



# Glia as neural progenitor cells

Steve Goldman

Department of Neurology, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642, USA

**Recent studies have substantially expanded our conception of the roles for glia in function and maintenance of the adult nervous system. Of these reports, several have re-examined the lineage relationships among neural stem cells, their early radial glial derivatives and their mitotically competent neurogenic daughters. These studies have highlighted the role of radial cells in development, and of their glial progeny postnatally, as both progenitors and regulators of neuronal production and phenotype. In the adult mammalian brain, radial cell populations are scant, but their glial derivatives participate in a gliovascular network that organizes not only the structural and functional architecture of the brain but also its generative niches for resident progenitors – glial as well as neuronal. As in other organs, these progenitors can reside as transit-amplifying pools, by which lineage-biased progenitors expand to replenish discrete mature phenotypes. This review will consider the types of transit-amplifying progenitor cells persistent in the adult mammalian CNS, and the extent to which these derive from glial phenotypes. It will also discuss the interactions of progenitor cells with their brethren that could specify their phenotype and fate, while defining the permissive niches for cell genesis in the adult CNS.**

Within the adult ventricular zone, there persist self-renewing and multipotential neural stem cells that share the features, but not necessarily the functions, of early astroglia. These cells are widely dispersed throughout the adult ventricular wall [1–3] yet generally appear to be tonically inhibited from producing neurons, save for discrete regions of permissive neurogenesis, such as the hippocampus and olfactory subependyma [4]. In these neurogenic zones, classically defined transit-amplifying cells can be evident as mitotic progenitors committed to neurogenesis. By contrast, cycling progenitor cells of apparent glial lineage persist throughout the brain parenchyma. These too could constitute a population of transit-amplifying cells, from which astrocytes and oligodendrocytes arise, both tonically and reactively. Yet at least some of these cycling cells appear to persist as uncommitted progenitors, biased towards glial production by their environment but as likely to generate neurons as glia when freed from their tissue surround [5–7]. This review will address the hypothesis that the germinal functions of the developing ventricular zone might be supplanted in adults, at least in part, by this derivative

population of nominally glial progenitor cells. Although dispersed throughout the parenchyma, these cells can be viewed as a secondary germinal population, comprising a minor pool of parental multipotential progenitors and a major pool of derived transit-amplifying glial progenitor cells, with the latter able to give rise to both astrocytic and oligodendrocytic progeny. This idea is presented in the context of the different progenitor pools of the adult brain, the niches in which competent progenitor pools persist, and the interactions between these cells and their local environment that predict their differentiated fates.

## **Astrocytes, ependymal cells and endothelial cells collaborate to define niches for cell genesis**

A series of recent studies has demonstrated that reciprocal paracrine interactions between astrocytes, endothelial cells and ependymal cells can both permit and regulate neurogenesis and gliogenesis from resident precursor cells. Astrocytes have especially visible roles in this process, both positively and negatively. In neurogenic regions of the adult brain, astrocytes can directly support neurogenesis [8,9]. Agents as diverse as fibroblast growth factor (FGF) [7], insulin-like growth factor-1 (IGF-1) [10,11], ATP [12], glutamate, glycosylated cystatin C [13] and sonic hedgehog (Shh) [14] have been implicated as permissive factors for neurogenesis in the adult ventricular zone and hippocampus. Yet more broadly, astrocyte-derived bone morphogenetic proteins (BMPs) typically suppress local neurogenesis, by directing astrocytic differentiation from competent neural progenitors [15]. In neurogenic regions alone, the ependymal expression of noggin protein, a competitive antagonist of the BMPs, might permit subependymal neurogenesis by depriving astrocyte-derived BMPs of access to local neural stem and progenitor cells [16,17]. This, in turn, permits the resident neural stem cells to respond to local mitogens, permitting their expansion and neuronal differentiation. Thus, astrocytes appear to have both positive and negative influences on neurogenesis, and the ultimate effects of this neurogenesis on the stem cell population appear to be at least modulated, if not frankly decided, by the ependymal cell. This mechanism could permit the establishment of neurogenic niches not only in the striatal subependyma but also in the dentate gyrus and olfactory bulb, each of which expresses high levels of noggin [18,19].

Neurogenic niches might also be supported by the paracrine interactions of neural precursor cells with other non-astrocytic phenotypes. In the higher vocal center of the adult songbird forebrain, testosterone stimulates the production and release of vascular endothelial growth factor (VEGF) from both astrocytes and neurons. This rise

Corresponding author: Steve Goldman (sgoldm@med.cornell.edu or steven\_goldman@urmc.rochester.edu).

in VEGF levels elicits a burst of mitotic angiogenesis, which is followed by the production of brain-derived neurotrophic factor (BDNF) by the stimulated microvascular cells [20]. The resultant local focus of BDNF production acts as both a migratory cue and a survival factor for neurons moving from the adult ventricular zone to the parenchyma of the higher vocal center, permitting their integration therein as new neurons. This process of endothelial support of adult neurogenesis finds a parallel in the adult hippocampus, in which neuronal progenitor cells are spatially associated with mitotic endothelial cells, in discrete foci of concurrent angiogenesis and neurogenesis [21,22]. Mammalian endothelial cells, like their avian counterparts, can express BDNF, and human brain endothelial cells can support the migration and survival of neurons arising from cultures of the adult striatal ventricular zone [23]. Thus, it would seem likely that hippocampal angiogenesis might also support local neurogenesis in a BDNF-dependent fashion. In each of these diverse systems, a common thread has been the collaboration of multiple non-neuronal cell types to provide a locally instructive environment for neuronal differentiation. Astrocytes could thus support neurogenesis in some regions and at some stages, but suppress neurogenesis at other times and places. Such is the nature of local niches for cell genesis, the cellular outputs of which need to be tightly modulated in response to environmental exigencies.

