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DANCE ROUND

WE DANCE ROUND IN A RING AND SUPPOSE,
BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.
ROBERT FROST

ARE THERE FUNCTIONAL PROGENITOR CELLS IN THE ADULT BRAIN PARENCHYMA?

Anton B. Tonchev
Division of Cell Biology, Department of Forensic Medicine, Medical University, Varna, Bulgaria

The subventricular zone (SVZ) of the anterior horn of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus are the only regions of the adult brain that are widely recognized to contain neural progenitor cells – precursors capable of producing both neurons and glia. However, recent evidence suggests that such cells may exist also outside SVZ and SGZ, in the parenchyma of neocortex and striatum. This opens new possibilities for progenitor cell manipulation in situ with consequent development of novel progenitor-based strategies for the treatment of human neurological disease.
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The adult brain retains progenitor cells in two well-recognized regions (Fig. 1): the subventricular zone (SVZ) of the anterior horn of the lateral ventricle and the subgranular zone (SGZ) of the hippocampal dentate gyrus (1). The SVZ progenitors migrate tangentially at a long distance to become interneurons in the olfactory bulb (2). The SGZ progenitors migrate radially at a short distance to become projection neurons in the dentate granule cell layer, immediately adjacent to SGZ (3). Both types of precursor cells are multipotent, i.e. capable of generating both neurons and glia (2,3), and both types are activated by brain injury or by external application of growth factors (Table 1).

Extensively studied in rodents, *in vivo* neurogenesis has been demonstrated also in the primate SVZ (23,24) and SGZ (25-27) in healthy subjects, while its existence outside these regions at normal conditions remains controversial (28-32). Recent data indicate of differences between the commonly used rodent models and the primates, related to neurogenesis. Thus, the human SVZ appears incapable of sending its precursors to the olfactory bulb (33). Further, while the phenomenon of postischemic precursor cell increase (see Table 1) is observed also in the monkey brain, the primate response is much smaller than the rodent one, especially regarding the neuronal differentiation of progenitor cells (12). Such results indicate of differential molecular control over the rodent and primate precursor cells, the revealing of which is a key factor for the development of successful strategies for the treatment of human neurological disease by means of neural progenitor cells.

In addition to the SVZ and SGZ progenitors, yet another source of such cells has gradually emerged, that offers an exciting possibility of progenitor cells manipulation *in situ*. Data in rodents implicate that precursor cells for neurons and glia may be present also in the parenchyma of the striatum and neocortex (10,34,35). Parenchymal progenitors were isolated *in vitro* also in primates (36,37), but their *in vivo*

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Correspondence and reprint requests to Dr Anton B. Tonchev, Division of Cell Biology, Department of Forensic Medicine, Medical University, BG-9002 Varna, Bulgaria. E-mail: atontchev@yahoo.com

