the adult mouse SVZ. Marker (left column) indicates the name of the protein or, in the case of LeX and CD133, glycoepitopes. Features (middle column) include a recapitulation of the expression pattern of each marker and the respective references.

Marker	Features	References
GFAP	Expressed by SEZ and SGZ astrocytes in rodents, primates and the human.	
	Not expressed by TAPs and neuroblasts.	[16, 40]
Gli1	Marker of Shh activity, is expressed by astrocytes as well as neural progenitors in the SEZ and SGZ.	[103, 104]
Notch1	Expressed by SEZ astrocytes, ependyma, neuroblasts and a lineage-population.	[68, 137,138]
Sox1, Sox2, Nestin	General markers of neural progenitors and possibly ependyma. A single Sox2+ cell in the SGZ can generate neurons and astrocytes	[41–44, 46, 48, 53]
Musahi1	An mRNA binding protein implicated in regulation of Notch signalling, is expressed by neural progenitors of the adult mammalian brain.	[46–48]
LeX	A secreted carbohydrate, expressed by neural progenitors and SEZ astrocytes, which include all the sphere forming cells.	[63, 166]
CD133	Expressed by ependymal cells. A glyco modification of Prominin-1	[51, 52]
PDGF-R	Expressed by a population which can give-rise to both neurons and oligodendrocytes in the adult mouse SEZ.	[85]
FGF-R	Expressed by SEZ astrocytes, the putative FGF responsive spherogenic cells.	[82–84]
Tlx	An orphan nuclear protein expressed by SGZ and SEZ progenitors.	[154–156]

Table 2. Signaling in the NSC niche. The niche signals that have been implicated in the control of the cell fate choices of aNSCs are listed. Factors (left column) indicate secreted molecules or signaling pathways of the aNSC niche. Features (middle column) include a recapitulation of the role of each signaling molecule/pathway in the control of adult NSCs and the respective references.

Factors	Features	References
FGF-2	One of the mitogens used to culture NSCs *in vitro*. Promotes oligodendrogenesis and neurogenesis.	[28, 29, 82–84, 86]
PDGF-AB	Promotes oligodendrogenesis and inhibits neurogenesis.	[85, 86]
Notch signaling	Required for the maintanance of NSCs *in vitro*. Promotes astrogenesis at the expense of neurogenesis during postnatal development and in the adult SGZ. May be required for the survival of NSCs.	[68, 129, 134–138]
BMP signaling	Induces astrogliogenesis, inhibition is required for proper neurogenesis.	
	Low levels may also be required for neuronal differentiation at the expense of oligodendrogenesis.	[62, 87–89, 90–93, 97]
gp130 signaling	Promotes astrogliogenesis at the expense of neurogenesis. LIF induced signalling induces NSC self-renewal.	[95–98]
EGF	One of the mitogens used to culture NSCs *in vitro*.	
	Induces cell migration and astrogliogenesis at the expense of neurogenesis.	[6, 7, 27, 29, 82–84, 86]
VEGF	Promotes NSC expansion and enhances neurogenesis	[105, 108]
GABA	May act on SEZ and SGZ astrocytes as a feedback loop to inhibit neurogenesis.	[110–114]
PEDF	Induces NSC self-renewal via activation of Notch signaling and Sox2.	[76]
Neurogenesin	Induces neurogenesis via inhibition of BMP signaling	[91]
Shh signaling	Induces NSC self-renewal and proliferation	[100–104]

Astrocytes as stem cells

The prevailing evidence accumulated since the mid-1990s indicates that aNSCs in rodents belong to astrocytic lineages. SEZ astrocytes and some neurogenic NSCs are labeled in transgenic mice expressing reporter proteins from regulatory elements of the human intermediate filament Glial Fibrillary Acidic Protein (*gfap*) gene [16, 40]. In addition, SEZ GFAP+ cells are quiescent and many survive anti-mitotic drug treatment. They rapidly enter the cell cycle upon withdrawal of the anti-mitotic drug supporting their

function as neurogenic progenitors in the regenerating SEZ [16]. Expression analysis and transgenic reporter mice indicate that neural progenitor cells, including some GFAP+ astrocytes in the adult SEZ, express the Sry-related HMG group transcription factors Sox1, Sox2 and regulatory elements of the rat *Nestin* gene [41–44]. Furthermore, inducible Cre-mediated lineage tracing of astrocyte-specific L-glutamate/L-aspartate transporter (GLAST) or Nestin expressing cells indicate that these populations are neurogenic and self-renewing *in vivo* [45]. In addition, some SEZ astrocytes express the receptors for FGF and platelet derived growth factor (PDGF), mitogens that affect neurogenesis *in vivo* and expand spherogenic cells *in vitro* (see below).