### **The brain is generally not friendly to new neurons**

The support of persistent neurogenesis in gaminal regions such as the subgranular zone and the olfactory and striatal subependymal layers might be exceptions to a more general rule of astrocytic delimitation of neurogenesis. In the bulk of the adult brain, neurogenesis does not occur, despite – as will be discussed – the persistence of large numbers of potentially neurogenic progenitor cells in the brain parenchyma. The astrocytes of the bulk of the brain clearly do not actively support neurogenesis, and are more likely to contribute to its widespread suppression, dampening rather than potentiating cellular plasticity in the adult nervous system.

Transplant studies have borne out the typically suppressive action of parenchymal glia upon extra gaminal neurogenesis. Spinal progenitors, which although neurogenic *in vitro* are typically gliogenic in their native environment, can generate neurons when transplanted to the pro-neurogenic environment of the hippocampus [24]. Conversely, highly neurogenic hippocampal and olfactory progenitors typically quickly cease neurogenesis once transplanted to non-neurogenic regions of brain. Similarly, X-irradiated hippocampus loses its neurogenic potential not because of the loss of resident progenitor cells but, rather, because the local gliovascular environment becomes non-permissive for neuronal production and differentiation from those progenitors [25,26]. The effect of the radiation is thus to render the hippocampal microenvironment non-permissive for neurogenesis, causing it to behave more like the vast stretches of the CNS within which neuronal addition is inhibited. Once again, the power of the local brain microenvironment – much of it

astrocytic – in determining the fate and lineage choices exercised by neural progenitor cells is evident. The overwhelmingly non-permissive nature of the adult brain for neurogenesis, by either resident or engrafted progenitor cells [27,28], provides a cautionary note on just how unsupportive most parenchymal astrocytes are of adult neurogenesis. In that context, the apparent restriction of parenchymal progenitor cells to gliogenesis must be viewed with caution – perhaps glial progenitors act as such simply by virtue of residing in an environment non-permissive for neurogenesis. If so, then might not glial progenitors be able to make neurons when faced with permissive conditions?

### **Radial glia as neural progenitor cells**

Several recent studies have expanded our conception of the role of astrocytes in the cellular homeostasis of the nervous system, by proposing that glia might not only regulate neurogenesis but also themselves be neuronal progenitor cells [29–31]. The case for such glial neurogenesis is strongest in development. As long as 15 years ago, McKay and colleagues reported that neurons of the developing forebrain might derive from radial cells of the developing neuroepithelium [32,33]. Subsequent studies in both the developing chick optic tectum [34] and adult songbird brain [35–37] revealed this to be the case in avian subcortical models. Because radial cells had already been recognized as a parental phenotype for parenchymal astrocytes, to which radial cells give rise upon their involution late in development [38], it stood to reason that they might act as neural stem cells, giving rise to both neurons and astrocytes. Thus, radial cells would appear to be individually multipotent, giving rise to neurons early in development and later involuting to generate glial precursors and parenchymal astrocytes [39]. However, although a strong case has been made for both radial cell neurogenesis and gliogenesis, and an inferential case has been made for the generation of both phenotypes by single radial cells, it remains unclear whether individual radial cells retain the capacity for multi-lineage generation throughout their life histories, or whether they do so in a self-renewing fashion. Until these points are established or refuted, it might be premature to consider radial cells as stem cells, although the generation of adult neural stem cells from a discrete subpopulation of fetal radial cells is an especially attractive hypothesis that bridges stem cell ontogeny in development and adulthood [40]. That having been said, the molecular events associated with the evolution of adult subependymal stem cells from fetal radial cells, with the loss of radial cell function and morphology despite the preservation of self-renewable multipotentiality, are wholly unknown.

### **Neural stem cells can express GFAP – but does that make them astrocytes?**

Because subependymal cells appeared to be the source of neural stem cells and neuronal progenitor cells of the adult mammalian brain, and as these cells express the glial fibrillary acidic protein (GFAP), Alvarez-Buylla and colleagues proposed that subependymal astrocytes might themselves be neural stem cells [41]. This claim was soon

extended to include parenchymal astrocytes, at least in young postnatal animals, blurring the distinction between subependymal cells and classically defined protoplasmic astrocytes [42]. Several investigators subsequently reported that postnatal neural stem cells either express GFAP [43] or have done so during their ontogeny. Indeed, Messing *et al.* reported that in GFAP-targeted Cre mice crossed with mice in which a loxP-flanked stop sequence was placed upstream of *lacZ*, virtually all CNS neurons developed *lacZ* expression [44]. Exceptions included Purkinje neurons of the cerebellum and a few other populations of pyramidal neurons. In these mice, the GFAP-promoter-driven Cre recombinase would have been expected to yield permanent *lacZ* expression in any cells that had ever activated the GFAP promoter. These results powerfully suggested that most CNS neurons arose from progenitors that at some point had expressed GFAP, or that at least had transcriptionally activated the 2.2 Kb 5' region of the *gfa2* promoter [45] by which Cre expression had been regulated.

