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REVIEW

LOCAL PRODUCTION OF ASTROCYTES IN THE CEREBRAL CORTEX

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Abstract—Astrocytes are the largest glial population in the mammalian brain. Astrocytes in the cerebral cortex are reportedly generated from four sources, namely radial glia, progenitors in the subventricular zone (SVZ progenitors), locally proliferating glia, and NG2 glia; it remains an open question, however, as to what extent these four cell types contribute to the substantial increase in astrocytes that occurs postnatally in the cerebral cortex. Here we summarize all possible sources of astrocytes and discuss their roles in this postnatal increase. In particular, we focus on astrocytes derived from local proliferation within the cortex.

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Key words: astrocyte, cerebral cortex, proliferation, radial glia, NG2 glia, SVZ.

Contents

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Abbreviations: P, postnatal; SVZ, subventricular zone; VZ, ventricular zone.

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NUMBER OF GLIA IN THE CEREBRAL CORTEX

There is no significant difference in neuronal number between neonates and adults in the rodent cortex, but most glia in the rodent cortex are produced early in the postnatal period (Bandeira et al., 2009). At birth, non-neuronal cells (most of which are glia) in the rat brain comprise ~6% of brain cells; in adult rats, however, they account for nearly 50% of brain cells. Glial number in the cortex increases sixfold to eightfold from four to six million during postnatal (P) days 1–6 to 35 million at P21 and remains stable throughout adulthood (Bandeira et al., 2009). Glial number in the brain of other mammals, such as cats, undergoes a similar postnatal increase (Brizzee and Jacobs, 1959). From P60 in cat (juvenile period) to adulthood, glial number in the cerebral cortex increases and is accompanied by a huge change in the glia-to-neuron ratio; this ratio is ~0.83 at P60 and reaches 1.42 in adulthood, and then it increases slightly to 1.48 in late adulthood. In addition, the density of glia in the juvenile cat cortex increases by 60% upon reaching adulthood, and then it increases slightly thereafter (Brizzee and Jacobs, 1959). Astrocytes are the largest glial population in the mammalian brain, and most astrocytes are produced postnatally (Sauvageot and Stiles, 2002; Freeman, 2010). Researchers have identified multiple sources of astrocyte production in the cerebral cortex, including radial glia, subventricular zone (SVZ) progenitors, NG2 glia, and locally proliferating glia (see Table 1). However, the contribution of each of these sources differs among developmental stages. Below, we address recent evidence pertaining to this developmental change.

RADIAL GLIA–DERIVED ASTROCYTES AND THEIR CONTRIBUTION

Radial glia were originally discovered by Camillo Golgi in 1885 (Rakic, 2003). They have radially oriented long processes spanning the entire cortical wall in the human fetal cortex and spinal cord (Rakic, 1972; Choi and Lapham, 1978). Based on their morphology illustrated with Golgi impregnation, Cajal posited that radial glia likely transform into astrocytes in the cortex (Cajal, 1911). In the early embryonic stage of rhesus monkey, transitional radial glia detach from the ventricle surface with a long process terminating at blood vessels during the first half of gestation (Schmechel and Rakic, 1979; Levitt and Rakic, 1980). They become astrocytes with subsequent loss of radial orientation and extension of multiple stellate processes

Table 1. Sources of astrocytes in the cerebral cortex

Sources	Methods	Species	References
Radial glia	Golgi staining	Monkey	Schmechel and Rakic (1979)
	Labeling with DiI	Ferret	Voigt (1989)
	Labeling with dyes (DiI/DiA)	Human (fetus)	deAzevedo et al. (2003)
	Organotypic slice cultures and time-lapse imaging	Rat	Noctor et al. (2004)
	Organotypic slice cultures and time-lapse imaging	Mouse	Burns et al. (2009)
	Genetic tracing	Mouse	Magavi et al. (2012)
	Adenovirus-Cre infection	Mouse	Tsai et al. (2012)
SVZ progenitors	Radioautography	Mouse	Smart (1961)
	Radioautography	Rat	Lewis (1968)
	Radioautography	Rat	Paterson et al. (1973)
	Radioautography	Mouse	Paterson (1983)
	Retroviral labeling	Rat	Levison et al. (1993)
	Retroviral labeling	Rat	Levison and Goldman (1993)
	Retroviral labeling	Mouse	Marshall and Goldman (2002)
NG2 glia	Genetic tracing	Mouse	Zhu et al. (2008)
	Genetic tracing	Mouse	Guo et al. (2009)
Locally proliferating glia	Radioautography	Rat	Kaplan and Hinds (1980)
	Retroviral labeling	Rat	Price and Thurlow (1988)
	Retroviral labeling	Rat	Levison and Goldman (1993)
	Organotypic slice culture and time-lapse imaging	Mouse	Burns et al. (2009)
	In vivo imaging, retroviral labeling, and genetic tracing	Mouse	Ge et al. (2012)
	Genetic tracing	Mouse	Magavi et al. (2012)