Comparisons show that we know even less about the identity of the human aNSCs. As described above, the human SEZ includes a population of GFAP+ astrocytes, which might include NSCs. Similar to rodents, Sox2 and Musashi1 are expressed in the human SEZ as well as by neurosphere cells derived from the human brain [46–48]. Antigen-based cell sorting of human brain tissue and subsequent analysis in culture suggests that NSCs in both fetal and adult human brains are included in a CD133+ CD34- CD45- fraction [49]. It is interesting that CD133, a glycoepitope expressed on the multi-pass membrane protein Prominin1, is also expressed by polarized radial progenitors in the embryonic mouse neural tube, where it is localized to the apical membrane [50]. In the adult mouse SEZ the situation is less clear, with conflicting reports claiming CD133 expression, which is mainly confined to the ependymal cell layer, by aNSCs *in vivo* [51, 52].

The ependymal controversy

Although it is clear that SEZ astrocytes include aNSCs, in 1999 Johannson et al. reported that multiciliated ependymal cells of the lateral ventricle walls overlying the SEZ generate NSC-like cells *in vitro* [37]. As ependymal cells are, under normal circumstances, mitotically inactive, these findings were criticised and rejected by most in the field. However, the flame of neurogenic ependymal cells has been rekindled by a number of reports also claiming to show neurogenesis from ependymal cells [51, 53]. At the protein level, cells within the ependymal layer express progenitor markers including Sox2 and Nestin and the ependyma is highly positive for the stem cell associated marker CD133. Using transgenic approaches, new findings support that cells in the ependyma generate neurons *in vivo* and can behave like aNSCs [51, 53]. Furthermore, the transgenic approaches using the regulatory elements of the human *gfap* gene do not clarify the situation, as the ependyma expresses GFAP at low levels together with another astrocytic protein S100β [16]. One tangible and plausible explanation for the finding that cells in the ependymal layer can generate neurons could be the presence of astrocytes in the ependymal sheet. Indeed, SEZ astrocytes are found interdigitated between ependymal cells and their numbers seem to increase with age [54, 55]. It is unclear whether these astrocytes play a role in ependymal maintenance replacing cells in the adult but aNSCs and ependymal cells have common ancestors in the radial progenitors spanning from the ventricle through the striatum during early postnatal development [56, 57]. It is plausible that SEZ astrocytes within the ependymal layer retain the potential to generate ependymal cells as well as contributing to neurogenesis. Thus, these new findings and reports of ependymal neurogenesis make the identity of the aNSC less clear. However, it remains possible that, under certain conditions including lesion and isolation for cell culture, ependymal cells or their progenitors are able to divide and may become neurogenic. It must be noted that, even the AraC experiments and regeneration of the SEZ does not clarify the question as, being postmitotic, ependymal cells survive the anti-mitotic drug treatment. Lineage tracing experiments provide the strongest evidence for the presence of ependymal aNSCs, but rely on the specificity of the Nestin, FoxJ1 and Prominin1 promoters used and must be critically evaluated [51, 53]. "Clean" genetic lineage-tracing experiments will be needed in the future.

The neurogenic niche and its factors

As neurogenesis is detectable mainly in two evolutionarily conserved regions of the adult mammalian brain, the SEZ and the dentate gyrus [2, 11, 58], these brain regions must contain a functional neurogenic microenvironment which also maintains NSCs in an undifferentiated and potent state [26, 59]. The cues that control the fate of the NSCs are provided by specialized support cells and the extracellular matrix of the germinal layers, which together likely form the NSC niche during adult neurogenesis [26, 59–63]. Astrocytes form a structural part of the adult neurogenic niche and express molecules implicated in adult neurogenesis *in vivo* [15, 64–68]. Cultured astrocytes from specific regions of the developing and adult brain can induce neurogenesis from neural progenitors *in vitro* [61, 69–71]. Furthermore, microglia and endothelial cells likely contribute to the niche as they can enhance neurogenesis *in vitro* [63, 72–75]. Similarly,

