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Review

# The human subventricular zone: A source of new cells and a potential source of brain tumors

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**Abstract**

The mammalian brain has been perceived as a quiescent organ incapable of postnatal neurogenesis for many years. Most recently, several studies have demonstrated that the adult mammalian brain is indeed capable of neurogenesis and that the process is primarily confined to the subventricular zone (SVZ) of the forebrain and the subgranular zone (SGZ) of the hippocampus. Of these regions, the SVZ is the largest niche of neurogenesis in the adult mammalian brain. Within this niche resides a subpopulation of astrocytes with stem cell-like features of self-renewal and multipotentiality. Interestingly, there is also a subpopulation of cells within brain tumors that possess these same characteristics. Based on these findings, the emerging hypothesis is that brain tumor stem cells may be derived from neural stem cells and that both of these populations may originate from the SVZ. This possible connection stresses the importance of studying and understanding the role that the human SVZ plays in not only harboring neural and brain tumor stem cells, but how this microenvironment may support both neurogenesis and tumorigenesis. Furthermore, the obvious differences in the SVZ between humans and other animals make it important to understand the human model when studying human disease. Such an understanding may lead to novel therapeutic strategies for both neurodegenerative diseases and currently intractable brain tumors.


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## Introduction

The brain, for hundreds of years, has been perceived as a quiescent organ incapable of postnatal neurogenesis. In fact, Ramon y Cajal in 1928 stated “in adult centres the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree” (DeFelipe and Jones,

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1991). This dogma was initially challenged by Altman's identification of neurogenesis in adult rats (Altman, 1962) and continued with Goldman and Nottebohm's work with female canaries (Goldman and Nottebohm, 1983). Since then, several studies have demonstrated that the adult mammalian brain is indeed capable of neurogenesis and that the process is primarily confined to the subventricular zone (SVZ) of the forebrain and the subgranular zone (SGZ) of the hippocampus (Alvarez-Buylla et al., 1998; Luskin, 1993; Reznikov, 1991; Sanai et al., 2004).

Of these regions, the SVZ is the largest neurogenic niche in the adult mammalian brain (Alvarez-Buylla and Garcia-Verdugo, 2002; Blakemore, 1969; Doetsch et al., 1997; Eriksson et al., 1998; Gould et al., 1990; McDermott and Lantos, 1990; Quinones-Hinojosa et al., 2006; Sanai et al., 2004). Within this niche resides a subpopulation of astrocytes with stem cell-like features of self-renewal and multipotentiality in rodents (Doetsch et al., 1999) and most recently also found in humans (Sanai et al., 2004). Recently, a subpopulation of cells within brain tumors that possesses these same characteristics has been found (Galli et al., 2004; Hemmati et al., 2003; Ignatova et al., 2002; Lee et al., 2006; Singh et al., 2004). The emerging hypothesis is that brain tumor stem cells (BTSCs) may be derived from neural stem cells (NSCs) and that both of these populations originate from the SVZ (Sanai et al., 2005; Vescovi et al., 2006). This possible connection stresses the importance of studying and understanding the SVZ as both a normal source of new cells and as a potential source of tumors.

In this review, we discuss and analyze the structure, cytoarchitecture and cellular composition of the human SVZ and provide a comparison to the well-studied rodent SVZ. In addition, we evaluate the SVZ as a potential source of brain tumors and, more specifically, BTSCs. Finally, we discuss the potential implications this may have on the clinical treatment of both neurodegenerative diseases and brain tumors.

