New roles for astrocytes: The nightlife of an ‘astrocyte’. La vida loca!

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Like a newly popular nightspot, the biology of adult stem cells has emerged from obscurity to become one of the most lively new disciplines of the decade. The neurosciences have not escaped this trendy pastime and, from amid the noise and excitement, the astrocyte emerges as a beguiling companion to the adult neural stem cell. A once receding partner to neurons and oligodendrocytes, the astrocyte even takes on an alter ego of the stem cell itself (S. Goldman, this issue of TINS). Putting ego aside, the ‘astrocyte’ is also (and perhaps more importantly) an integral component of neural progenitor hotspots, where the craziness or ‘la vida loca’ of the nightlife might not be so wild when compared with our traditional understanding of the astrocyte. Here, astrocytes contribute to the instructive confluence of location, atmosphere and cellular neighbors that define the daily ‘vida loca’ or everyday local life of an adult stem cell. This review discusses astrocytes as influential components in the local stem cell niche.

In development, neuroepithelial stem cells of the ventricular zone produce the majority of the neurons and glia present in the newborn brain. As development nears completion, stem cell activity switches to the distinct and relatively restricted patterns of activity present throughout adult life. In the unperturbed brain, this activity yields two end products: gliogenesis, which persists throughout the CNS, and neurogenesis, which is restricted to the olfactory bulb and hippocampus. There appears to be considerable overlap in the cells and signals that mediate gliogenesis versus neurogenesis and discrimination between these two outcomes could, in part, rest in the hands of the local astrocyte. Distinguished by their expression of glial fibrillary acidic protein (GFAP), astrocytes could contribute to cell genesis both as the stem cells themselves and as an influential component of the gliogenic or neurogenic stem cell niche.

In the adult brain, dividing cells are antigenically distinct in different regions. For example, in white and gray matter, the predominant dividing cell is immunoreactive for NG2, O4, and/or A2B5 – early ganglioside markers for glial progenitors [1–5]. The use of these markers as indicating glial commitment is a distinction earned primarily from the well-documented fact that these cells generate only glia in vivo. However, these same glial progenitors can produce neurons if their environment is sufficiently altered [6–9]. These data form a tantalizing premise that the brain is divided into zones or ‘niches’ that control cell fate decisions and not the other way around. This article discusses the various guises that stem-like cells don within an instructive niche and contrasts the varying roles of ‘astrocytes’ within these niches.

As reviewed by Steve Goldman in this issue of TINS, the concept of glia as stem cells has gained considerable weight with the observation that cortical neurogenesis is mediated by radial glia within the early ventricular zone [10–12]. The production of neurons slowly turns into the production of glia in a temporal and region-specific manner [13]. Near birth, neurons and glia are simultaneously produced and the migrating stem cell progeny are antigenically distinct [14] and show clear differential migration depending on the lineage chosen [15,16]. In the adult, stem cells that remain in the subventricular zone retain attributes that are reminiscent of radial glia and under most circumstances would be identified as astrocytes in histological evaluation [12]. But it is likely that the cells that are generically labeled as GFAP-positive astrocytes are diverse. For example, Filippov and colleagues evaluated nestin-positive precursors within the hippocampus and found that ‘progenitors’ within the subgranular zone can be divided into two categories: those that display traditional astrocyte properties (i.e. GFAP immunoreactivity, passive currents under patch-clamp conditions, and a process-bearing morphology, some of these processes forming vascular endfeet) and a putative actively dividing progenitor pool that expresses nestin but not astrocytic passive currents or GFAP [17]. Although many of the relatively quiescent nestin-positive process-bearing cells are GFAP positive, none are positive for the astrocytic marker S100β that is common to neighboring astrocytes. The implication is that the term ‘astrocyte’ in the context of stem cells might not be sufficient to distinguish the roles of GFAP-positive cells as stem cells versus their role as traditional S100β-positive astrocytes or as ‘instructor’ cells within a stem cell niche.

When considering stem cells within various niches of the adult brain, it is clear that patterns of cell behavior and fate correlate strongly with changes in antigenic phenotype. Early patterning events within stem cell progeny orchestrate this segregation and, if left unperturbed,
Astrocytes express S100 protein. Labeling studies in the adult spinal cord indicate that astrocytes divide in glial-restricted zones [28,29]. Acute mitotic inhibition becomes primarily a local phenomenon (rather than via migration of progenitors from the subventricular zone [16]). With local production of glioma, also come regional differences in the type of glia produced. Subcortical white matter progenitor cells produce primarily oligodendrocytes whereas spinal cord progenitors produce similar numbers of astrocytes and oligodendrocytes [18,19]. So not all gliogenic zones are created alike and most are likely to serve specialized functions based on the territory they occupy.