(Schmechel and Rakic, 1979). Similar observations were reported in the ferret brain (Voigt, 1989). Radial glia can be labeled via injection of tracers into the pial surface where radial glia endfeet are numerous. The tracers spread from the endfeet to the entire cell body of radial glia, so it is possible for researchers to follow the radial glia lineage (Voigt, 1989). In newborn ferrets, most tracer-labeled radial glia were found to become astrocytes in postnatal week 3 (Voigt, 1989). These results were confirmed by labeling translocating radial glia via DiI injection under the pial surface in the brain of human fetuses (deAzevedo et al., 2003) or by labeling foci of radial glia via adenovirus-Cre infection in the mouse cortex (Tsai et al., 2012). However, direct live imaging results to demonstrate that radial glia transform into astrocytes were obtained using cultured rat brain slices (Noctor et al., 2004). After 114 h of time-lapse imaging with confocal microscopy, the clonal progeny of labeled radial glia were traced after they were infected with GFP-expressing viruses. Individual radial glia began to transform into astrocytes after they completed neurogenesis in late embryonic stages (Noctor et al., 2004). Radial glia translocated from the ventricular zone (VZ) to the intermediate zone and became immature astrocytes by retracting their long leading processes (Noctor et al., 2004). The transformed cells were characterized based on their astrocytic electrophysiological properties (Noctor et al., 2004). Given that astrocytes undergo a dramatic change in morphology during culture, it will be necessary to validate these results using *in vivo* imaging.

How do astrocytes derived from radial glia contribute to the entire mature astrocyte population in the cerebral cortex? After neurogenesis is completed in the mammalian brain, individual radial glia transform into individual astrocytes (Schmechel and Rakic, 1979; Voigt, 1989; Gressens et al., 1992; Noctor et al., 2004). However, because the astrocyte population of an adult brain is much larger than the radial glial population in a developing brain, the contribution of radial glia–derived astrocytes is believed to be small. Recent results suggest that a single radial glia might yield multiple astrocytes in the cerebral cortex. This is supported by genetic fate mapping with a Thy1.2-Cre mouse line (Magavi et al., 2012). Crossing this line with a reporter line resulted in a low rate of recombination. This enabled the analysis of a single column of clustered cells within the mouse cortex that were produced from an individual radial glia or neural progenitor. The cells in this single column included neurons and astrocytes at a relative ratio ranging from 1:6 to 1:8 (Magavi et al., 2012). In such columns, ~70% of neurons were projection neurons (Jones, 1993; Wonders and Anderson, 2005). According to the calculations of Magavi et al. (2012), most of the cortical astrocytes were originally derived from such developmental columns. Interestingly, most labeled cortical columns contained ~3 multiple-astrocyte clusters (a group of GFP-expressing astrocytes each within 25 μm of another GFP-expressing astrocyte). The authors mentioned that a single radial glia likely transforms into multiple astrocytes, but so far direct evidence is lacking. Each cluster comprised 1–15 astrocytes (average, 3.6; Magavi et al., 2012). The phenomenon of multiple astrocytes in a single cluster strongly indicates active proliferation of astrocytes within the cortex shortly after their transformation from radial glia. This phenomenon is consistent with time-lapse imaging results from brain slices and *in vivo* results showing that astrocytes enter the cell cycle and proliferate locally in cortical layers (Burns et al., 2009; Ge et al., 2012). Based on the observations of Magavi et al., radial glia contribute one of every 3.6 astrocytes (~30%)

