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Glial influences on neural stem cell development: cellular niches for adult neurogenesis

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Neural stem cells continually generate new neurons in very limited regions of the adult mammalian central nervous system. In the neurogenic regions there are unique and highly specialized microenvironments (niches) that tightly regulate the neuronal development of adult neural stem cells. Emerging evidence suggests that glia, particularly astrocytes, have key roles in controlling multiple steps of adult neurogenesis within the niches, from proliferation and fate specification of neural progenitors to migration and integration of the neuronal progeny into pre-existing neuronal circuits in the adult brain. Identification of specific niche signals that regulate these sequential steps during adult neurogenesis might lead to strategies to induce functional neurogenesis in other brain regions after injury or degenerative neurological diseases.

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Current Opinion in Neurobiology 2005, **15**:514–520

This review comes from a themed issue on
Neuronal and glial cell biology
Edited by Fred H Gage and A Kimberley McAllister

Available online 6th September 2005

0959-4388/$ – see front matter

DOI 10.1016/j.conb.2005.08.003

Introduction

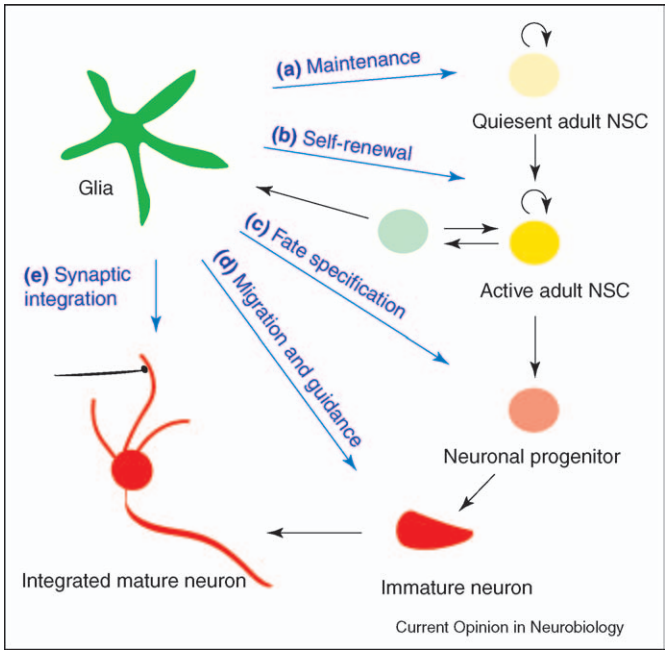
Neurons in the mammalian central nervous system (CNS) are generated from neural stem cells (NSCs) primarily before birth [1,2]. Traditionally regarded as an inhibitory environment for neuronal regeneration, it was believed for a long time that neurogenesis did not take place in the adult CNS, with gliogenesis occurring only in certain circumstances [3]. Since Altman's initial findings in the 1960s [4], however, active adult neurogenesis has now been unambiguously confirmed in two discrete CNS regions of almost all mammals examined: the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus [5–8]. Newly generated neurons exhibit striking abilities to migrate and integrate into pre-existing neuronal circuits in the adult CNS environment and contribute to specific brain functions [6–10]. Interestingly, cells with NSC properties also appear to reside in many other adult CNS regions where neurogenesis occurs rarely, if at all, under unperturbed conditions [6–8]. The neurogenic potential of these apparently dormant NSCs has been demonstrated in culture, after transplantation in neurogenic brain regions (fetal brains, adult SGZ or SVZ), and *in situ* after injury [7,8]. Adult neurogenesis exemplifies an unforeseen regenerative capacity of the mature mammalian CNS and raises an intriguing question: why is active neurogenesis only retained and restricted to limited regions in adult mammals?

The idea that somatic stem cells reside within specific anatomical locations termed 'niches' was first suggested on the basis of transplantation studies of hematopoietic progenitors in the 1970s [11]. Recent studies in several model systems, such as *Drosophila* germline and mammalian skin, intestine and bone marrow, have provided cellular and functional descriptions of niches as microenvironments that not only anatomically house stem cells but also functionally control their development *in vivo* [12]. In the adult mammalian brain, we are just beginning to identify the cellular and molecular elements that characterize the neurogenic niches in the SVZ and SGZ, and the mechanisms by which the full range of adult NSC development is regulated (Figure 1). Here, we review recent advances in understanding the extrinsic mechanisms that regulate adult neurogenesis in the neurogenic niches. Several of the key components of neurogenic niches, including vascular structures [13] and extracellular matrix [14], have been previously reviewed, and we focus our discussion on the special roles of glia. Several recent reviews on adult neurogenesis can also be consulted [5–8,15–17].