Before discussing components of the glial niche, it is important to understand that gliogenic zones are instructive and not a passive vessel for pre-programmed progenitors. When epidermal growth factor (EGF) is infused directly in the cortex, progenitor cells are re-directed from the rostral migratory stream and migrate into cortical layers [24,33]. Despite the fact that these progenitor cells have neurogenic capacity and do form neurons in the olfactory bulb, they do not form new neurons in the cortex when diverted. Similarly, the adult spinal cord contains progenitor cells that have neurogenic capacity in vitro but these cells do not spontaneously generate neurons when reintroduced in to the intact spinal cord [34].

Astrocyte cell division and the gliogenic niche
So what are the progenitor cells of the gliogenic niche? First, it is important to note that traditional astrocytes divide in glial-restricted zones [28,29]. Acute mitotic labeling studies in the adult spinal cord indicate that astrocytes express S100β during S-phase and comprise ~5% of all dividing cells [19]. Although progenitors that produce both astrocytes and oligodendrocytes have been demonstrated in classic in vitro experiments [35,36], it is not clear how astrocytes are generated in vivo. Key questions remain. Do traditional astrocytes divide from immature progeny or are they themselves gliogenic progenitors or even stem cells (Figure 1)? As will be discussed, this question has been explored in neurogenic zones of the brain but has not to date been adequately addressed in the gliogenic brain.

The most prominent component of the gliogenic niche is the common glial progenitor cell, which does not bear resemblance to an astrocyte. Glial progenitor cells express A2B5 antigen, platelet-derived growth factor (PDGF) receptor a and Nkx2.2 at early stages of commitment [1]. It has been thought that when glial progenitor cells become restricted to an oligodendrocyte fate they upregulate the markers NG2, proteolipid protein (PLP) and O4, among others [2,3]. Importantly, these glial progenitors continue to divide in the adult brain and spinal cord [3,19] and comprise as many as 70% of all dividing cells in the adult CNS. Within a month of undergoing S-phase, a small subset of the NG2 progenitors (~2.5%) downregulate NG2 and begin to express mature oligodendrocyte proteins [37]; however, most NG2 cells remain as pre-oligodendrocytes [4,38]. Although cell division in the adult gliogenic niche is reduced when compared with the postnatal peak of myelination, the birth of new glia, including astrocytes, remains significant.

Traditional astrocytes and their instructive role in gliogenic niches
What role then might traditional GFAP-positive astrocytes play within the glial progenitor niche? The adult glial-instructive microenvironment is still largely unexplored but there are clues from development and injury that might shed light on the adult niche and a potential instructive role for astrocytes, such as the temporal and spatial production of growth and/or trophic factors. Glial progenitors are produced by a sequence of events starting early in development. Sonic hedgehog (Shh) is initially necessary to prime stem cells to become competent to generate oligodendrocytes [39]. Later, leukemia inhibitory factor, ciliary neurotrophic factor and bone morphogen protein-4 (BMP4) become inducers of astrocytic fate, while fibroblast growth factor (FGF)-2 and thyroid hormone induce an oligodendrocyte fate [1]. Subsequently, the Shh responsiveness of glial progenitors diminishes and the oligodendrocyte progenitor becomes responsive to PDGF [40]. Concurrent signaling from neighboring neurons involves neuregulins (NRGs), which amplify the number and solidify the commitment of oligodendrocytes, depending upon the neuregulin-receptor components expressed by the progenitor [41]. For the glial progenitor, timing of cell division and commitment to myelinate is crucial for producing the appropriate number of myelinating cells. During development, this timing is programmed locally and varies from region to region [42]. Cell cycle and commitment encoding is directed by astrocytes through the release of PDGF during postnatal gliogenesis [35,43]. This developmental correlate suggests that astrocytes could play an important role in the gliogenic niche by...
Astrocytes could play a crucial role in altering the fate of injury or disease. The specific developmental status of the progenitor cell, as well as the status of the local astrocyte, then becomes important in defining outcome.