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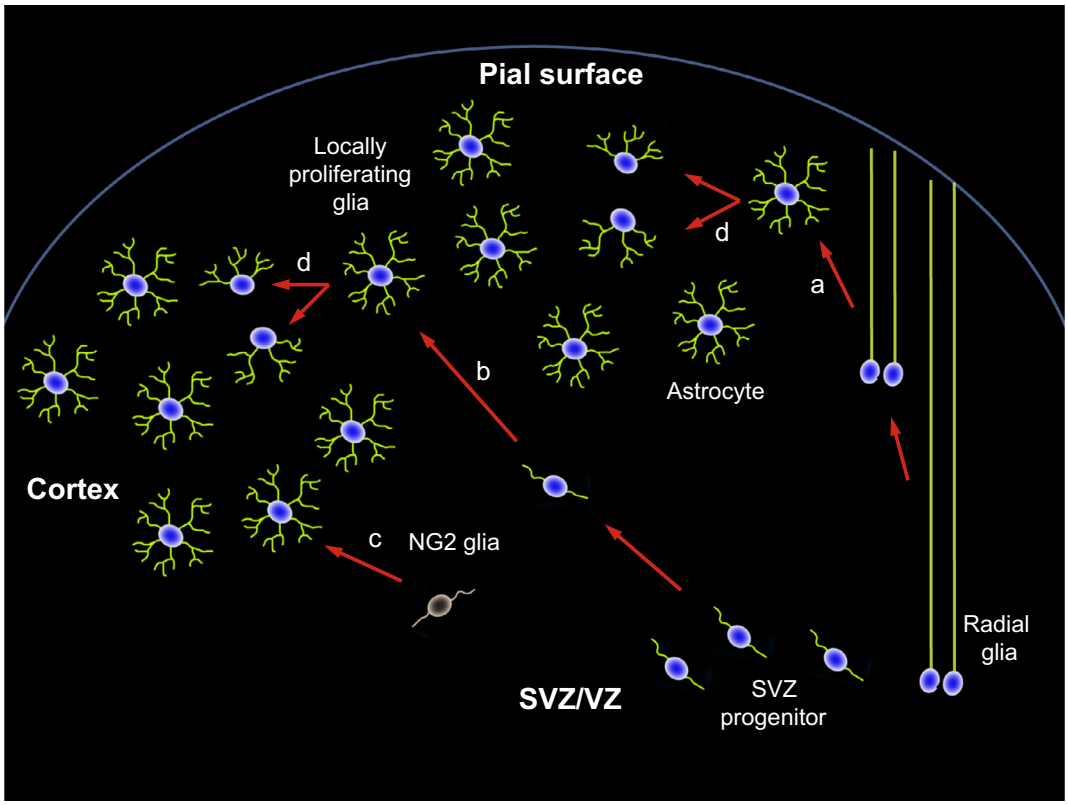

Fig. 1. Four astrocyte sources in the postnatal cerebral cortex. There are four astrocyte sources in the cerebral cortex: radial glia, SVZ-derived progenitors, locally proliferating glia, and NG2 glia. (a) Radial glia translocate from the VZ to the cortex and become immature astrocytes by retracting their long leading processes. (b) Astrocytes derived from the SVZ migrate into the cerebral cortex likely along radial glial shafts. Most radial glia in rodents start to disappear during late embryonic stages, and few remain after postnatal week 2. (c) NG2 glia produce a portion of astrocytes in the ventral cortex of the forebrain. (d) Locally proliferating astrocytes in the cortex undergo symmetric division to generate additional astrocytes. These locally produced astrocytes are a major astrocyte source in the postnatal cortex. Note: locally proliferating astrocytes are originally produced from progenitors in the SVZ and radial glia.

present in the mature cerebral cortex. It is also possible that one radial glia transforms into one astrocyte progenitor (Noctor et al., 2004). These astrocyte progenitors are migratory and retain the capacity to proliferate (Burns et al., 2009; Ge et al., 2012), and consequently a single radial glia–derived progenitor can produce clusters with multiple astrocytes in the cortex (Fig. 1).