ependymal cells express several genes involved in the generation of a permissive environment for neurogenesis and NSC maintenance [62, 68, 76].
Several extrinsic factors provided by the niche are implicated in the control of maintenance and differentiation of NSCs as well as their early progeny. Irrespective of their spatial origin, transplanted NSCs can integrate throughout the SEZ and retain neurogenic potential, suggesting that the niche maintenance signals are constant [77, 78]. On the other hand, it has been reported that adult NSCs located at distinct positions in the SEZ have a restricted potential to give-rise-to specific interneuron subtypes in the olfactory bulb [78]. The restricted neurogenic potential of NSCs is independent of environmental cues, suggesting that intrinsic factors control their potential to generate specific neuronal subtypes [78]. The spatial pattern and fate restriction is claimed to be established during embryonic development [79]. In addition, the type of interneurons generated is dependent on the temporal origin of the NSC, suggesting that either NSCs or the niche could be constantly changing [80, 81]. Elucidating the molecular factors that underlie the patterning of NSCs might have important implication for clinical applications that aim to generate specific types of neurons and might lead to deviations from the original description of a stem cell that can generate any cell in the adult brain.

Signaling within the aNSC niche

Classically, EGF and FGF2 have been used to isolate and expand aNSC-like cells. Although their roles *in vivo* remain unclear, intra-ventricular infusion of these factors into mice has a pronounced effect on neurogenesis. In contrast to claims that a common progenitor responds *in vitro* to both EGF and FGF2, *in vivo* these factors have very different effects [82, 83]. EGF induces a marked proliferation of GFAP+ cells in the SEZ, which is normally not seen in the neurogenic zone, and their infiltration into the surrounding tissue as a hyperplastic mass. This increase in proliferation is associated with a reduction in neurogenesis, suggesting that EGF-responsive cells, which generate neurons under normal conditions, are stimulated by EGF to proliferate and give-rise to astrocytes. In contrast, FGF2-infusion into the lateral ventricles results in an expansion of neuroblasts and increased neurogenesis in the SEZ. In addition, FGF2 induces migration of progenitors to the olfactory bulb. Thus, rather than increasing NSC expansion as may have been predicted from the neurosphere assay, exogenous FGF2 does not result in expansion of SEZ astrocytes *in vivo* in the way EGF does. The effect of FGF *in vivo* could be interpreted as an increase in neuronal differentiation. A similar effect has been seen following FGF2 treatment of embryo-derived NSCs, which proliferate in response to high levels of FGF2 *in vitro* but undergo neurogenesis when exposed to reduced FGF2 concentrations [82–84].
PDGF has also been shown to be a mitogen for spherogenic NSCs isolated from the adult mouse brain, however, only in combination with FGF2 and not EGF [85]. PDGF-receptors on SEZ cells are phosphorylated *in vivo,* suggesting that signaling is active in the adult neurogenic forebrain. In contrast to FGF, but similar to EGF, PDGF infusion into the lateral ventricles of adult mice results in activation of SEZ astrocytes, hyperplasias and gliogenesis at the expense of neurogenesis [85, 86]. Due to the effects of PDGFs to reduce neurogenesis, neurogenic NSCs must respond to activation of the pathway, although an indirect mechanism cannot be ruled out.
Bone morphogenic protein (BMP) signaling has been shown to affect neurogenesis both *in vitro* and *in vivo* by increasing astrocyte formation at the expense of neurogenesis [62, 87–89]. Over expression of BMP7 in the adult brain results in decreased proliferation and a reduction in neuroblast production, while Noggin, a soluble antagonist of BMP signaling expressed by the ependymal cells of the adult SEZ, promotes neurogenesis [62, 89].
BMPs act as morphogens through activation of the transcriptional regulators Smads but can also activate phosphatase and tensin homologue (PTEN) to inhibit cell cycle progression of neural progenitors [90]. Neurogenesin1, a factor secreted by the astrocytes, can promote neurogenesis through the inhibition of BMP signaling [91]. Although these gain-of-function experiments indicate that BMP counteracts neurogenesis, constitutive activation of BMP-receptor1a does not affect neuronal differentiation [87, 92]. In contrast to BMPs reported role in blocking neurogenesis and activating gliogenesis in the brain, genetic loss of Smad4 function revealed a role in suppressing oligodendrogenesis through down-regulation of the transcriptional regulator Olig2 [93]. Smad4 is a central component of the BMP pathway and conditional knockout mice surprisingly showed reduced neurogenesis in the SEZ [93]. These seemingly contradictory results remain to be clarified but dose-dependent effects of BMPs could be at work in the different paradigms. It should be noted that Smad4 is also a downstream component of the tumor growth factor-beta (TGF-beta) signaling, which promotes cell cycle arrest in various tissues [94]. Conditional inactivation of TGF-beta receptor-2, however, did not result in neurogenic defects [93].