Potential roles of astroglia in the neurogenic niches for adult neurogenesis

Traditionally regarded as supporting cells, astrocytes are abundant in the adult CNS and structurally and functionally poised as ideal sensors and regulators of local microenvironments [18]. Emerging evidence suggests that astrocytes perform a much wider range of functions than previously appreciated, such as regulation of axon guidance, synapse formation and plasticity [18,19]. Interestingly, astrocytes from the neonatal brain were also shown to increase neurogenesis from cultured adult SVZ NSCs [20]. In addition, astrocytes derived from the adult hippocampus, but not from the adult spinal cord, promote neurogenesis from adult hippocampal NSCs in co-culture by increasing proliferation and instructing neuronal fate specification [21]. Consistent

Figure 1



Schematic view of adult NSC development and its regulation by glia. The cell lineage begins from the quiescent adult NSCs (light yellow), to active adult NSCs (yellow), glial (green) and neuronal (red) progenitors and to mature neurons and glia. Multiple aspects of adult NSC development are probably regulated by glia: **(a)** stem cell maintenance, **(b)** activation and self-renewal, **(c)** neuronal fate specification, neuronal maturation, **(d)** migration and nerve guidance, and **(e)** synaptic integration.

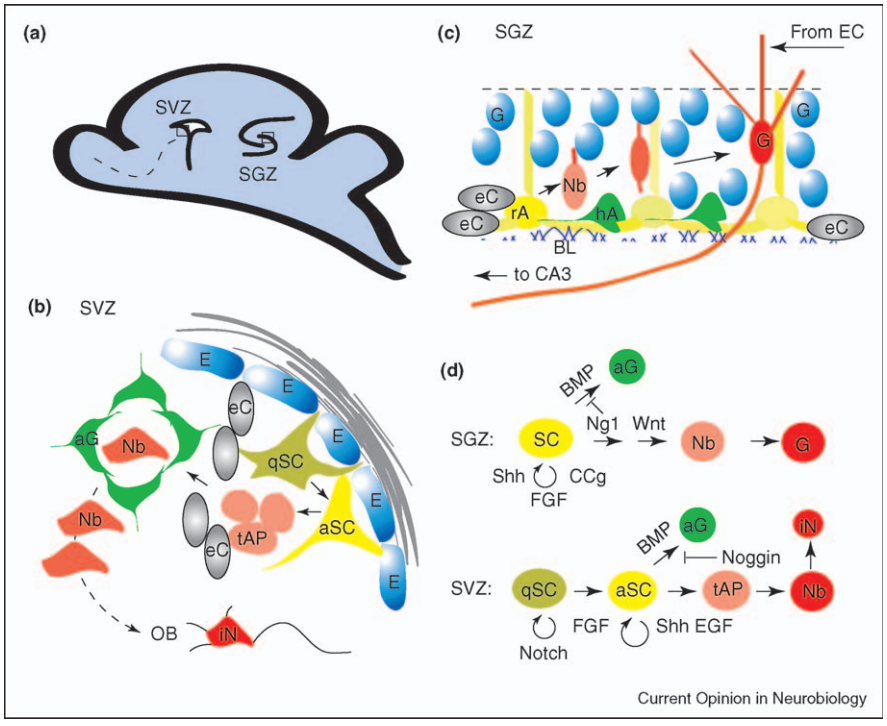
with the *in vivo* observation that neurogenesis decreases with age, neonatal hippocampal astrocytes are also more efficient than their adult counterparts in promoting neurogenesis. This apparent developmental and regional specificity of astrocytes in promoting neurogenesis from adult NSCs suggests the intriguing possibility that neuronal production in the adult brain is regulated, at least in part, by distinct properties of local astrocytes. Furthermore, hippocampal astrocytes also promote the neuronal maturation and synapse formation of adult NSC-derived neurons [22,23]. These *in vitro* findings, together with the unique involvement of astrocytes in the organization of local environments for adult NSCs *in vivo* ([24,25•]; and see below), suggest that astrocytes are a key component of the neurogenic niches, providing both structural support and instructive signals for adult neurogenesis. Below we summarize the roles of astrocytes in regulating multiple aspects of adult neurogenesis (Figure 1), and discuss how glia, as niche cells, might regulate adult NSC development at the molecular level.