SVZ PROGENITOR–DERIVED ASTROCYTES AND THEIR CONTRIBUTION TO THE TOTAL ASTROCYTE POPULATION

Abundant evidence has shown that SVZ progenitors produce both astrocytes and oligodendrocytes in the postnatal rodent cerebral cortex (Smart, 1961; Lewis, 1968; Privat and Leblond, 1972; Paterson et al., 1973; Paterson, 1983; Levison and Goldman, 1993; Levison et al., 1993; Marshall and Goldman, 2002; Burns et al., 2009). Retroviral infection is frequently used to analyze the progeny of the labeled SVZ progenitors *in vivo*. Because only a small portion of SVZ-derived progenitors are labeled with this method, however, direct evidence demonstrating the contribution of SVZ-derived astrocytes to the overall astrocyte population is still needed. The difficulty of traditional methods, such as [^{3}H]thymidine or BrdU labeling, is that they cannot be used to distinguish the contribution of SVZ-derived astrocytes from that of radial glia–derived astrocytes and locally produced astrocytes.

Astrocytes derived from the SVZ are believed to migrate to the cerebral cortex along radial glial shafts, as do projection neurons in embryos. In rodents, most radial glia start to disappear beginning in the late embryonic stages, and few remain after postnatal week 2. Shortly after birth, many axons pass through the white matter in the rodent forebrain (Wang et al., 2007; Zhou et al., 2013) and likely form a physical barrier to astrocyte migration after disappearance of radial glia; moreover, the number of SVZ progenitor–derived astrocytes that migrate into the cortex with assistance from radial glia also decreases substantially (Burns et al., 2009). Our group used electroporation to label both SVZ-derived progenitors and VZ radial glia in P0–2 mice and analyzed their progeny 1–2 weeks later. Approximately 25% of astrocytes derived from the VZ and SVZ migrated into six cortical layers, and ~75% remained in the SVZ and white matter (Ge et al., 2012). After P14, SVZ progenitor–derived astrocytes in rats do not colonize the cerebral cortex (Levison et al., 1993). Because no good method has been developed to efficiently label all SVZ progenitors, we still do not know the percentage of SVZ progenitor–derived astrocytes that contribute to the entire astrocyte population in the postnatal cortex.

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NG2 GLIA-DERIVED ASTROCYTES AND THEIR CONTRIBUTION THE TOTAL ASTROCYTE POPULATION

NG2 glia account for 5–8% of the glial population (Levine et al., 2001) and form synapses with neurons (Bergles et al., 2000; Lin and Bergles, 2004). These glia are the major dividing cells in the nervous system outside of neurogenic regions in the adult rodent brain (Levine et al., 1993; Horner et al., 2000; Dawson et al., 2003; Kukley et al., 2008; Ge et al., 2009; Geha et al., 2010). After pulse-chase with BrdU, 70–75% of BrdU+ cells in the rat cerebral cortex were found to be NG2 glia (Dawson et al., 2003). It is well established that NG2 glia have the potential to produce both oligodendrocytes and astrocytes *in vitro* (Raff et al., 1983). Recently, NG2 glia were found to produce astrocytes in the ventrolateral forebrain of *NG2CreBac;Z/EG* mice, including the temporal cortex, ventrolateral stratum, septum, hippocampus, and thalamus (Zhu et al., 2008). NG2 glia–derived astrocytes contributed 18% and 36% of all astrocytes in the ventral cortical regions of the anterior and posterior forebrain, respectively; however, very few astrocytes were derived from NG2 glia in the dorsal cortex (Zhu et al., 2008). Moreover, because NG2 glia of these *NG2CreBac;Z/EG* mice began producing astrocytes in the late embryonic stage (Zhu et al., 2008), two independent groups did fate mapping by crossing *PdgfraCreER* mice with different reporter lines including *Rosa26-YFP*, *Z/EG*, and *ROSA26-mGFP*. They administrated tamoxifen at P4, P30, P45, and P180 and then analyzed the progeny after days or months to analyze whether NG2 glia produced astrocytes in the postnatal brain (Rivers et al., 2008; Kang et al., 2010; Clarke et al., 2012). Interestingly, both groups found that astrocytes were not produced from NG2 glia in the cerebral cortex. However, another group used *Plp-Cre-ERT2;Rosa26-EYFP* (Plp implies proteolipid) mice and obtained different results (Guo et al., 2009). *Plp* promoter activity is restricted to the oligodendrocyte lineage (Doerflinger et al., 2003). When Guo et al. administered mice with tamoxifen at P7 and carried out immunochemistry at P15, they observed that astrocytes from NG2 glia were distributed in the ventral forebrain including the piriform cortex, amygdala, and hypothalamus. Of the astrocytes in the ventral cortex, 15.9% were from NG2 glia in these mice (Guo et al., 2009). Interestingly, no astrocytes were seen from NG2 glia in the dorsal cortex, which is consistent with the results from *NG2creBac;Z/EG* (Zhu et al., 2008). In short, the contribution of astrocytes derived from the oligodendroglial lineage to dorsal cortical astrocytes is zero and to the ventral cortex is possibly small in the postnatal rodent brain.