Possible crosstalk between BMP signaling and other pathways could mediate alternative cell-fate choices made by aNSCs. Interleukin-6 (IL-6) family cytokines (IL-6, IL-11, Ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), Oncostatin M, Cardiotrophin) activate gp130-mediated Stat signaling to synergize with BMP and induce astrogenesis *in vitro* [95–97]. Consistently, Smad and Stat are suggested to form a complex with p300 [97]. Interestingly, LIF over expression in the adult brain results in increased self-renewal of NSCs and inhibits neurogenesis [98].

Adult SEZ astrocytes, like most cells, have primary cilia [99]. Ablation of Kif3a, a central component of the kinesis II motor complex, inhibits the function of primary cilia and affects aNSC numbers in the dentate gyrus [100]. In addition, NSCs require functional primary cilia during development, and disruption results in disturbed neural tube development with phenotypes similar to mutations in the Sonic Hedgehog (Shh) pathway [100, 101]. Primary cilia are required for Shh signaling and the key receptor components of the Hedgehog pathway accumulate in primary cilia [102]. Shh has been strongly implicated in adult neurogenesis and as a maintenance signal for NSCs [103]. Shh activates expression of its downstream target and effecter Gli1. Consistent with the single cell RT-PCR data, analysis of Gli1-lacZ transgenic mice indicates that Shh signaling is active in SEZ astrocytes, TAPs and neuroblasts [103, 104]. Lineage tracing of Gli1+ cells indicated that the population includes NSCs in the SEZ [104]. Systemic administration of the Shh inhibitor cyclopamine results in decreased proliferation in the SEZ *in vivo* and a decrease in spherogenic cells [103].

Vascular endothelial growth factor (VEGF) is essential for angiogenesis and hematopoiesis through its cognate receptors Flt1 and Flk1 [105–107]. VEGF is produced by endothelial cells and in the brain by the choroid plexus. Flk1 is expressed in the adult brain germinal zones and VEGF has been proposed to play a role as a growth factor for NSCs during development and in the adult brain. VEGF enhances, and blocking Flk1 activity reduces NSC expansion *in vitro,* and infusion of VEGF into the lateral ventricles of rats increases neurogenesis potentially by acting as a trophic survival factor for neural progenitors [108]. The survival effect of VEGF on NSCs is also seen during embryonic development and may reflect the close interplay between angiogenesis and neurogenesis [74, 109]. Similarly, pigment epithelium-derived factor (PEDF) is secreted by the ependymal and endothelial cells of the SEZ and specifically promotes NSC self-renewal *in vivo* and *in vitro* without affecting proliferation [76]. The effects seem to be specific for SEZ astrocytes and not for TAPs and neuroblasts, although genetic analysis is required. The mechanism by which PEDF acts in the SEZ is unclear, but activation of Notch signaling and the increase in the Notch targets Hes1 and Hes5 as well as Sox2 might be partially responsible [76].

Recent data suggest that not only do resident cells in adult germinal zones regulate NSC activity, but a feedback mechanism may also be active. Gamma-aminobutyric acid (GABA) joined the pallet of factors regulating the NSC and as a putative niche component. The GABAergic system can control the rate of adult neurogenesis modulating the proliferation of neural progenitors. Although predominantly know as an inhibitory neurotransmitter through activation of chloride channels, neural progenitors in the SEZ with high levels of intracellular chloride can be depolarized by tonic non-synaptic GABA activation [110–113]. Indeed, SEZ astrocytes express GABA receptors and increase proliferation in response to GABA inhibition, suggesting a role in the control of NSC activation [114]. The source remains unclear, but neuroblasts potentially secrete GABA. Thus, the GABA response could be a negative feedback to the progenitors regulating aNSC proliferation and differentiation.