## Human subventricular zone: A source of new cells

The "no new neuron" dogma that the brain is incapable of adult neurogenesis was initially challenged in the 1960s when Altman demonstrated, using tritiated thymidine, that the subependymal areas lining the lateral ventricles in rats possessed postnatal mitotic cells (Altman, 1962; Altman and Das, 1966). This finding was confirmed in 1977 by Kaplan and Hinds (1977). Approximately 20 years after Altman's discovery, Goldman demonstrated persistent neurogenesis in the ventricular zones of adult female canaries (Goldman and Nottebohm, 1983). These findings later led to the discovery of neurogenesis in the SVZ of several animal species including mice (Morshead et al., 1994; Reynolds and Weiss, 1992), rabbits (Gueneau et al., 1982), tree shrews (Gould et al., 1997) and monkeys (Gould et al., 1998). Despite these discoveries, however, many still believed that the adult human brain was immutable and incapable of neurogenesis (Kornack and Rakic, 2001; Seress et al., 2001).

Also contributing to this controversy was the actual identity of the SVZ stem cells. Johansson et al. in the 1990s suggested that the ciliated ependymal cells that line the ventricles were the source of postnatal neurons (Johansson et al., 1999a). However, shortly thereafter, Doetsch et al. demonstrated that SVZ astrocytes, and not ependymal cells, were the putative NSCs within this germinal niche (Doetsch et al., 1999). These cells remained labeled for a longer period of time following administration of proliferation markers, and, more importantly, were capable of forming the three cell lineages of astrocytes, oligodendrocytes and neurons *in vitro* (Doetsch et al., 1999). This led to speculation that astrocytes were also the stem cells present in many glial tumors including astrocytomas and glioblastoma multiforme (GBMs) (Galli et al., 2004; Hemmati et al., 2003; Ignatova et al., 2002; Singh et al., 2003).

Findings that support human neurogenesis started in the mid-1990s (Kirschenbaum et al., 1994; Pincus et al., 1997). Human SVZ explants derived from temporal lobectomies in patients with refractory epilepsy were utilized to demonstrate that the adult human forebrain was capable of *in vitro* neuronal production (Kirschenbaum et al., 1994; Pincus et al., 1997). *In vivo* evidence, however, started with Gage and colleagues (Eriksson et al., 1998). They obtained postmortem brain tissue from patients with upper respiratory tract squamous cell carcinomas, who were diagnostically infused with bromodeoxyuridine (BrdU) to label mitotically active cells. Through immunofluorescent labeling, they were able to show that new neurons were generated in both the SVZ and the SGZ of the hippocampus (Eriksson et al., 1998).

While these findings indicate that the human brain is indeed capable of persistent neurogenesis (Eriksson et al., 1998; Kirschenbaum et al., 1994; Pincus et al., 1997), these studies did not definitively prove that the human brain possessed NSCs, which are cells capable of self-renewal and multipotency (Vescovi et al., 2006). The current standard for determining the presence of NSCs is through neurosphere assays (Chaichana et al., 2006; Reynolds and Rietze, 2005). These assays create a serum-free, growth factor supplemented, non-adherent condition in which stem-like cells are able to continually divide and form multipotent, undifferentiated clones called neurospheres *in vitro* (Reynolds and Weiss, 1992). The neurospheres that form from these conditions can be serially dissociated and re-plated to generate additional spheres, while cells not capable of self-renewal eventually die off (Reynolds and Rietze, 2005; Vescovi et al., 2006). The clonal cells within these neurospheres are multipotent because they can generate neurons, astrocytes and/or oligodendrocytes with the addition of serum, removal of mitogens and/or transfer to adherent plates (Reynolds and Rietze, 2005; Vescovi et al., 2006).

The identification of adult human NSCs using neurosphere assays began with Steindler and colleagues, who were able to isolate multipotent cells from both the SVZ and SGZ in adult humans (Kukekov et al., 1999). These cells formed neurospheres *in vitro* and were capable of generating cells with neuronal (β-III tubulin positive), oligodendrocyte (O4 positive) and glial markers (glial fibrillary acidic protein positive) (Kukekov et al., 1999), confirming similar findings previously made from human fetal-derived neuroepithelial cells (Chalmers-Redman et al., 1997). Johansson et al. subsequently