LOCAL PROLIFERATION OF GLIA IN THE DEVELOPING CORTEX

Cell proliferation in the cortex has been reported for over a century in different species including dogs, cats, rats, and mice (Buchholtz, 1890; Sclavunos, 1899; Hamilton, 1901; Addison, 1911; Allen, 1912). The huge advancements in the study of radial glia and SVZ progenitors have drawn much attention from researchers in the past three decades, but the importance of local glial production has been neglected. There are two peaks of local proliferation of glia in the rat cerebral cortex after birth: the first is at P3–7, and the second is at P16 (Allen, 1912; Ichikawa et al., 1983). Dividing astrocytes mainly contribute to the first peak (Ge et al., 2012), and dividing NG2 glia mainly contribute to the second peak (Levison et al., 1993; Zerlin et al., 1995; Parnavelas, 1999; Kukley et al., 2008; Ge et al., 2009, 2012). The abundance of locally proliferating glia varies in different layers. In P0 rat brain, more dividing glia (~70%) are located within the inner layers of the cerebral cortex. However, this is reversed in the P4 brain, in which ~70% of all dividing cells from the cerebral cortex are located in the outer layers. At P6–P8, there is no significant difference in the density of proliferating cells between layers (Ichikawa et al., 1983). It remains unknown why astrocyte proliferation peaks during postnatal week 1 but then ceases shortly after week 2 in the rodent brain.

GLIA CONTINUE TO PROLIFERATE LOCALLY IN ADULT MICE

Although cell proliferation outside the SVZ and VZ is quite rare in the adult brain, cell division in glia occurs in nearly all major rodent brain regions including the cerebral cortex, corpus callosum, stratum, hypothalamus, and septum (Messier et al., 1958; Walker and Leblond, 1958; Hain et al., 1961; Smart and Leblond, 1961; Dalton et al., 1968; Dawson et al., 2003). The mean percentage of dividing cells at four ages (at age 23, 100, 200, and 400 days) in mouse brain was determined to be: 0.142% in the septum, 0.445% in the corpus callosum, 0.048% in the corpus stratum, 0.058% in the hypothalamus and 0.090% in the cerebral cortex (Dalton et al., 1968).

Dividing astrocytes can be identified via electron microscopy after [^{3}H]thymidine labeling (Kaplan and Hinds, 1980; Reyners et al., 1986). Thirty days after one injection of [^{3}H]thymidine, 0.077% of astrocytes in the rat visual cortex underwent division and were labeled (Kaplan and Hinds, 1980). With Ki67 staining in h*GFAP-GFP* mouse cortical sections, our group observed that 0.30% of astrocytes were undergoing cell division at P48–52 (Ge et al., 2012).

FREQUENCY OF LOCAL PROLIFERATION OF GLIAL CELLS

Do astrocytes undergo cell division multiple times within the first two postnatal weeks in rodents? Clusters with large numbers of glia labeled with [^{3}H]thymidine (with subsequent visualization via autoradiography) could be observed in the cerebral cortex of both young adult rat and cat brains (Altman, 1963). Retrovirus-mediated gene transfer is an ideal tool for lineage tracing because replication-incompetent retroviruses can be used to introduce new genes (e.g., *lacZ* or *EGFP*) into the genome of dividing cells (Turner and Cepko, 1987). The progeny of infected mother cells retains these marker genes. Ventricular cells were labeled via retroviruses at E16 and clonal analysis carried out at P14; clones with 2–3 closely