The traditional astrocytes remain competent to divide. They also provide local instructive signals to resident stem and/or progenitor cells and can synthesize many ligands known to influence oligodendrocyte or neuron proliferation and maturation. Thus, traditional astrocytes can actively control whether a local niche is neurogenic or gliogenic by organizing many of the signals that support neuronal or glial fate choices in stem cells. Neurogenic astrocytes are found in neurogenic regions, such as the granule cell layer of the hippocampus (green) where they promote maturation of the neuronal progenitor cells and immature neurons (blue). Astrocytes in gliogenic zones (gray) potentially suppress neurogenesis in favor of the recruitment and maturation of oligodendrocyte progenitors and immature oligodendrocyte (red). The exact lineage transitions between the putative astrocyte stem cell and the more committed progenitors are not well understood in vivo (dashed arrows). The exact instructive or selective molecules expressed by the astrocyte in the respective gliogenic or neurogenic niches also remain unknown but it is clear that signaling is regionally specialized and influences location-specific stem cell fate. Commonly considered candidates for the molecular and cellular substrates of instructive niches are listed in the indicated boxes but there is much to be learned. Traditional astrocytes and astrocytes with stem cell qualities represent new players in these niches but there are many other contributors, including the immune system, that remain to be fully appreciated. Unraveling the components that control 'la vida local' or the local environment of a neurogenic niche holds hope for deciphering the code of neural cell replacement in health and disease. Abbreviations: BMP, bone morphogenetic protein; EGF, epidermal growth factor; FGF-2, fibroblast growth factor 2; IGF-1, insulin-like growth factor 1; PDGF, platelet-derived growth factor; Shh, sonic hedgehog; TGFα, transforming growth factor α; VEGF, vascular endothelial growth factor.

Figure 1. Astrocytes of the adult CNS play two potential roles in the production of newborn glia and neurons. In a novel role for the astrocyte, cells that express the astrocytic marker glial fibrillary acidic protein can take on the role of the stem cell itself and produce both neurons and glia. Astrocytes do remain mitotically active and it is difficult to distinguish clearly between the stem cell 'astrocyte' (purple) and the differentiated astrocytes (A), which play a more traditional role in blood–brain barrier function and mediate a variety of local metabolic and neuronal signaling functions. Unlike most differentiated neural lineage cells, such as neurons and oligodendrocytes, the traditional astrocytes remain competent to divide. They also provide local instructive signals to resident stem and/or progenitor cells and can synthesize many ligands known to influence oligodendrocyte or neuron proliferation and maturation. Thus, traditional astrocytes can actively control whether a local niche is neurogenic or gliogenic by organizing many of the signals that support neuronal or glial fate choices in stem cells. Neurogenic astrocytes are found in neurogenic regions, such as the granule cell layer of the hippocampus (green) where they promote maturation of the neuronal progenitor cells and immature neurons (blue). Astrocytes in gliogenic zones (gray) potentially suppress neurogenesis in favor of the recruitment and maturation of oligodendrocyte progenitors and immature oligodendrocyte (red). The exact lineage transitions between the putative astrocyte stem cell and the more committed progenitors are not well understood in vivo (dashed arrows). The exact instructive or selective molecules expressed by the astrocyte in the respective gliogenic or neurogenic niches also remain unknown but it is clear that signaling is regionally specialized and influences location-specific stem cell fate. Commonly considered candidates for the molecular and cellular substrates of instructive niches are listed in the indicated boxes but there is much to be learned. Traditional astrocytes and astrocytes with stem cell qualities represent new players in these niches but there are many other contributors, including the immune system, that remain to be fully appreciated. Unraveling the components that control 'la vida local' or the local environment of a neurogenic niche holds hope for deciphering the code of neural cell replacement in health and disease. Abbreviations: BMP, bone morphogenetic protein; EGF, epidermal growth factor; FGF-2, fibroblast growth factor 2; IGF-1, insulin-like growth factor 1; PDGF, platelet-derived growth factor; Shh, sonic hedgehog; TGFα, transforming growth factor α; VEGF, vascular endothelial growth factor.