Dopamine is another neurotransmitter implicated in the control of adult neural progenitor proliferation in the SEZ. The primary target of the dopaminergic afferents in the SEZ are TAPs, which express the D2-type dopamine receptors and proliferate in response to dopamine stimulation [115, 116]. Consistently, experimental ablation of dopaminergic afferents results in reduced SEZ proliferation which is mainly attributable to TAPs [115, 117, 118]. Interestingly, recent evidence suggests that the dopamine induced increase in cell proliferation and neurogenesis in the adult SEZ is dependent on CNTF [119]. While dopamine signaling has been suggested to inhibit stem cell proliferation, whether aNSCs respond directly to dopamine signals needs to be elucidated. The expression of dopamine receptors by SEZ NSCs has not been convincingly demonstrated [115, 120].

The basal lamina is in contact with all cells in the neurogenic niche, and the extracellular matrix (ECM) might be involved in the control of the NSC fate, mainly through the control of mitogenic stimuli [72, 121]. Heparin and chondroitin sulphate proteogylcans, Collagen-1, LewisX (LeX) and Tenascin-C are abundantly expressed in adult neurogenic niches [63, 72, 77, 122–125]. Tenascin-C is expressed by SEZ astrocytes and suggested to mark the border of the neurogenic niche [122, 125]. The proteoglycan LeX is secreted by SEZ astrocytes and is a putative marker of NSCs *in vivo* and *in vitro.* LeX might promote NSC proliferation by direct interaction with FGF2 and

Wnt1 to present the mitogens to neural progenitors [63,126]. Indeed, several components of the Wnt signaling pathway are expressed in the SEZ and SGZ of the adult mice [127, 128]. Although the role of the canonical Wnt signaling in the adult SEZ is unknown, Wnt1-mediated β-catenin signaling is implicated in the induction of neurogenesis in the SGZ. Whether NSCs directly respond to Wnt signaling is not clear [128]. Furthermore, integrin activity regulates neurogenesis at multiple levels, from synergizing with Notch in NSCs and regulating proliferation and differentiation [129], to chain migration of neuroblasts in the RMS [123]. The interplay between the basement membrane, ECM and growth factors in the niche may play an important role in fine-tuning neurogenesis.

Notch and lateral signaling during adult neurogenesis

Although the role of Notch signaling to block neurogenesis and maintain undifferentiated progenitors during development has been addressed, the role of Notch signaling in adult neurogenesis remains unknown. Notch signaling requires a complex proteolytic activation process, the final and critical step of which involves a Presenilin (PS) containing gamma-secretase [130]. PS1-mutant mice die *in utero* with a phenotype similar to that observed for Notch signaling mutants [131–133]. However, $PS1^{+/-}$ mice survive to adulthood but show a decreased neurogenesis in the SEZ and a reduction in spherogenic cells [134, 135]. Similarly, pharmacological inhibition of PS-activity results in reduced proliferation and increased cell death in SEZ-derived progenitors [136]. However, the cell autonomous role of PS in NSCs has not been demonstrated convincingly, as a reduction in gamma-secretase activity could lead to developmental defects or altered niche activity. During development, PS are required to maintain proper neurogenesis, similar to Notch [134]. However, PS and gamma-secretases have dozens of targets in addition to Notchs, thus it cannot be excluded that the effect of reducing PS on neurogenesis is indeed restricted to its action on Notch signaling.
Components of the Notch signaling pathway including Notch1, Jagged1 and the downstream target Hes5 are expressed in the adult SEZ, suggesting that, as in the embryo, Notch may play a role in adult neurogenesis [137, 138]. Conditional inactivation of *Notch1* from adult-derived NSCs results in a complete loss of self-renewal and stem cell character without any apparent cell death or change in lineage potential [68]. The putative ligand for Notch1 in the adult neurogenic niche is Jagged1, which is also required for NSC maintenance and can replace mitogens to promote NSCs self-renewal and maintenance *in vitro* and *in vivo* [68]. Jagged1 is expressed by ependymal cells and SEZ astrocytes and might provide the maintenance signal to Notch expressing NSCs. In agreement, Notch1 and Jagged1 double-hemizygous mice show defects in postnatal neurogenesis [68], and activation of Notch signaling via soluble ligand infusion into the ventricles results in enhanced proliferation [136].
Despite effects on the spherogenic cell population and proliferation, it is still unresolved whether Notch signaling acts directly at the level of NSCs. Genetic analysis of mutant mice is required to address the function of Notch signaling and, indeed, which Notch receptors are involved in adult SEZ neurogenesis. Notch signaling via a non-canonical pathway through activation of a Stat3-mTOR pathway in the SEZ activates Shh expression to increase progenitor cells survival in a non cell-autonomous way [136]. Consistent with this, the pro-survival effects of Notch activation can be mimicked by expression of activated Stat3 or Hes3 [136].