But do these observations mean that some astrocytes, or even any astrocytes, are neural stem cells? To answer this, we need to have firm and rigorous criteria for what constitutes an astrocyte. The bulk of studies that have addressed this issue have taken the position, if by inference alone, that GFAP is a definitive marker for astroglial phenotype and that its expression is both necessary and sufficient to assign astrocytic identity to a cell. But GFAP is an intermediate-filament protein whose expression neither causally nor necessarily correlates with that of other markers of astrocytic phenotype or function [46]. The water transport molecules aquaporin 4 and aquaporin 9 [47], the Ca<sup>2+</sup>-binding protein S100 $\beta$ , and the glutamate transporters GLAST, EAAT2 and EAAT 4 [48] are all markers of astrocytic functional phenotype, and yet none of them have been shown to correspond necessarily with GFAP expression patterns, either within the subependyma or otherwise. Indeed, if one takes the position that astrocytes are best defined functionally – by their participation in the blood–brain barrier and gliovascular unit, their high-capacity uptake of glutamate, and their strongly hyperpolarized resting membrane potential – then one might expect antigenic expression of both aquaporins and glutamate transporters by neural stem cells if they were of astrocytic phenotype. To date, although the radial cell glutamate transporter GLAST is coexpressed with GFAP in subependymal astrocytes [12], neither the aquaporins nor any other excitatory amino acid transporter has yet been localized to these cells. Similarly, if neural stem cells were indeed astrocytes, one would expect to identify their anatomical relationship with the vasculature, and to see both vascular endfeet and junctional contacts with endothelial cells [49]. However, none of these conditions has yet been met in the anatomical investigation of neural stem cells, either in the fetal ventricular zone or adult subependyma.

Thus, as we await more rigorous assessment both of the phenotype of the subependymal neural stem cell and of the lineage potential of mature astrocytes, it might be most parsimonious to set aside the concept that GFAP is a necessary marker of astrocytes. It might clarify the

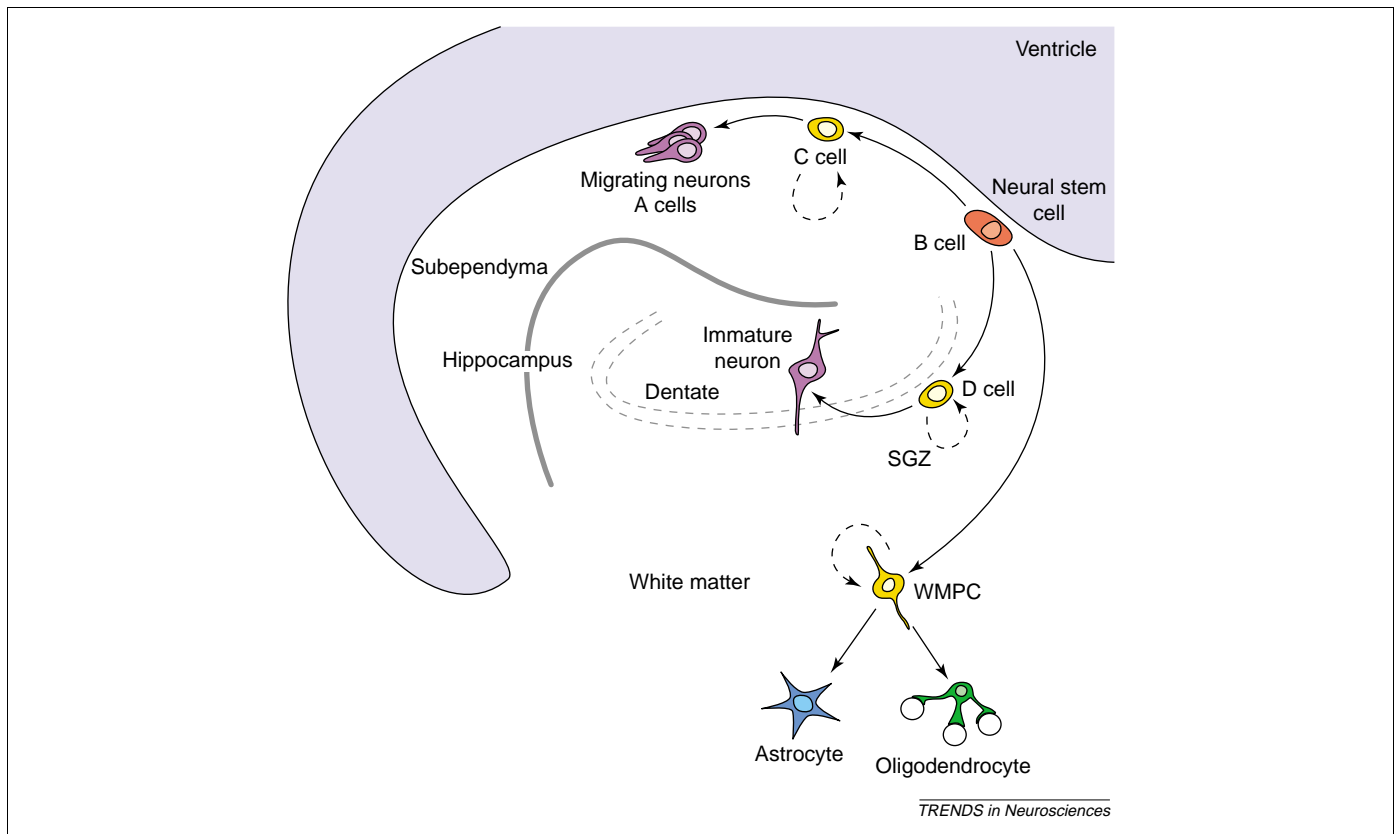
underlying biology, while engendering less semantic controversy, to view GFAP instead as a non-exclusive intermediate-filament protein of immature progenitor cells as well as of mature astrocytes, with expression that might be dynamically regulated but not in a manner intrinsically bound to astrocytic form or function. As such, there might be stages during which neural stem and progenitor cells express GFAP without necessarily being astrocytes at those points in time.

