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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%)