Astrocytes and the control of gliogenesis in pathology

Injury or disease is one area where the traditional astrocyte could play a crucial role in altering the fate of a glial progenitor cell. Disease or injury induces traditional astrocytes to assume a new role in 'la vida de la lesion', releasing a barrage of cytokines including interleukin-6 (IL-6) [48,49]. IL-6 might not modulate only the immune response to injury but also the fate choice of immature progenitor cells to become astrocytes. Astrocytes also release NRGs in response to injury [50]. Depending on the erbB-receptor components of surrounding progenitors, astrocyte-derived NRG can signal proliferation or commitment in the oligodendrocyte lineages. Reactive astrocytes also increase expression of vascular endothelial growth factor (VEGF) and FGF-2, which are potent amplifiers of progenitor proliferation [51,52]. Of course, the function of a single cytokine can be difficult to establish because their effects are pleiotropic and their appearance can resemble that of a mixed soup of injury-derived factors. However, the temporal nature of these cues, as well as the phenotype and capacity of endogenous progenitors to respond to these cues, will provide important insight into how astrocytes might orchestrate gliogenesis and neurogenesis following...
injury or following attempts to utilize stem and/or progenitor cell transplants for repair.

**Astrocytes and the neurogenic niche**

*Gliogenesis and neurogenesis: intrinsic versus environmental control of stem cell fate*

Unlike the abundant and widespread production of oligodendrocytes, neurogenesis in the naïve rodent brain is restricted to the hippocampus and olfactory bulb. The actively dividing precursors that produce glia are antigenically distinct from those that generate neurons and this lineage dichotomy is established well before stem cell progeny acquire the lineage-specific markers of myelin basic protein, GFAP or type III β-tubulin [14]. This suggests that commitment to an eventual fate begins before cells exit the cell cycle but, in spite of the phenotypic dichotomy, this early patterning in adult gliogenic regions can be reversible when cells are removed from the local environment [6–9]. Cells long thought to be ‘glial’ or oligodendrocyte progenitors are readily converted to (or selected for) stem cells, which go on to make neurons in primary culture or following transplant into a neurogenic zone of the adult brain [34]. This suggests that there is a window of commitment in which local environment plays a larger role in determining cell fate than does the intrinsic expression patterning of the precursor genome.

As an alternative to their stem cell role, GFAP-positive cells (presumably ‘traditional’ astrocytes) participate in the creation of an instructive niche that influences the fate of stem cell progeny. Astrocytes isolated from the hippocampus (but not those from spinal cord) promote stem-cell-mediated neurogenesis in culture, suggesting that astrocytes can take on region-specific instructive or selective roles in promoting neurogenesis or gliogenesis [53,54]. In addition, once immature neurons are produced, astrocytes further instruct newborn cells to form functional synapses [55]. Astrocytes are an important component of this instructive niche but are unlikely to act alone in this role.

The architecture of the subventricular zone and hippocampus provide evidence that GFAP-positive cells are in intimate contact with the newly generated neuronal precursors [56,57] and, although astrocytes can provide a myriad of signals that could be instructive, it appears that simple cellular contact with an astrocyte (even with a dead astrocyte [54]) is sufficient to provide the neurogenesis-promoting effects measured in stem cell cultures. This raises the concept that fate choice depends on a location-specific profile of soluble growth and/or trophic factors, as well as on an appropriate local environment consisting of extracellular matrix and/or cell-membrane-anchored ligands.

**Vasculature and the neurogenic niche**

Within the adult hippocampus, the neurogenic microenvironment takes on an intriguing format that suggests a specific role for astrocytes as well as vascular cells in the immediate locale of the dividing neural progenitor. Although the location of stem cells within the hippocampus is debatable [33,56,58], their progeny manifests as a transient amplifying pool of progenitor cells that divide in tight foci that form along the walls of small capillaries. Astrocytes and their vascular endfeet form a local niche that envelops the dividing precursors. After a brief expansion within this niche, the proliferative cells begin to express neuronal progenitor markers and subsequently migrate from the proliferative foci to take up residence as maturing neurons within the adjacent granule cell layer [59–61]. Coincidently, endothelial cells also proliferate at the site of focal progenitor recruitment, suggesting that an angiogenic stimulus accompanies the early proliferative stage of neurogenesis. Although not yet directly demonstrated in mammals, elegant data demonstrate a role for angiogenesis in the seasonal production of higher vocal center neurons in canaries [62], and infusion of the potent angiogenic factor VEGF upregulates neurogenesis in rodents [63]. Not only might an angiogenic factor stimulate a change in signaling within the vascular microenvironment but also neural progenitors might themselves proliferate in response to VEGF [63,64].