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packed glia were observed within the rat cortex, and these clones were produced by local glial proliferation after they migrated into the cortex (Price and Thurlow, 1988). A similar phenomenon was also reported in glial clusters by labeling SVZ cells with two retroviruses at extremely low multiplicity of infection that expressed two different markers to ensure that each cluster of cells was derived from an individual cell after its progeny migrated into the rat cerebral cortex (Levison and Goldman, 1993). The study yielded very interesting results from one of the *Thy1.2-Cre* mouse lines in that there was a low rate of recombination after the line was crossed with a reporter line (Magavi et al., 2012). In the progeny, Magavi et al. found that an individual column of cells was produced from a single progenitor or radial glia. Most labeled cortical columns contained astrocyte clusters (a group of GFP + astrocytes within 25 μm of another GFP + astrocyte). Each cluster contained an average of 3.6 astrocytes, indicating that cortical astrocytes entered the cell cycle approximately two times within the cortex. At 2–4 days after dividing, astrocytes in the cerebral cortex can be labeled using GFP-encoding retroviruses (Ge et al., 2012), and ~10% of the retrovirus-infected astrocytes (i.e., that had divided) can be stained by an antibody against Ki67 (Ge et al., 2012). These observations suggest that some astrocytes enter the cell cycle again shortly after their initial division. In glia, DNA synthesis during S-phase lasts ~10 h (Korr et al., 1973), and the subsequent G2 lasts 2–3 h (Hommes and Leblond, 1967; Korr et al., 1973). Dividing astrocytes complete mitosis (from metaphase to telophase) in 2–3 h (Ge et al., 2012), and the time needed for an astrocyte to complete one cell cycle is less than 24 h in the developing mouse brain (Burns et al., 2009). Therefore, cortical astrocytes can potentially amplify their number sixfold to eightfold via local proliferation within a period of 1–2 weeks. Whether all astrocytes in the cerebral cortex—or only a small percentage—have comparable potential to frequently divide remains an open question.

LOCALLY PRODUCED ASTROCYTES AND THEIR CONTRIBUTION TO THE TOTAL ASTROCYTE POPULATION

Although we have known about local glial proliferation in the brain for a very long time, owing to the diversity of astrocytes from different sources, it was not until recently that we started to understand that the local production of glia is a major source of astrocytes in the cerebral cortex. The main challenge to studying astrocyte generation in the cortex is the lack of specific markers for labeling cortical astrocytes. To date, the efficient way of identifying cortical astrocytes is to fluorescently label them by expressing an exogenous gene such as *GFAP-GFP* (Zhuo et al., 1997; Matthias et al., 2003) or *Aldh1L1-GFP* (Heintz, 2001) under control of the respective promoter. Alternatively, some researchers have used *Aldh1l1-Cre* and *GFAP-CreER* to label astrocytes after a mouse line is crossed with an appropriate reporter line (Gong et al., 2003; Casper et al., 2007; Chow et al., 2008; Ge et al., 2012; Tien et al., 2012; Tsai et al., 2012). In such genetic labeling methods, the astrocytes must be distinguished from other glia types (especially NG2 glia) using another method such as electrophysiology or immunostaining (Matthias et al., 2003; Ge et al., 2012). To determine the contribution of astrocytes derived from local proliferation, we injected retroviruses having a high titer into the cerebral cortex of P0–2 mice with subsequent comparison of the number of virally infected astrocytes with the total number of astrocytes within an infected region after 1 week post-infection. We found that approximately half (46.8%) of the astrocytes were locally produced (Ge et al., 2012). Because the half-life of infectivity of the retrovirus we used is nearly 8 h at 37 °C and retroviruses likely cannot infect all dividing cells, the actual contribution of astrocytes from local production is likely >46.8%. These results demonstrate that local production accounts for a major portion of astrocytes in the postnatal cerebral cortex (Fig. 1).

Although astrocyte generation has been studied for more than a century, certain fundamental questions remain unclear including the following: (1) What is the molecular mechanism underlying the difference in astrocyte sources from different brain regions and different developmental stages? (2) What is the role of neuronal activity in astrocyte production? (3) What mechanisms underlie the interaction between astrocytes and vascular cells and the formation of astrocytic endfeet in the developing brain? New techniques and approaches for glia-specific studies would greatly enhance the ability of researchers to answer these questions.

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