### Multiple classes of transit-amplifying cells persist in the adult brain

In systems as diverse as the bone marrow, skin and gastrointestinal mucosae, stem cells have been identified in discrete loci that provide permissive niches for undifferentiated expansion [50–52]. As stem cell progeny leave these localized regions of stem cell expansion, their daughters can commit to given phenotypes, or at least to more restricted lineages than their parental progenitors. The latter category of cells, phenotypically restricted but still mitotic, has been designated transit-amplifying [52,53]. The concept of a transit-amplifying progenitor has recently been extended to the brain, in which the neuronal progenitor cells of the forebrain subependyma have been proposed to represent a transit-amplifying cell type, corresponding to the C cell of Alvarez-Buylla and colleagues [54]. Indeed, because the neuronally committed progenitor cells of the forebrain subependyma and migratory stream, corresponding to Alvarez-Buylla's A cells, continue to divide and expand while migrating [55], they too comprise a transit-amplifying phenotype [56]. Similarly, the neuronal progenitor cell of the hippocampal subgranular zone and the glial progenitor cell of the adult human white matter could represent additional categories of transit-amplifying cells, each able to divide and yield variably restricted daughters, yet exhibiting neither unbiased multipotentiality nor self-renewal capacity (Figure 1). Each of these phenotypes will now be discussed in turn.

### Are hippocampal neuronal progenitor cells transit amplifiers?

Hippocampal neurogenesis occurs within the subgranular zone of the dentate gyrus, with neuronal production followed by migration into the dentate proper and integration therein as granular neurons [57]. Relatively few dividing astrocytes are noted in the dentate, and the overwhelming majority of newly generated cells in the adult dentate are neurons. The hippocampal progenitor that gives rise to these neurons has been reported to express GFAP and, hence, has been classed as glial in nature [58]. In addition, this cell can have a radial morphology, reminiscent of the radial progenitor cells of early ontogeny and adulthood. However, although this GFAP-positive subgranular progenitor has been reported to behave as a stem cell, neither adult rodent nor human dentate gyrus appear to manifest evidence of clonogenic neural stem cells *in vitro* [59,60]. To the contrary, cultured dissociates of the adult rodent dentate gyrus typically fail to generate multipotential neurospheres. This is in sharp contrast to the adjacent ventricular wall, from which clonogenic neurospheres are readily generated and



**Figure 1.** The basic categories of progenitor cells in the adult brain, and their known interrelationships. The human temporal lobe is illustrated as an example. It includes ventricular zone neural stem cells (red), which generate at least three populations of potentially neurogenic transit-amplifying progenitors, of both neuronal and glial lineages (yellow). These include the neuronal progenitor cells of the ventricular subependyma, those of the subgranular zone (SGZ) of the dentate gyrus, and white matter progenitor cells (WMPC) of the subcortical parenchyma (which, although nominally glial, remain potentially neurogenic). Such parenchymal progenitors can also persist in gray matter, although the relationships of parenchymal gray-matter and white-matter progenitor pools have not yet been elucidated. Each transit-amplifying pool might then give rise to differentiated progeny appropriate to their location, including neurons (purple), oligodendrocytes (green) and astrocytes (blue). This scheme can be viewed as an expanded version of the classification proposed by Alvarez-Buylla and colleagues, in which neural stem cells (B cells) give rise to mitotically active progenitor cells (subependymal C cells and hippocampal D cells) that, in turn, generate neuron-committed progeny appropriate to their region (e.g. A cells in the olfactory subependyma) [40,54]. The present scheme expands upon this base to incorporate parenchymal glial progenitors, and categorizes both neuronal and glial progenitors as transit-amplifying derivative lineages of the neural stem cell pool. Figure courtesy of Fraser Sim.

maintained *in vitro* [59]. Similarly, when adult ventricular zones and dentate gyri were separately removed and cultured from a cohort of eight adult humans, the ventricular zones of each patient generated multipotential neurospheres, but none of the matched dentate dissociates did so (N. Roy and S. Goldman, unpublished). Thus, although the neuronal progenitor cell of the adult hippocampus expresses GFAP, and might even have a radial morphology, it cannot yet be comfortably or accurately designated as a stem cell. Rather, its status might be most similar to the ultimately neurogenic transit-amplifying cells of the olfactory subependyma [61].