Intrinsic control of NSCs and neurogenesis

NSCs are a rare population in the adult neurogenic SEZ making up a minor fraction of the proliferating cells, but they display unique cell cycle features [139]. Retroviral birth-dating in adult mice revealed that putative NSCs divide slowly, with an average cell cycle time of over 15 days, which has been proposed to allow them to retain their potential throughout life [7]. Their progeny, TAPs, divide multiple times with an estimated cell cycle time of 12 hours and are the majority of the dividing cells in the SEZ. The major progeny of the TAPs, neuroblasts, retain a similar proliferative capacity but gradually become post-mitotic during migration *en route* to the olfactory bulb. The differences in cell cycle kinetics have been exploited to preferentially label specific cell populations using nucleoside analogue administration and markers of cell cycle progression.
BrdU is a thymidine analogue incorporated into newly replicated DNA and is frequently used to label proliferating cells and their progeny. BrdU is relatively short-lived *in vivo*, being excreted within a few hours after i. p. administration. Thus, a brief exposure to BrdU, single injection or < 24 hours *per os*, labels fast dividing cells in the SEZ, whereas NSCs are rarely labeled. On the other hand, prolonged exposure (>>24 hours) of animals to BrdU results in labeling of NSCs which, due to their long cell cycle, should retain the label over an extended period of time [140, 141]. Although label-retaining cells include putative NSCs, the evidence to date is indirect and the func-

tional data are still lacking [142]. In addition, markers of proliferation such as proliferating cell nuclear antigen (PCNA) and Ki67 are frequently used to label cells within the cell cycle; however, their association with NSCs has not been demonstrated, partially due to the lack of markers. Mcm2, an essential component of the origin of replication complex, is expressed by adult neural progenitors as well as label retaining cells and might play a role in actively cycling NSCs [143]. However, the current theories on the NSC are based on a single population of cells that are continuously in the cell cycle and have homogenous kinetics. Although this simplifies the interpretation of labeling experiments, in reality NSCs may be a dynamic cell population that can leave and enter the cell cycle and respond to local environmental cues. For instance, a mitotically active aNSC could undergo a few rounds of division before falling into a mitotically inactive state, while an inactive aNSC could contribute to brain regeneration by transiting into an active state. In addition, it is slowly becoming clear that the SEZ contains multiple populations of NSCs and it needs to be clarified whether these different populations may have distinct cell cycle characteristics [78]. It remains a major question whether all NSCs in the adult brain are active and contribute to neurogenesis throughout life or whether some become exhausted and are replaced or replenished by a potentially mitotically inactive NSC population.

Genetic analysis has revealed roles for specific genes involved in the intrinsic regulation of the cell cycle of adult neural progenitor populations, including NSCs. However, caution is needed in evaluating the data concerning the cell cycle of aNSCs due to the absence of definitive markers and *in vivo* assays. Cyclin genes promote progression through the cell cycle in cooperation with the cyclin-dependent kinases (CDKs), an activity regulated by CDK inhibitors (CDKIs). In the absence of the G_1-specific cyclin D_2, but not cyclin D_1, proliferation ceases and neurogenesis in the SEZ fails, indicating that neural progenitors are either not established or fail to be replenished in cyclin D_2 mutants [144].