Cellular niches for NSCs and neurogenesis in adulthood

The cell types, lineage, and architecture of the germinal zones in the adult SVZ and SGZ have been extensively studied [5,15,24,25•,26]. Current evidence suggests that some stem cells in these neurogenic regions retain attributes reminiscent of radial glia and would be identified as astrocytes by their morphological and histological characteristics, yet the true identities of adult NSCs still remain controversial [27–29]. In accordance to the general stem cell lineage, primary NSCs in the adult SVZ transit from quiescent to active state (qSC and aSC) and give rise to migratory neuroblasts (Nb) through transient-amplifying progenitors (tAP; Figure 2b; [5,15]). The radial glia-like astrocytes express glial fibrillary acidic protein (GFAP), but not s-100β, both of which are astrocyte markers; thus, they might represent a unique astrocytic population in the SVZ. The bona fide astrocyte, expressing both GFAP and s-100β, also constitute essential components of the local environment, keeping in close contact with all other cell types in the adult SVZ. Notably, a large population of astrocytes forms a glial tunnel that guides the migration of neuroblasts through the rostral migratory stream (RMS) to the olfactory bulb (Figure 2b). Considering the heterogeneity and complexity of astrocytes, it remains to be determined whether the same type of 'astrocytic' cells function simultaneously as stem cells and cells that constitute part of the neurogenic niche or if these two roles are temporally and/or spatially segregated.

In the SGZ of the dentate gyrus, at least two types of $GFAP^+$ astrocytes have been characterized: 'horizontal' and 'radial' astrocytes (hAs and rAs, Figure 2c) [25•,30]. hAs extend highly branched processes along the border of SGZ and do not express nestin, a marker for immature

Figure 2



Cellular niches and molecular regulators of adult NSCs and neurogenesis. **(a)** Sagittal view of two germinal regions (SVZ of forebrain and SGZ of the hippocampal dentate gyrus) that generate neurons throughout adult life in mammals. **(b)** In the SVZ, primary stem cells transit from a quiescent state (qSC) to an active state (aSC) and give rise to transient-amplifying progenitors (tAP), which in turn differentiate into neuroblasts (Nb). Neuroblasts migrate within a tunnel formed by astroglia (aG) to the olfactory bulb where they differentiate into interneurons (iN). Ependymal cells (E) demarcate the ventricular boundary for the SVZ niche. Abbreviations: eC, endothelial cell; hA, horizontal astrocyte. **(c)** In the SGZ, new neurons are generated from radial astrocytes (rA) expressing GFAP and nestin. In close contact with rAs and other types of astrocytes, the new-born neuroblasts (Nb) migrate for a short distance and mature into granule neurons (G). Granule neurons receive synaptic inputs from the entorhinal cortex (EC) and project axons to the hilus regions and the CA3 region. The lattice structure represents basal lamina (BL) and endothelial cells (eC) posit close to radial astrocytes (rAs). **(d)** Lineage hierarchy of adult neurogenesis and its molecular regulators from glia. Notch probably functions to maintain the stem cell state. FGF signaling might activate quiescent stem cells and maintain self-renewal of the active NSCs. A plethora of glia-derived BMP antagonists (Noggin, Ng1, CCg) and Wnts, among others, promote neuronal differentiation of adult NSCs, whereas EGF and Shh function to amplify the adult NSC and progenitor pool.

progenitors; thus, they represent traditional astroglia. In comparison, rAs possess prominent radial projections into the granule cell layer and thin lateral processes intercalating nearby granule neurons. Many proliferative rAs are found to be in close proximity to blood vessels. A subset of rAs express nestin and probably function as stem cells that give rise to neuroblasts and eventually to new granule neurons [30]. Serial-section reconstructions by electron microscopy showed that SGZ astrocytes harbor extensive basal processes and form basket-like structures that cradle the clustered neuroblasts [25•]. Some of the neuroblasts generated from rAs send out apical neurites and migrate along the prominent radial processes of rAs.

The recurring theme in the organization of both the adult SVZ and the adult SGZ is that astrocytes are intimately associated with differentiating immature neurons and are functionally diversified to behave as niche cells and/or stem cells. The possible dual functionality of astrocytes as niche and/or stem cells presents an intriguing anatomical feature that might facilitate the construction and operation of the niche. In addition to providing structural support, astrocytes are known to express secreted and membrane-associated molecules, including cytokines, growth factors, and neurotransmitters, in response to physiological and pathological stimuli [31,32]. Astrocytes are also well suited to integrate local environmental signals because of their unique syncytium structure formed via gap junctions between astrocytes, through which intercellular signaling might propagate [33].