#### Parenchymal glial progenitors include multipotential progenitors

Several populations of multipotential precursor cells have been identified in brain parenchyma [62,63], including in the adult human cortex [64] and subcortical white matter [5]. The latter cells were initially isolated from the white matter as oligodendrocyte progenitor cells, on the basis of: (i) their expression of the  $\alpha$  receptor for platelet-derived growth factor (PDGF $\alpha$ R) and the A2B5 epitope; (ii) their transcriptional activation of the early P2 promoter for cyclic nucleotide phosphodiesterase (CNP); and (iii) their predominant differentiation as oligodendrocytes in both

high-density and serum-supplemented culture [65] and upon transplantation to recipient adult brain [66]. Yet upon removal to low-density, serum-free culture, in which the cells were separated from both autocrine and paracrine influences, they generated neurons as well as astrocytes and oligodendrocytes, and were able to do so for at least three monthly passages *in vitro* [5]. These data suggested that the parenchymal glial progenitor of the adult human white matter, nominally an oligodendrocyte progenitor cell, is in fact a multipotential neural progenitor cell, restricted to generate glia by virtue of the adult parenchymal environment, and not because of any autonomous lineage commitment [52].

These parenchymal multipotential progenitors do not seem to be astrocytes. *In vivo*, they appear as small, highly ramified cells with many thin processes that lack overt endothelial endfeet or even contact. Most express neither GFAP nor aquaporins, nor do they transcriptionally activate the GFAP promoter (M. Nunes, N. Roy and S. Goldman, unpublished). Although a small number do express GFAP, these appear to comprise a minor and possibly transitional, fraction of GFAP expressors within the much larger pool of A2B5-defined parenchymal progenitors [5]. By contrast, virtually all express nestin and the NG2 chondroitin sulfate proteoglycan (markers of

immature neural progenitors) and S100 $\beta$  (a glial marker expressed by immature cells of both the astrocytic and oligodendrocytic lineages). Importantly, although the parenchymal progenitor seems to be fundamentally multipotential, it is subject to replicative senescence and does not express telomerase activity *in vitro* [5]. As a result, it typically ceases expansion after 3–4 months *in vitro*, spanning no more than 18 population doublings. In light of its rapid but self-limited expansion capacity and multi-lineage capacity (with clear glial bias), the parenchymal progenitors might be considered a transit-amplifying population directed largely to the production of astrocytes and oligodendrocytes.

### Glial progenitors of the subcortical white matter are transit-amplifying cells

Just as the transit-amplifying neuronal precursor of the adult rat ventricular zone can revert to a multipotential state in the presence of epidermal growth factor (EGF) [56], the dividing glial progenitor of human white matter is similarly able to revert to a multi-lineage neurogenic precursor *in vitro* [5]. Although this is especially evident when the cells are expanded in the presence of basic FGF, the cells are in fact potentially neurogenic as soon as they are removed from the local tissue environment. This contrasts somewhat with the observations of Martin Raff and colleagues, who had similarly generated multipotential progenitors from nominally oligodendrocyte progenitors, using cells derived from the postnatal rat optic nerve [67]. However, these investigators had used BMP treatment to induce an astrocytic intermediate before attempting neuronal differentiation. By contrast, three groups have since reported that oligodendrocyte progenitor cells can act as multipotential progenitors directly upon their isolation from tissue, without any astrocytic intermediate, whether extracted on the basis of CNP promoter activation [5], NG2 expression [6] or immunoselection for the A2B5 or O4 epitopes, in each case typically GFAP-negative cells [5]. In fact, in each of these reports, removal of the cells from all environmental influences appeared to be the most important variable in ensuring the appearance of multipotential progenitors in these isolates. Accordingly, when freshly sorted parenchymal progenitors were introduced via transuterine xenograft into the fetal rat brain, all neural phenotypes arose in a context-dependent manner [5]. Together, these data suggested that parenchymal progenitor cells of adult brain tissue include both multipotential and glial-restricted progenitors. These could represent differentially restricted phenotypes of transit-amplifying glial progenitors, neither of which necessarily or even commonly expresses GFAP. However viewed, these data indicate that acutely isolated parenchymal progenitors are by no mean simply mature astrocytes.

### Overview

Over the past several years, the term stem cell has been used with abandon in describing mitotic and multipotential cells of the adult nervous system. Yet adult tissues are typically characterized by more restricted mitotic lineages, in various stages of lineage restriction and differentiation, on the way to functional maturation

