Feature Review

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# Adult neural stem cells stake their ground

**Daniel A. Lim[1,2,3] and Arturo Alvarez-Buylla[1,2]**

[1] Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA 94143, USA
[2] Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, University of California, San Francisco, San Francisco, CA 94143, USA
[3] Veterans Affairs Medical Center, University of California, San Francisco, San Francisco, CA 94143, USA

**The birth of new neurons in the walls of the adult brain lateral ventricles has captured the attention of many neuroscientists for over 2 decades, yielding key insights into the identity and regulation of neural stem cells (NSCs). In the adult ventricular–subventricular zone (V–SVZ), NSCs are a specialized form of astrocyte that generates several types of neurons for the olfactory bulb. In this review, we discuss recent findings regarding the unique organization of the V–SVZ NSC niche, the multiple regulatory controls of neuronal production, the distinct regional identities of adult NSCs, and the epigenetic mechanisms that maintain adult neurogenesis. Understanding how V–SVZ NSCs establish and maintain lifelong neurogenesis continues to provide surprising insights into the cellular and molecular regulation of neural development.**

Since the discovery of adult brain neurogenesis [1,2], a finding that overturned the long-held notion 'of no new neurons' in the adult central nervous system, exploration into the cellular and molecular regulation of adult neural stem cells (NSCs) has continued to generate fundamental insights into both neural developmental and adult brain function. One of the most interesting questions unique to the study of adult neurogenesis is how adult NSCs – which are derived from progenitor cells in the embryo – retain both their neurogenic capacity and regional specificity for long periods of time.

In the postnatal brain of many mammals, a large population of NSCs is present within an epithelium called the ventricular–subventricular zone (V–SVZ) that lines the walls of the lateral ventricle [3,4]. In rodents, V–SVZ NSCs generate large numbers of neurons that migrate very rapidly along the rostral migratory stream (RMS) into the olfactory bulb (OB), where they differentiate into multiple types of local circuit interneurons. The OB function and structure relies on this constant inflow of new neurons that contribute to neural plasticity of olfactory information processing [5,6].

The identification of a subpopulation of astroglial cells (B1 cells) as the V–SVZ NSCs [7] provided some of the first clues about the glial nature of NSCs, a concept that has been generalized to embryonic development [8]. In both the embryo and adult brain, NSCs are a specialized form of glia that reside in neurogenic niches [9]. However, in contrast to the embryonic brain – wherein neural precursors are inherently transient, continually changing their developmental potential and location over time – adult V–SVZ NSCs are more stable and harbored in a well-defined niche that includes ependymal cells, mature vasculature, and axonal terminals. This unique niche provides multiple regulatory controls for the production of neurons within the fully assembled adult brain. Importantly, recent findings indicate that NSCs within the V–SVZ have distinct regional identities (see Glossary) related to their embryonic origin. Thus, the adult NSC populations appear to 'remember' positional cues that pattern the developing brain. Alongside advancement in the field of epigenetics – studies of the V–SVZ have revealed how chromatin-modifying factors play critical roles in adult brain neurogenesis.

In this review, we focus on selected recent findings that illustrate how the study of adult V–SVZ and OB neurogenesis offer unique advantages for discovery of developmental processes and molecular mechanisms that have long been thought to be restricted to embryonic development.

## Glossary

**Regional identity:** the developmental specialization of precursor cells based on their physical location.
**Epigenetics:** the study of heritable patterns of gene expression that do not involve changes to the DNA sequence.
**Chromatin:** the dynamic polymer of DNA and histone proteins. The nucleosome – approximately 146 bp of DNA wrapped approximately twice around an octamer of the four core histone proteins (H2A, H2B, H3, H4) – is the basic subunit of chromatin. Chromatin can undergo non-covalent and covalent changes, which corresponds to differences in local transcriptional activity. Some of these chromatin-based changes are heritable through cell division.
**Non-coding RNA:** While only 1–2% of the mammalian genome codes for protein, approximately 80% of the genome is transcribed, and most of these transcripts have essentially no protein coding potential. While some non-coding RNAs such as microRNAs have been studied in detail, long non-coding RNAs (lncRNAs) – those longer than 200 nucleotides (nt) – are less understood.

*Corresponding authors:* Lim, D.A. (limd@neurosurg.ucsf.edu); Alvarez-Buylla, A. (abuylla@stemcell.ucsf.edu).
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### Type B1 cells: a 'displaced' form of radial glia?

Consistent with their astrocytic morphology and ultrastructure, B1 cells express glial markers such as the glial-fibrillary acidic protein (GFAP), glutamate aspartate transporter (GLAST), and brain lipid binding protein (BLBP). Recent work indicates that B1 cells can exist in either a quiescent or activated state [10,11]. Interestingly, quiescent B1 cells do not appear to express Nestin, an intermediate filament protein that has long been considered to be a marker of NSCs. By contrast, activated B1 cells, which generate transitamplifying precursors (C cells), do appear to express Nestin. C cells divide symmetrically approximately three times before becoming migratory neuroblasts (A cells), which divide one or two more times while *en route* to the OB [12]. Type A cells migrate within a network of interconnecting paths that coalesce at the anterior ventricle, forming the rostral migratory stream (RMS) [13], which carries the neuroblasts into the OB where they then migrate radially and differentiate into interneurons of several different types, as we later discuss.