Naturally coupled to astrocytes through astrocytic endfeet, endothelial cells are also important components of the niche structure and maintain close coordination with astrocytes to regulate adult neurogenesis [34,35•]. *In vivo* studies showed that proliferation hot spots in the SGZ are concentrated around blood vessels [34]. In accordance, endothelial cells greatly promote self-renewal of fetal

NSCs in co-culture [35•]. Surprisingly, adult NSCs might even 'differentiate' into the endothelial lineage *in vitro* [36•]. These findings highlight the complexity of cellular interactions within the niche and raise the intriguing possibility that adult NSCs are not only regulated by their niche but also, when necessary, able to populate their niche with glial and endothelial cells, forming a likely unitary ensemble for local adult neurogenesis.

Regulation of adult NSC proliferation and cell fate specification

Adult neurogenesis is dynamically regulated by many physiological and pathological stimuli [6,7]. Thus, the niche must be able to coordinate events including stem cell activation, self-renewal and differentiation in response to varying conditions [12]. Recent studies suggest that these processes are under a complex, yet stringent control of a multitude of molecular signals [6] (Figure 2d).

Stem cell maintenance and self-renewal are probably coordinated by Notch and mitogen signaling [37]. Gain-of-function of Notch signaling in postnatal SVZ cells leads to the accumulation of stem-like cells and abolishes precocious neurogenic events including neuronal differentiation and migration [38]. Once maintained, the quiescent stem cells might require mitogen signaling to engage a state of self-renewal. Several mitogens, including fibroblast growth factors (FGFs), sonic hedgehog (Shh), and ligands of the epidermal growth factor (EGF) receptor family are able to propagate adult NSCs in culture and appear to perform similar functions *in vivo* [39–42,43•]. Though the exact *in vivo* source of these mitogens remains to be fully characterized, astrocytes are known to express at least several FGFs [44] and Notch ligands [45]. Interestingly, in the rodent hippocampus, the fraction of FGF-2-synthethizing astrocytes, but not the total number of astrocytes, declines along with the decreased neurogenesis during aging [44]. Initially identified as an FGF-2 co-factor, Cystatin C (CCg) is expressed by adult NSCs and astrocytes [46]. CCg might function with FGF-2 to increase adult NSC proliferation and to modulate neurogenesis by counteracting TGF-β signaling [47] and/or mobilizing endogenous transposable elements [48•]. Although most studies focused on individual molecules, it should be emphasized that niche signals are highly complex; developmentally coupled events and extensive signaling crosstalk must be implemented to ensure the exquisite process of neurogenesis. Different mitogens might exert different influences on or function in different stages of NSC development. It remains to be examined precisely how various factors in the niche choreograph stem cell maintenance and self-renewal.

The neurogenic signals for adult NSCs are just beginning to be identified (Figure 2d). *In vitro* studies showed that activation of Ca^{2+} channels and NMDA receptors in adult NSCs profoundly biases their fate towards neuronal specification, suggesting an important role of Ca^{2+} signaling in neurogenesis [49]. Recent studies showed that sFRP3, a Wnt inhibitor expressed in the adult dentate gyrus, partially blocks astroglia-induced neurogenesis of adult NSCs, whereas Wnt3 promotes neurogenesis of adult NSCs [50••]. Manipulation of Wnt signaling *in vivo* by over-expressing Wnt3 or a Wnt inhibitor in the dentate gyrus leads to enhanced or diminished adult neurogenesis, respectively. These studies identified astroglia-derived Wnt signaling as a key pathway to promote neurogenesis of adult NSCs. By contrast, signaling from the bone morphogenic protein (BMP) family instructs adult NSCs to adopt a glial fate [51,52]. In the SVZ, adult NSCs express both BMPs and their receptors; thus, adult NSCs might adopt a 'default fate' as astrocytes [51]. Ependymal cells, which are considered to be another type of glia, secrete the BMP antagonist Noggin and divert stem cells from glial to neuronal fate. Recently, neurogenesin-1 (Ng1), a novel secreted factor from astrocytes, was found to promote neuronal differentiation of adult NSCs by preventing the adoption of a glial fate by antagonizing BMP signaling [53]. Given the abundant expression of Ng1 by astrocytes in the adult SGZ [53], Ng1 might also modulate adult neurogenesis *in vivo*. It is interesting to note that the majority of currently identified neurogenic factors are associated with a specific population of local astrocytes in the SVZ and SGZ, implicating their specific roles in instructing neurogenesis of adult NSCs in the niche.

Regulation of neuronal migration and nerve guidance

In the adult rodent SVZ, a chain of neuroblasts migrate anteriorly along the RMS to the olfactory bulb through a tunnel formed by astrocytes (Figure 2b; [6]). Here, astrocytes play multiple roles, first creating a physical route for the neuronal migration, and second communicating with the migrating neurons and regulating their speed of migration. Electrophysiological analysis showed that migrating neuroblasts express functional $GABA_A$ receptors and respond to ambient GABA in the RMS [54••]. Through GABA transporters, astrocytes control the amount of local GABA and regulate the migration speed of neuroblasts. Surprisingly, the RMS structure that supports neuronal migration, in mammals from rodents to primates, does not appear to exist in adult humans [55•], raising the perplexing question of whether niches and NSC development in the human SVZ are fundamentally different from those in other mammals.