and cell cycle exit. These mitotic cells continue to divide and their numbers expand – they amplify – while they are nonetheless transitional – in transit – between their parental stem cells and their mature progeny. Such transit-amplifying cells are incapable of either self-maintenance or extended self-renewal, and their tissue regenerative capabilities are thus limited and exhaustible. In the brain and spinal cord, several cell types and populations have been described as neural stem cells, some of which might be more accurately considered as transit-amplifying cells of the CNS. In development, these can comprise in part radial cells, which potentially include both stem cells and their more restricted mitotic derivatives [68]. In adults, these transit-amplifying pools appear to include the glial progenitor cells of the brain parenchyma, and probably the neuronal progenitor populations of the major granular zones (the olfactory subependyma and the dentate gyrus of the hippocampus). In each case, resident stem cells must give rise to these transit-amplifying lineages, and in each case evidence has been found for some transit amplifiers reverting back to a multipotential and self-renewing phenotype when exposed to stem cell mitogens. Regardless of the antigens expressed by these cells, they appear to be neither functionally mature nor terminally differentiated. As such, it would be overstating matters to consider them committed members of any defined phenotype, whether astrocytic or otherwise. Rather, we are left with the image of an adult brain harboring multiple parallel, restricted but still-uncommitted progenitor lineages, each contributing its progeny to different brain compartments but all ultimately co-derived from a common set of parental stem cells. This is a dynamic brain endowed with substantial cellular plasticity that might have been scarcely recognizable to investigators as recently as 20 years ago, when ventricular zone neurogenesis was first identified in adulthood [69]. In that context, the identification and persistence of transit-amplifying progenitors, both of the ventricular zone and parenchyma, might now provide us the cellular substrates with which to direct neurogenesis and gliogenesis in the adult brain and spinal cord.

### Acknowledgements

I thank Maiken Nedergaard for her helpful comments, Neeta Roy and Anjali Kukreja for making available unpublished data, and Fraser Sim for his expert illustration.

### References

- Weiss, S. *et al.* (1996) Multipotent CNS stem cells are present in the adult mammalian spinal cord and ventricular neuroaxis. *J. Neurosci.* 16, 7599–7609
- Morshead, C.M. *et al.* (1994) Neural stem cells in the adult mammalian forebrain: a relatively quiescent subpopulation of subependymal cells. *Neuron* 13, 1071–1082
- Kirschenbaum, B. and Goldman, S.A. (1995) Brain-derived neurotrophic factor promotes the survival of neurons arising from the adult rat forebrain subependymal zone. *Proc. Natl. Acad. Sci. U. S. A.* 92, 210–214
- Gage, F. (2000) Mammalian neural stem cells. *Science* 287, 1433–1438
- Nunes, M.C. *et al.* (2003) Identification and isolation of multipotential neural progenitor cells from the subcortical white matter of the adult human brain. *Nat. Med.* 9, 439–447
- Belachew, S. *et al.* (2003) Postnatal NG2 proteoglycan-expressing