On the other hand, the phosphatase PTEN decreases levels of cyclin D_1 through inhibition of AKT and might contribute to the long cell cycle time of adult SEZ NSCs by restricting G1-S transition [145–147]. In parallel, retinoblastoma gene family members (Rb, p107, p130) are well-known for their role in inhibiting cell cycle progression by binding to E2F family members [148]. In the absence of p107, mice display an increase in label-retaining cells in the SEZ, which correlates with an elevation in the number of spherogenic cells [149]. This strongly suggests an increase in aNSC in p107 mutant mice. Roles of Rb and p130 in adult neurogenesis remain elusive, while during embryogenesis Rb is up-regulated upon initiation of differentiation and p130 is expressed in most-mitotic neurons [150,151]. In addition, Rb mutant mice display a general deficit in the embryonic progenitor cell pool with no apparent NSC phenotype [149]. Thus, Rb family members seem to have distinct, non-redundant functions in the regulation of adult neurogenesis.

In support of a connection between the cell cycle progression and regulation of progenitor cell fate choices, mutants of several cyclin dependent kinase inhibitors (CDKI) display striking defects in adult neurogenesis. Evidence suggests that $p21^{cip1/waf1}$ promotes a more quiescent state and, in its absence, NSCs initially expand beyond wild type levels but are eventually exhausted [141]. An up-stream factor of $p21^{cip1/waf1}$, the tumor suppressor protein p53, is also implicated in promoting quiescence of adult NSCs [152]. In addition, genetic data support a role of $p27^{Kip1}$ in the inhibition of neural progenitor proliferation, although the phenotype can be attributed at least partially to an effect on TAPs [153]. Proliferation of SGZ and SEZ progenitors requires the orphan nuclear receptor Tlx, which is implicated in the inhibition of $p21^{cip1/waf1}$ but not $p27^{Kip1}$, further confirming differential functions of specific cell cycle regulators [154–156]. Tlx functions, at least partially, by recruiting histone deacetylases, stressing the importance of epigenetic regulation in the control of NSC maintenance [157]. In agreement, the polycomb family repressor Bmi1 is required for postnatal maintenance of NSCs [158]. Once again connecting cell cycle regulation to other cell fate regulators, increased levels of the tumor suppressor $p16^{Ink4a}$ in Bmi1-deficient mice lead to reduced self-renewal and depletion of NSCs early in postnatal life, mimicking its function during ageing [159, 160]. Multiple pathways converge on the regulators of the cell cycle progression which might represent key switches governing NSC fate choices.

Crosstalk between cell cycle components and extracellular signals

It is tempting to speculate that specific molecular components that control cell cycle progression in neural progenitors might be directly associated with the factors that govern NSC self-renewal, longevity and differentiation potential. This is elaborated in neural progenitors, where p107 binds to the promoter and elevates the expression of *Notch1* resulting in increased Notch activity in adult derived neuro-

spheres *in vitro* [149]. Activation of Notch signaling in the adult spinal cord in response to injury induces proliferation linking environmental signals to cell cycle progression [161]. In muscle stem cells (MSCs), Notch signaling is also implicated in the control of CDKI expression. It inhibits the expression of p15^{Ink4b}, p16^{Ink4a}, p21$^{cip1/waf1}$ and p27 ^{Kip1} induced by the inhibition of TGFβ-dependent Smad3 activity [162]. In contrast to embryonic neurogenesis, decreased levels of Notch signaling in MSCs of aged mice leads to a loss of proliferative and regenerative capacity rather than precocious differentiation [163]. In a reciprocal pathway, p16^{Ink4a} has been implicated in the inhibition of Hes1, a target of Notch signaling [164]. It will be interesting to further investigate the role of Notch signaling and other pathways in the regulation of the NSC cell cycle.

Conclusions and perspectives

NSCs persist in the adult mammalian brain throughout life and generate functional neurons. The proliferation and differentiation of the neural progenitors is governed by multiple signaling mechanisms provided by the specialized microenvironment of the niche. The striking regenerative capacity of NSCs raises hopes for therapy for multiple degenerative disorders including stroke, Parkinson's, Huntington's and Alzheimer's disease. Correct generation and manipulation of specific neuronal subtypes require extensive understanding of the identity of different neural progenitor populations and the signals that govern their fate. Although the presence of NSCs is accepted, whether a single population of aNSCs exist *in vivo*, or multiple functionally distinct populations constitute the endogenous pool remains to be substantiated. It is, however, of critical importance to elucidate the lineage potential of NSCs using *in vivo* experimental paradigms.

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