In the SGZ of adult hippocampus, newborn neurons migrate locally and closely along the radial processes of rAs [25•], reminiscent of the classic mode of radial migration in the developing cortex. These new neurons extend dendrites into the outer molecular layer and project their axons to the CA3 region of the hippocampus (Figure 2c).

Immunoelectron microscopic studies have revealed that astrocytic radial processes direct the bidirectional dendritic and axonal outgrowth of newborn neurons by providing a scaffold and perhaps also by supplying signaling factors [56].

The molecular cues for directed migration and nerve guidance of the newborn neurons from adult SVZ and SGZ are less well understood [6]. Given the characterized roles of glia in controlling these events during early development [57], we might anticipate that many developmental regulatory pathways retain their functionality in the adult neurogenic niches [6]. Indeed, the glia-derived guidance cue Slit plays composite roles in shaping the directionality of neuroblast chain migration in the RMS during development and adulthood [58,59]. In addition to Slit, astrocytes appear to release another unknown factor(s) to induce repulsive neuronal migration from SVZ explants [60].

Regulation of neuronal maturation and synaptic integration

Newborn neurons must eventually integrate into the preexisting neuronal circuitry in order to contribute to specific brain functions [6,9]. In the mature CNS, astrocytes are tightly associated with synapses and regulate synaptic transmission [61,62••]. Emerging evidence suggests that astrocytes also regulate synapse formation and maintenance in the context of functional and structural plasticity [61,62••]. In co-culture experiments, adult hippocampal astrocytes were shown to promote functional maturation and synaptic integration of neural progeny of the adult hippocampal NSCs [22]. The astrocyte-derived synaptogenic factors for newborn neurons in the adult brain remain to be identified. It has been shown that activity-dependent neurotrophic factor, a protein secreted by vasoactive intestinal polypeptide-stimulated astrocytes, promotes functional maturation and synaptogenesis of embryonic hippocampal neurons in culture [63]. Recently, astrocyte-derived Thrombospondins (TSP) -1 and -2 have been shown to induce synapse assembly by retinal ganglion cells [62••]. Given the high level of expression of TSP-4 in the adult dentate granular cell layer [64], it would be interesting to examine whether TSPs also modulate synaptogenesis of newborn neurons from adult NSCs. Furthermore, neurotransmitters and various ion fluxes during neuronal maturation are under the subtle control of glia in modulating the type of synapses to be formed and spatial or temporal aspects of synaptogenesis [19,65,66]. In addition to secreted factors from astrocytes, integrin signaling contributes to the synaptogenic effects via cell–cell contact between astrocytes and immature neurons [67].

Conclusions

The existence of functional adult neurogenesis demonstrates a striking regenerative capacity of the adult mammalian CNS. Astrocytes have emerged as key components in the neurogenic niche for adult neurogenesis. Together with other niche components, including basal lamina [14] and vasculature [34], astrocytes provide the structural basis to house adult NSCs and support their development. Probably of more importance, astrocytes might also function as key sensors of local environmental changes and subsequently provide instructive signals to regulate different aspects of adult neurogenesis. A daunting yet fascinating question is how NSCs in the niche integrate extrinsic signals, including those from glia, with intrinsic genetic programs to make distinct developmental decisions. The functions of astrocytes are likely to be diverse, ranging from being stem cells themselves to being regulators of various neuronal developmental steps. Because the differential properties of local astrocytes might underlie the neurogenic potentials in different adult CNS regions, understanding the mechanisms of astrocytic regulation of adult neurogenesis might, therefore, lead to strategies for induction of neurogenesis in diverse CNS regions after injury or degenerative neurological diseases.

Acknowledgements

We would like to thank F Gage, N Gaiano, X Zhao, F Doetsch and members of Song and Ming laboratories for critical comments. Research in our laboratories is supported by the National Institutes of Health (NINDS and NIA) and a Klingenstein Fellowship Award in the Neuroscience to H Song, and by NINDS, a Charles E. Culpeper Scholarship in Medical Science, the Whitehall Foundation, the March of Dimes, an Alfred P. Sloan Research Fellowship and a Klingenstein Fellowship Award in the Neuroscience to G-l Ming. DK Ma is partially supported by a pre-doctoral fellowship from the American Heart Association.

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