- progenitor cells are intrinsically multipotent and generate functional neurons. *J. Cell Biol.* 161, 169–186
- 7 Palmer, T.D. *et al.* (1995) FGF-2-responsive neuronal progenitors reside in proliferative and quiescent regions of the adult rodent brain. *Mol. Cell. Neurosci.* 6, 474–486
  - 8 Song, H. *et al.* (2002) Astroglia induce neurogenesis from adult neural stem cells. *Nature* 417, 39–44
  - 9 Lim, D.A. and Alvarez-Buylla, A. (1999) Interaction between astrocytes and adult subventricular zone precursors stimulates neurogenesis. *Proc. Natl. Acad. Sci. U. S. A.* 96, 7526–7531
  - 10 Jiang, J. *et al.* (1998) Insulin-like growth factor-1 is a radial cell-associated neurotrophin that promotes neuronal recruitment from the adult songbird ependyma/subependyma. *J. Neurobiol.* 36, 1–15
  - 11 Aberg, M. *et al.* (2000) Peripheral infusion of IGF-1 selectively induces neurogenesis in the adult rat hippocampus. *J. Neurosci.* 20, 2896–2903
  - 12 Braun, N. *et al.* (2003) Expression of the ecto-ATPase NTPDase2 in the germinal zones of the developing and adult rat brain. *Eur. J. Neurosci.* 17, 1355–1364
  - 13 Taupin, P. *et al.* (2000) FGF2-responsive neural stem cell proliferation requires CCG, a novel autocrine/paracrine cofactor. *Neuron* 28, 385–397
  - 14 Lai, K. *et al.* (2003) Sonic hedgehog regulates adult neural progenitor proliferation *in vitro* and *in vivo*. *Nat Neurosci.* 6, 21–27
  - 15 Gross, R.E. *et al.* (1996) Bone morphogenetic proteins promote astroglial lineage commitment by mammalian subventricular zone progenitor cells. *Neuron* 17, 595–606
  - 16 Lim, D. *et al.* (2000) Noggin antagonizes BMP signaling to create a niche for adult neurogenesis. *Neuron* 28, 713–726
  - 17 Paine-Saunders, S. *et al.* (2002) Heparan sulfate proteoglycans retain noggin at the cell surface: a potential mechanism for shaping BMP gradients. *J. Biol. Chem.* 277, 2089–2096
  - 18 Chmielnicki, E. and Goldman, S.A. (2002) Induced neurogenesis by endogenous progenitor cells in the adult mammalian brain. *Prog. Brain Res.* 138, 451–464
  - 19 Chmielnicki, E. *et al.* Adenoviral overexpression of noggin and BDNF cooperate to induce neuronal recruitment to the adult neostriatum. *J. Neurosci.* (in press)
  - 20 Louissaint, A. *et al.* (2002) Coordinated interaction of angiogenesis and neurogenesis in the adult songbird brain. *Neuron* 34, 945–960
  - 21 Palmer, T. *et al.* (2000) Vascular niche for adult hippocampal neurogenesis. *J. Comp. Neurol.* 425, 479–494
  - 22 Palmer, T. (2002) Adult neurogenesis and the vascular Nietzsche. *Neuron* 34, 856–858
  - 23 Leventhal, C. *et al.* (1999) Endothelial trophic support of neuronal production and recruitment from the adult mammalian subependyma. *Mol. Cell. Neurosci.* 13, 450–464
  - 24 Horner, P.J. *et al.* (2000) Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord. *J. Neurosci.* 20, 2218–2228
  - 25 Monje, M. *et al.* (2002) Irradiation induces neural precursor cell dysfunction. *Nat. Med.* 8, 955–962
  - 26 Monje, M. and Palmer, T. (2003) Radiation injury and neurogenesis. *Curr. Opin. Neurol.* 16, 129–134
  - 27 Goldman, S.A. and Luskin, M.B. (1998) Strategies utilized by migrating neurons of the postnatal vertebrate forebrain. *Trends Neurosci.* 21, 107–114
  - 28 Englund, U. *et al.* (2002) Migration patterns and phenotypic differentiation of long-term expanded human neural progenitor cells after transplantation into the adult rat brain. *Brain Res. Dev. Brain Res.* 134, 123–141
  - 29 Malatesta, P. *et al.* (2000) Isolation of radial cells by fluorescent activated cell sorting reveals a neuronal lineage. *Development* 127, 5253–5263
  - 30 Miyata, T. *et al.* (2001) Asymmetric inheritance of radial glial fibers by cortical neurons. *Neuron* 31, 727–741
  - 31 Noctor, S. *et al.* (2001) Neurons derived from radial cells establish radial units in neocortex. *Nature* 409, 714–720
  - 32 Frederiksen, K. and McKay, R.D. (1988) Proliferation and differentiation of rat neuroepithelial precursor cells *in vivo*. *J. Neurosci.* 8, 1144–1151
  - 33 McKay, R. (1997) Stem cells in the central nervous system. *Science* 276, 66–71
  - 34 Gray, G. and Sanes, J. (1992) Lineage of radial glia in the chicken optic tectum. *Development* 114, 271–283
  - 35 Alvarez-Buylla, A. *et al.* (1990) Proliferation ‘hot spots’ in adult avian ventricular zone reveal radial cell division. *Neuron* 5, 101–109
  - 36 Goldman, S.A. *et al.* (1993) Migration of newly generated neurons upon ependymally derived radial guide cells in explant cultures of the adult songbird forebrain. *Glia* 8, 150–160
  - 37 Goldman, S.A. *et al.* (1996) Ependymal/subependymal cells of the postnatal and adult songbird brain generate both neurons and non-neuronal siblings, *in vitro* and *in vivo*. *J. Neurobiol.* 30, 505–520
  - 38 Rakic, P. (2003) Elusive radial glial cells: Historical and evolutionary perspective. *Glia* 43, 19–32
  - 39 Tramontin, A. *et al.* (2003) Postnatal development of radial glia and the ventricular zone: A continuum of the neural stem cell compartment. *Cereb. Cortex* 13, 580–587
  - 40 Alvarez-Buylla, A. *et al.* (2001) A unified hypothesis on the lineage of neural stem cells. *Nat. Rev. Neurosci.* 2, 287–293
  - 41 Doetsch, F. *et al.* (1999) Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell* 97, 703–716
  - 42 Laywell, E. *et al.* (2000) Identification of a multipotent astrocytic stem cell in the immature and adult mouse brain. *Proc. Natl. Acad. Sci. U. S. A.* 97, 13883–13888
  - 43 Imura, T. *et al.* (2003) The predominant neural stem cell isolated from postnatal and adult forebrain but not early embryonic forebrain expresses GFAP. *J. Neurosci.* 23, 2824–2832
  - 44 Zhuo, L. *et al.* (2001) hGFAP-cre transgenic mice for manipulation of glial and neuronal function *in vivo*. *Genesis* 31, 85–94
  - 45 Besnard, F. *et al.* (1991) Multiple interacting sites regulate astrocyte-specific transcription of the human gene for glial fibrillary acidic protein. *J. Biol. Chem.* 266, 18877–18883
  - 46 Barres, B. (2003) What is a glial cell. *Glia* 43, 4–5
  - 47 Rash, J. *et al.* (1998) Direct immunogold labeling of aquaporin-4 in square arrays of astrocyte and ependymocyte plasma membranes in rat brain and spinal cord. *Proc. Natl. Acad. Sci. U. S. A.* 95, 11981–11986
  - 48 Anderson, C. and Swanson, R. (2000) Astrocyte glutamate transport: review of properties, regulation, and physiological functions. *Glia* 32, 1–14
  - 49 Simard, M. *et al.* Signaling at the gliovascular interface. *J. Neurosci.* (in press)
  - 50 Niemann, C. and Watt, F.M. (2002) Designer skin: lineage commitment in postnatal epidermis. *Trends Cell Biol.* 12, 185–192
  - 51 Watt, F.M. (2001) Stem cell fate and patterning in mammalian epidermis. *Curr. Opin. Genet. Dev.* 11, 410–417
  - 52 Potten, C.S. and Loeffler, M. (1990) Stem cells: attributes, cycles, spirals, pitfalls and uncertainties. Lessons for and from the crypt. *Development* 110, 1001–1020
  - 53 Loeffler, M. and Potten, C.S. (1997) Stem cells and cellular pedigrees. In *Stem Cells* (Potten, C.S., ed.), pp. 1–28, Academic Press
  - 54 Garcia-Verdugo, J. *et al.* (1998) Architecture and cell types of the adult subventricular zone: In search of the stem cells. *J. Neurobiol.* 36, 234–248
  - 55 Menezes, J.R. *et al.* (1995) The division of neuronal progenitor cells during migration in the neonatal mammalian forebrain. *Mol. Cell. Neurosci.* 6, 496–508
  - 56 Doetsch, F. *et al.* (2002) EGF converts transit-amplifying neurogenic precursors in the adult brain into multipotent stem cells. *Neuron* 36, 1021–1034
  - 57 Palmer, T.D. *et al.* (1997) The adult rat hippocampus contains primordial neural stem cells. *Mol. Cell. Neurosci.* 8, 389–404
  - 58 Seri, B. *et al.* (2001) Astrocytes give rise to new neurons in the adult mammalian hippocampus. *J. Neurosci.* 21, 7153–7160
  - 59 Seaberg, R.M. and van der Kooy, D. (2002) Adult rodent neurogenic regions: the ventricular subependyma contains neural stem cells, but the dentate gyrus contains restricted progenitors. *J. Neurosci.* 22, 1784–1793
  - 60 Roy, N.S. *et al.* (2000) *In vitro* neurogenesis by progenitor cells isolated from the adult human hippocampus. *Nat. Med.* 6, 271–277
  - 61 Alvarez-Buylla, A. and Garcia-Verdugo, J.M. (2002) Neurogenesis in adult subventricular zone. *J. Neurosci.* 22, 629–634
  - 62 Richards, L.J. *et al.* (1992) *De novo* generation of neuronal cells from the adult mouse brain. *Proc. Natl. Acad. Sci. U. S. A.* 89, 8591–8595
  - 63 Palmer, T.D. *et al.* (1999) Fibroblast growth factor-2 activates a latent