B1 cells retain epithelial features similar to those of their predecessors [14], the radial glia, which are the precursors to most neurons and mature glia in the embryo. B1 cells have apical processes that contact the ventricle and end-feet on blood vessels [3,4]. This elongated structure allows B1 cells to bridge all compartments of the V–SVZ (Figure 1). The V–SVZ can be subdivided into three domains based on the structure and spatial arrangement of B1 cells: domain I (apical) contains the apical process of B1 cells and the ependymal layer; domain II (intermediate) contains the cell body of most type B1 cells, which are in contact with the type C and A cells; and domain III (basal) contains the B1 cell's basal process with end-feet upon blood vessels. These subdomains likely play unique roles in type B1 cell regulation, perhaps by providing NSCs with extrinsic signals that are distinct to each region.

Prior to studies of the V–SVZ, the lateral ventricle ependyma was generally described as a layer of multiciliated epithelial cells forming a 'barrier' between the brain parenchyma and the ventricle lumen, which contains cerebrospinal fluid (CSF). However, in domain I, B1 cells contact the ventricle with a thin cellular process that is interdigitated between ependymal cells [7,15,16]; when the surface of the ventricle is viewed *en face*, these thin apical endings are observed at the center of pinwheels formed by the large apical surfaces of the surrounding ependymal cells [3]. While ependymal cells bear many long, motile cilia, the apical surface of type B1 cells has a single, nonmotile primary cilium.

Interestingly, primary cilium and ventricular contact are cellular features common to embryonic radial glial cells [9]. In early neural precursors, the primary cilium is required for Sonic hedgehog protein (SHH) signaling [17]. In the V–SVZ, SHH-signaling regulates neurogenesis [18], and the cerebrospinal fluid (CSF) is known to contain a number of extrinsic signals including SHH, Wingless (Wnt), retinoic acid (RA), bone morphogenetic proteins (BMPs), and insulin-like growth factor 2 (IGF-2) [19,20]. IGF-2 in the CSF regulates the proliferation of type B1 cells [20], supporting the notion that the CSF provides extrinsic regulatory cues to the V–SVZ niche; however, it remains to be determined whether the ventricular contact and/or the primary cilium of B1 cells are required for the transduction of factors in the CSF.

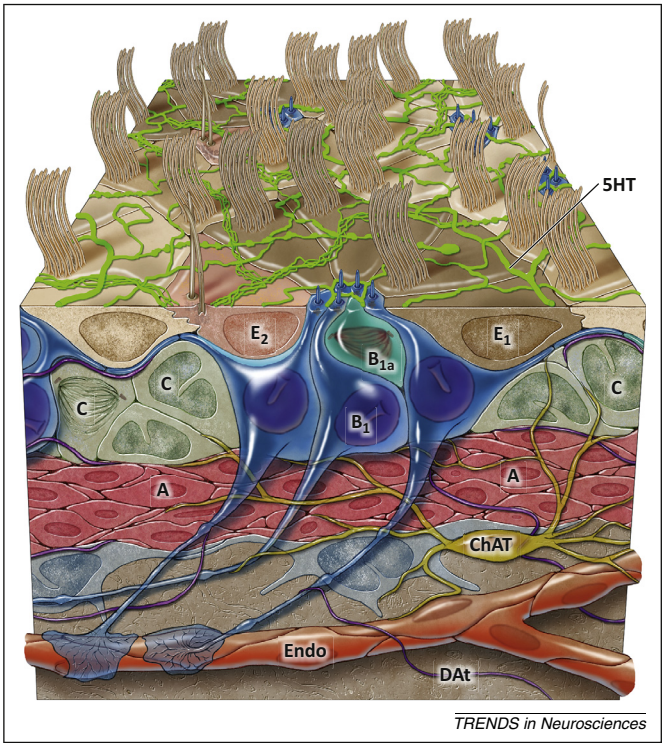


**Figure 1**. Schematic of the ventricular–subventricular zone (V–SVZ) organization. Astroglial B1 cells, V–SVZ NSCs (dark blue), give rise to activated B1 cells (B1a, light blue) that actively divide [10,11]. Activated B1 cells generate the transit-amplifying C cells (green) which, after three rounds of divisions, give rise to A cells, the migrating neuroblasts [12]. Note that B1 cells contact the ventricle with an apical process. This adult VZ is also populated by ependymal cells, multiciliated cells that together with the apical endings of B1 cells from pinwheel structures on the surface [3]. Coursing along this ventricular surface is a rich network of serotonergic axons (5HT, bright green) [44]. The basal processes of B1 cells have endings on blood vessels. Choline acetyltransferase (ChAT)-positive neurons found in the region have endings in the SVZ (olive brown) [51]. Dopaminergic terminals (DAt, purple) are also observed in this region.

The spatial and morphological similarities between B1 cells and embryonic radial glia, and the direct lineage relationship between these populations of neural precursors, suggest that B1 cells 'preserve' certain embryonic-like characteristics throughout adult life. The persistence of long-term neurogenesis likely involves both cell-intrinsic neurogenic 'competence' of B1 cells and cell-extrinsic signals that are instructive or permissive for neuronal differentiation. During early embryonic development, morphogens pattern the brain, inducing radial glial cells to acquire regional identities. As we discuss below, B1 cells also maintain similar regional identities throughout adult life. This long-term maintenance of regional identity in NSC populations raises important questions about how such spatial information is maintained as the brain grows much larger.

### The regional identity of V–SVZ NSCs

NSCs located in geographically distinct regions of the ventricle walls produce different types of OB neurons [21,22] (Figure 2). For instance, dorsal NSCs produce superficial granule cells (GCs) and anteriorly TH-positive periglomerular cells (PGCs), but few, if any, calbindin-positive PGCs. By contrast, ventral NSCs produce