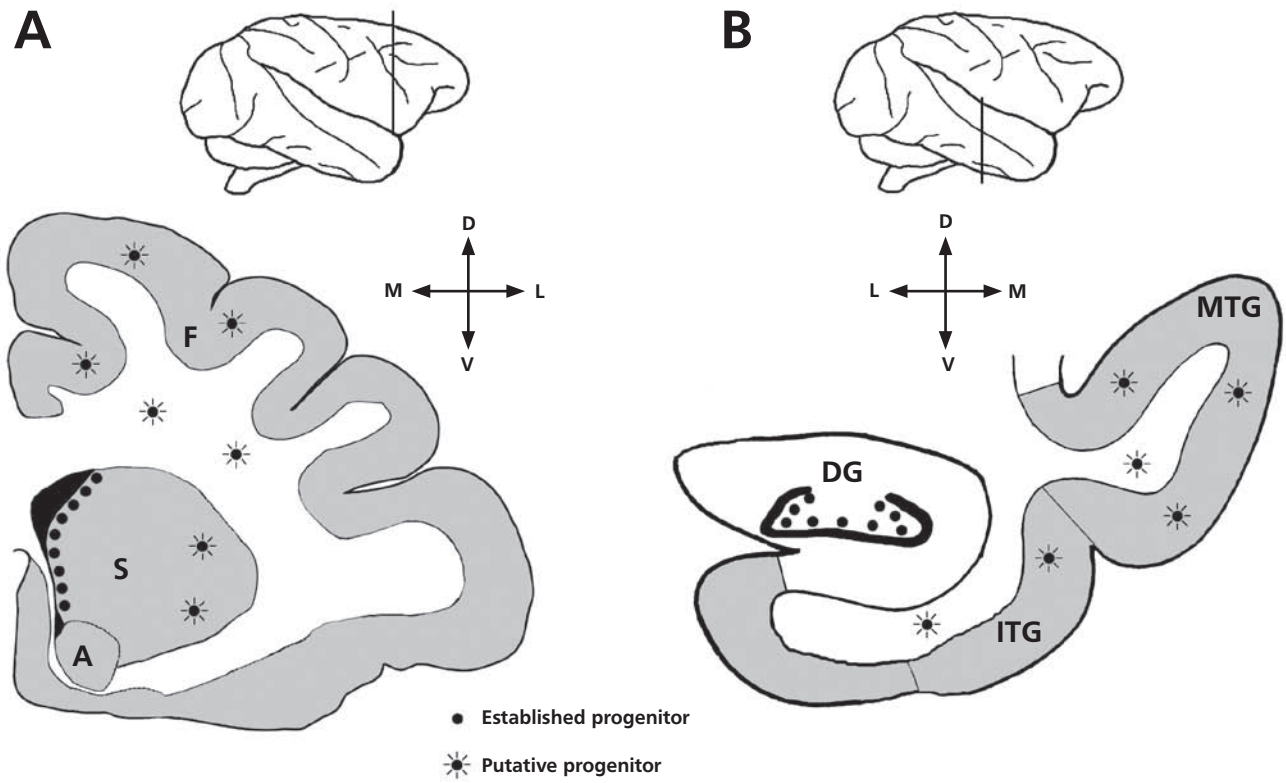

Figure 1. *Schematic maps of the adult monkey brain.* ***(A)*** *Coronal section through the frontal lobe (lower image) at the level depicted on the whole-brain map (upper image). The SVZ progenitors are located around the walls of the anterior horn of the lateral ventricle (V). Putative progenitors may be present in the frontal neocortex (F) or the striatum (S). A, accumbens nucleus.* ***(B)*** *Coronal section through the temporal lobe (lower image) at the level depicted on the whole-brain map (upper image). The SGZ progenitors are located in the hippocampal dentate gyrus (DG). Putative progenitors may be present in the temporal neocortex, including the middle (MTG) and inferior (ITG) temporal gyri. Directions: D, dorsal; V, ventral; M, medial; L, lateral.*

capabilities remain elusive. If parenchymal (e.g. in neocortex or striatum, see Fig. 1) progenitors really exist in the adult brain and are functional, i.e. capable of neuronal replacement *in vivo*, they offer a great clinical potential because of their spatial proximity to sites of injury in the brain parenchyma. The spatial proximity is of a particular importance in the case of the large primate brain, in which it may take weeks or months for the SVZ progenitors to travel from their site of origin to a distant portion of the brain parenchyma in order to replace lost cells.

A significant step toward the understanding that parenchymal progenitors may exist *in vivo* was made by a recent study of Ourednik *et al* (38). The authors implanted human neural stem cells in the lateral ventricles of embryonic monkey brains, and investigated the fate of these cells 4 weeks later. While most of the implanted cells had adopted a differentiated cell fate – either neuronal or glial – in the prefrontal neocortex, Ourednik *et al* also observed a few cells with features of undifferentiated progenitors in the brain parenchyma (38). While it is unclear whether this phenomenon is applicable also to the adult monkey brain, the results of Ourednik *et al* suggest that the adult primate brain might retain some kind of progenitors in the parenchyma.

Our recent data in adult monkeys represent additional evidence in this direction. We used a model of global cerebral ischemia in adult macaques (39) that completely but transiently blocks all blood flow to the brain structures, causing a major neuronal injury to the hippocampus, and a lesser injury to the striatum and neocortex (40,41). We found increased progenitor cell proliferation in the hippocampal dentate gy-

Table 1. *Selected pathological conditions and growth factors that increase the proliferation of SVZ and/or SGZ progenitors.*

Conditions	References
Ischemia	4-12
Seizures	13-16
Growth factors	
EGF	8
bFGF	8,17
BDNF	18,19
TGFα	20
IGF-I	21
VEGF	22

Abbreviations: EGF, epidermal growth factor; bFGF, basic fibroblast growth factor; BDNF, brain-derived neurotrophic factor; TGFα, transforming growth factor-α; IGF-I, insulin-like growth factor-I; VEGF, vascular endothelial growth factor.

rus within the second postischemic week (12), similarly to the rodent brain after ischemia (4,5,7,8). However, the proliferation and neuronal differentiation of progenitor cells were much smaller in the monkey than in the rodent dentate gyrus (12). Further, in the same monkey model, we showed *in vivo* evidence of actively proliferating precursor cells in the core white matter of the olfactory bulb (42), in coherence with previous *in vitro* results in humans (43) and rodents (44). The finding of multipotent progenitors residing in the olfactory bulb is important, because it shows that such cells may exist outside SVZ and SGZ, the two established germinal zones of the adult brain. Our yet unpublished observations (Tonchev and Yamashima, in preparation) suggest that the striatal and neocortical parenchyma is another location containing neural progenitor cells. We found *in vivo* evidence of actively proliferating cells with progenitor immunophenotype in the adult monkey parenchyma, in combination with data for a limited neuronal replacement in these regions after ischemia. Importantly, we found no evidence of progenitor cell migration from SVZ to these areas, suggesting that the new neocortical and striatal neurons are derived from a local pool of precursors.

Taken together with previous *in vitro* data in primates (36,37), our results argue that the parenchymal progenitors of the adult primate brain exist and are functional, i.e. capable of neuronal replacement *in vivo*. Instruction of proliferation and neuronal differentiation to these cells by genetic manipulations such as pro-neuronal transcription factor overexpression (45) might further improve their ability to replace dead neurons *in situ*. Over 4 decades after Joseph Altman, the pioneer of the adult neurogenesis research, asked "Are new neurons formed in the brains of adult mammals?" (46), we ask ourselves whether neurogenesis may also take place by parenchymal progenitors at sites of injury in the adult brain. The clinical implications of such cells in the treatment of human neurological disease could be enormous.

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