- neurogenic program in neural stem cells from diverse regions of the adult CNS. *J. Neurosci.* 19, 8487–8497
- 64 Arsenijevic, Y. *et al.* (2001) Isolation of multipotent neural precursors residing in the cortex of the adult human brain. *Exp. Neurol.* 170, 48–62
- 65 Roy, N.S. *et al.* (1999) Identification, isolation, and promoter-defined separation of mitotic oligodendrocyte progenitor cells from the adult human subcortical white matter. *J. Neurosci.* 19, 9986–9995
- 66 Windrem, M. *et al.* (2002) Progenitor cells derived from the adult human subcortical white matter disperse and differentiate as oligodendrocytes within demyelinated regions of the rat brain. *J. Neurosci. Res.* 69, 966–975
- 67 Kondo, T. and Raff, M. (2000) Oligodendrocyte precursor cells reprogrammed to become multipotential CNS stem cells. *Science* 289, 1754–1757
- 68 Malatesta, P. *et al.* (2003) Neuronal or glial progeny: regional differences in radial glia fate. *Neuron* 37, 751–764
- 69 Goldman, S.A. and Nottebohm, F. (1983) Neuronal production, migration, and differentiation in a vocal control nucleus of the adult female canary brain. *Proc. Natl. Acad. Sci. U. S. A.* 80, 2390–2394

### Articles of interest in other *Trends* journals

#### 3D structure perceived from dynamic information: a new theory

Fulvio Domini and Corrado Caudek

*Trends in Cognitive Sciences* 10.1016/j.tics.2003.08.007

#### Bubbles in the brain?

John G. Taylor

*Trends in Cognitive Sciences* 10.1016/j.tics.2003.08.009

#### How does the hippocampus contribute to memory?

Howard Eichenbaum

*Trends in Cognitive Sciences* 10.1016/j.tics.2003.08.008

#### In two minds: dual-process accounts of reasoning

Jonathan St. B. T. Evans

*Trends in Cognitive Sciences* 10.1016/j.tics.2003.08.012

#### After the viewpoint debate: where next in object recognition?

William G. Hayward

*Trends in Cognitive Sciences* 10.1016/j.tics.2003.08.004

#### Mood-dependent memory

Penelope A. Lewis and Hugo D. Critchley

*Trends in Cognitive Sciences* 10.1016/j.tics.2003.08.005

#### The journey of tetanus and botulinum neurotoxins in neurons

Giovanna Lalli *et al.*

*Trends in Microbiology* 10.1016/S0966-842X(03)00210-5

#### Aberrant protein kinases and phosphoproteins in amyotrophic lateral sclerosis

Charles Krieger, Jie Hong Hu and Steven Pelech

*Trends in Pharmacological Sciences* 10.1016/j.tips.2003.08.003

#### Pharmacology of absence epilepsy

Jon-Paul A. Manning, Douglas A. Richards and Norman G. Bowery

*Trends in Pharmacological Sciences* 10.1016/j.tips.2003.08.006