**The role of cell ‘status’ in defining the instructive influence of a stem cell niche**

Astrocytes and vasculature cells are widespread in the adult brain, yet neurogenesis clearly does not occur in every instance where an astrocyte and blood vessels coincide. Just as developmental patterning regulates regional cell fate choice, the adult brain must also establish subtle distinctions in gene expression patterns within an otherwise ubiquitously distributed instructive cell population. When the potential role of astrocytes in the hippocampal neurogenic niche is considered with both adjacent granule cell layer and vascular signaling in mind, one derives several interesting possibilities suggesting that a confluence of events creates a uniquely activated population of cells within this instructive niche.

Neural precursors within the subgranular zone reside in a niche that is rich in axonal projections from the adjacent granule cell layer. This zone is also rich in vascular profiles that show an unusually high degree of endothelial cell division that correlates tightly with local precursor proliferation [59]. Finally, the subgranular zone and hilus are particularly rich in astrocytes that show subtle signs of activation (elevated levels of GFAP immunoreactivity). The imagination is led to the concept that a major part of the local lifestyle of stem cells in the hippocampus is the driving local rhythm of neuronal activity in the context of animated compatriots of activated astrocytes and vascular endothelium.

Although fanciful, there could be a kernel of truth underlying the analogy that the demands placed on vasculature and astrocytes by local neuronal signaling stimulate a unique activated status for cells in the local microenvironment. Neuronal activity requires metabolic support and one mechanism for inducing a change in vascular function is via the activity-dependent action of hypoxia-inducible factor 1 [65]. Parallel activity-dependent activation of nitric oxide synthase in neurons, as well as in local glia and endothelium, leads to increased circulation. Included in the local glial and vascular response to nitric oxide is upregulated production of brain-derived neurotrophic factor (BDNF; a key element of angiogenesis-mediated avian neurogenesis [62]).
neuronal activity is artificially increased (e.g. by seizures or electroshock therapy [66–68]) or if nitric oxide levels are directly manipulated [69], the result is a significant increase in neurogenesis. Astrocytes are integral members of this activity-dependent signaling network and could provide the context-specific cues that define where neurogenesis is to occur.

The hypothetical stem cell niche in brain injury and repair

Brain injury results in a coordinated reaction of neurons, astrocytes and vascular cells that, in some regions of the brain, is sufficient to stimulate an abortive neurogenesis. This intriguingly supports the ‘activated cell status’ hypothesis but even this injury-induced response appears to be context specific. For example, focal ischemia in rats stimulates massive angiogenic and astrocytic responses in the affected striatum and overlying cortex, yet abortive neurogenesis is observed only within the striatum [23]. A more mild global insult has little effect in striatum and cortex but results in loss of hippocampal CA1 neurons. As in the cortical response to focal ischemia, the hippocampal CA1 region activates astrocytes and vasculature but does not natively replace neurons (although the neighboring granule cell layer does respond robustly with increased neurogenesis [70]. Amazingly, this failure can be overcome if the if recombinant FGF and EGF are infused into the ventricle following ischemia [22]. The role of these growth factors and their ability to convert a non-permissive ‘activated’ niche into a permissive niche is unknown but it does indicate that there could be a balance of competing gliogenic versus neurogenic cues that might be easily swayed if their mechanisms were better understood.

Does inflammation antagonize the neurogenic niche?

One clear difference between the native neurogenic niche of the hippocampus and that of the niche created by activated astrocytes and vasculature of the injured brain is the inflammatory response to injury. Although there is clear potential for inflammatory cells and cytokines to influence neural progenitor cell fate, only recently has the full extent of this influence begun to be realized. For example, cranial radiation for the treatment of brain tumors results in a chronic and irreversible decline in hippocampal function. In rodents, this declining function is accompanied by a nearly complete and permanent loss of neurogenesis (even though fully functional stem cells remain in the hippocampus) [71]. The inflammatory response within the hippocampus is robust and unusually persistent, and recent work indicates that the presence of activated microglia and pro-inflammatory cytokines is a significant impediment to normal signaling and survival of the newborn neuron within the neurogenic niche [71,72]. The same mechanisms appear to be involved in seizure-induced hippocampal injury (O. Lindvall, unpublished) and it seems that neuroinflammation could be a general antagonist of the mammalian neurogenic niche [72]. Should this hold true, specific intervention in one or more components of neuroinflammatory signaling might significantly unmask the native neurogenic response to injury that is predicted by the activated status vascular cells and astrocytes.

Summary

Control by local stem and/or progenitor cells is influenced by factors that are expressed by many cell types present within the niche consisting of progenitor cells, mature oligodendrocytes and neurons, as well as astrocytes and cells of the vasculature. Although factors provided by mature astrocytes are at least a part of the equation and glia are clearly involved in influence neural progenitor cell fate, only recently has the full extent of this influence begun to be realized. For example, cranial radiation for the treatment of brain tumors results in a chronic and irreversible decline in hippocampal function. In rodents, this declining function is accompanied by a nearly complete and permanent loss of neurogenesis (even though fully functional stem cells remain in the hippocampus) [71]. The inflammatory response within the hippocampus is robust and unusually persistent, and recent work indicates that the presence of activated microglia and pro-inflammatory cytokines is a significant impediment to normal signaling and survival of the newborn neuron within the neurogenic niche [71,72]. The same mechanisms appear to be involved in seizure-induced hippocampal injury (O. Lindvall, unpublished) and it seems that neuroinflammation could be a general antagonist of the mammalian neurogenic niche [72]. Should this hold true, specific intervention in one or more components of neuroinflammatory signaling might significantly unmask the native neurogenic response to injury that is predicted by the activated status vascular cells and astrocytes.

Table 1. The astrocyte and neural cell genesisa

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<th>Role</th>
<th>Characteristics</th>
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<tr>
<td>Stem cell</td>
<td>Astrocytes that have characteristics of traditional astrocytes, such as expression of glial fibrillary acidic protein, formation of vascular endfeet and astrocyte-like membrane potentials, are multipotent and self-renewing. Stem-cell-like astrocytes are localized to periventricular zones and have non-traditional astrocyte characteristics, such as nestin expression and formation of cilia.</td>
<td>[12,17,56,57]</td>
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<tr>
<td>Astrocyte progenitor</td>
<td>Astrocytes that express S-100β continue to divide in the adult CNS and following injury or pathology.</td>
<td>[19,28,29]</td>
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<td>Organizer of neurogenic niches</td>
<td>Traditional astrocytes in the developing CNS and those from neurogenic regions of the adult CNS contain the necessary cues to support the formation and maturation of neurons from adult progenitor cells.</td>
<td>[53,54,55]</td>
</tr>
<tr>
<td>Organizer of gliogenic niches</td>
<td>Traditional astrocytes found outside of neurogenic zones support gliogenesis and potentially inhibit neurogenesis of adult progenitor cells.</td>
<td>[35,36,52]</td>
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<tr>
<td>Component of injury-induced</td>
<td>Following specific types of injury, astrocytes and local vasculature adopt an ‘activated’ status similar to that seen in the intact neurogenic niche of the hippocampus. The astrocyte in this context can switch from gliogenic to neurogenic signaling, allowing neurons to be born in a normally non-neurogenic region.</td>
<td>[20,22,23]</td>
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<tr>
<td>neurogenic niche</td>
<td>Traditional astrocytes outside of neurogenic zones are capable of supporting neurogenesis following injury but this response reverts to gliogenic instruction, perhaps owing to local inflammatory signaling. Suppression of the local inflammatory response can disinhibit neurogenesis.</td>
<td>[71,72]</td>
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aAstrocytes can be heterogeneous in morphological and molecular characteristics and can serve unique functions that stretch beyond the traditional role of a neuronal-support cell and inducer of the blood–brain barrier. New observations suggest that astrocytes with traditional characteristics as well as those with previously undescribed features play key roles in neural cell genesis in the adult nervous system.

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instructive signaling that produces neurons and glia are not yet known (Figure 1). By sheer numbers and wide distribution, la vida local for the adult stem cell is one of oligodendrocyte production. However, under more stimulating conditions, la vida loca prevails and stem cells produce neurons. A prediction is that brain injury, such as ischemic stroke, should induce neurogenesis by virtue of recreating a neurogenic environment within the normally gliogenic parenchyma (e.g. with its massive glutamate stimulation, neuronal activity and robust ischemia-induced angiogenesis). However, neurogenesis is fleeting at best and completely absent in many areas of injury [23,20]. Who or what plays the role of the local constitutary in quelling the party? Is there a role for local variation in astrocytes and their ability or inability to produce appropriate growth factors or substrates [22]? Or, is the failure of intrinsic replacement of both neurons and oligodendrocytes due to the intervention of an otherwise silent partner in CNS biology, such as neuroinflammation? Finally, within each locale, which cell plays the role of the astrocyte in driving neural progenitor genesis is fleeting at best and completely absent in many areas of injury [23,20].

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