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Adult neural stem cells and their niche: a dynamic duo during homeostasis, regeneration, and aging

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Stem cells persist in specialized niches in the adult mammalian brain. Emerging findings highlight the complexity and heterogeneity of different compartments in the niche, as well as the presence of local signaling microdomains. Stem cell quiescence and activation are regulated not only by anchorage to the niche and diffusible signals, but also by biophysical properties, including fluid dynamics. Importantly, the adult neural stem cell niche integrates both local and systemic changes, reflecting the physiological state of the organism. Moreover niche signaling is bidirectional, with stem cells and their progeny and niche cells dynamically interacting with each other during homeostasis, regeneration and aging.

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Introduction

Neural stem cells reside in specialized microenvironments that support their self-renewal and differentiation throughout life. Two regions continuously generate new neurons that functionally integrate into neural circuits: the ventricular–subventricular zone (V/SVZ) of the lateral ventricles (LV), which gives rise to olfactory bulb neurons, and the subgranular zone (SGZ) of the hippocampal formation, which generates granule cells in the dentate gyrus (Figure 1). In both regions, the stem cells display radial-like morphology and exhibit hallmark ultrastructural and molecular features of astrocytes [1].

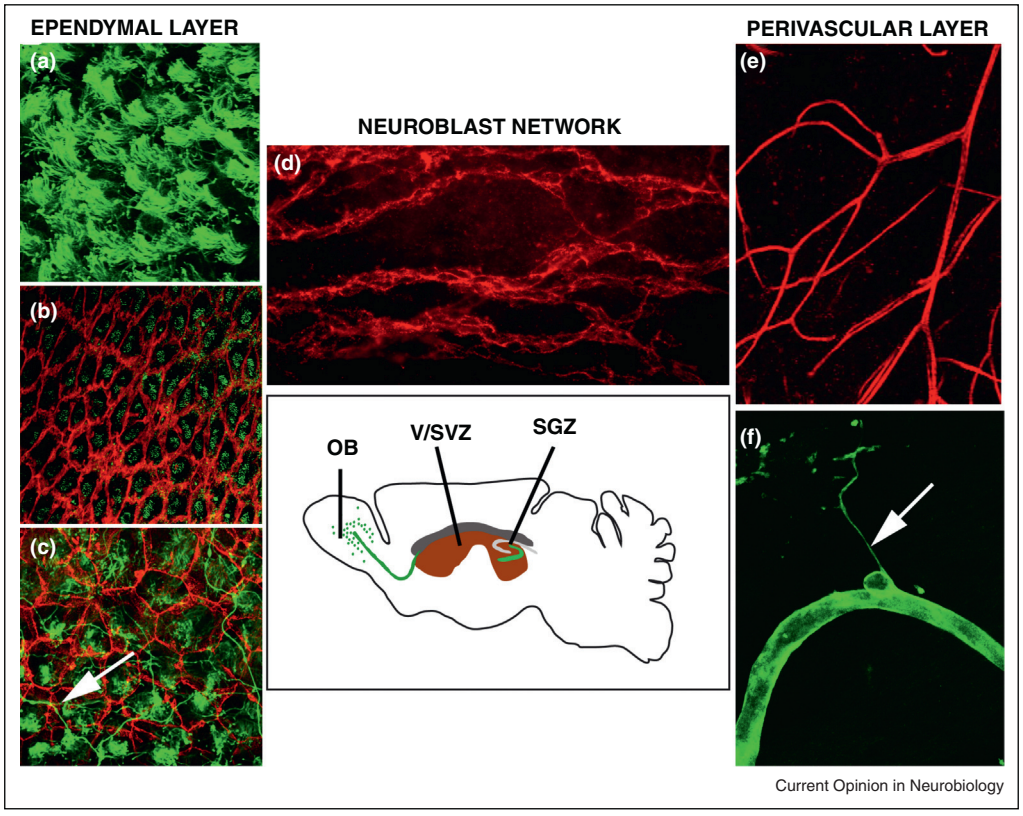
An exquisite balance between intrinsic and extrinsic signals is essential to mediate stem cell quiescence, activation, self-renewal and differentiation. Different physiological and pathological states, as well as aging, modulate stem cell behavior and cell fate decisions. Importantly, extrinsic signals can exert stage-specific effects, reflecting differential sensitivity of stem cells and their progeny to cues in the niche. In this review, we do not discuss the intrinsic regulation of adult neural stem cells, but instead highlight recent insights into novel features of the adult neural stem cell niche, and how it changes with aging. We focus primarily on the V/SVZ, but discuss interesting differences with the SGZ stem cell niche.

Anatomy of the V-SVZ stem cell niche

The V/SVZ is a thin layer of dividing cells adjacent to the lateral walls of the LV (Figures 1 and 2) and is the largest germinal area in the adult mammalian brain. Stem cells (Type B cells) divide under both homeostasis and during regeneration to give rise to transit amplifying cells, which in turn generate neuroblasts that migrate to the olfactory bulb [1]. A small number of oligodendrocytes are also produced in the adult V/SVZ [1]. Type B stem cells are largely quiescent *in vivo*, and occasionally become activated to divide; however, the activating signals are unknown.

The architecture of the V/SVZ and its niche are best visualized in whole mount preparations of the lateral wall of the ventricle, which have allowed key niche features to be discovered. A unique feature of the V/SVZ stem cell niche is its proximity to the cerebrospinal fluid (CSF), which fills the ventricles. Ependymal cells line the ventricles and are arranged as a series of pinwheels (Figure 1a–c) [2]. Neuroblasts are organized as a network of chains throughout the SVZ (Figure 1d) [3]. A planar vascular plexus also extends throughout the length of the SVZ (Figure 1e) [4,5]. Several populations of astrocytes are present in the V/SVZ, with differing morphologies and locations in the niche [1]. B1 stem cells have a highly polarized morphology and contact the CSF at the center of pinwheels via a small apical process, the intermediate SVZ with their soma, and the vasculature via a long basal process (Figure 2) [2]. As such, individual B1 stem cells are exposed to signals from three niche compartments simultaneously: the CSF/ependymal cell niche (apical), the intermediate SVZ niche (SVZ cells and other niche

Figure 1



Architecture of the V/SVZ niche. Sagittal schema of the adult mouse brain showing the location of the two adult neurogenic niches, the V/SVZ and SGZ. Schema shows the lateral ventricle in its entirety. The V/SVZ lies along the walls of the lateral ventricle (red) and generates olfactory bulb interneurons. The SGZ in the hippocampal formation gives rise to granule neurons in the dentate gyrus. Whole mount preparations reveal the three main layers of the V/SVZ (ependymal layer, neuroblast network and perivascular layer). **(a–c)** Multi-ciliated ependymal cells line the ventricles and are arranged as pinwheels. (a) Their long motile cilia (acetylated tubulin, green) are arranged in tufts. (b) Pinwheel organization of the wall of the ventricle is revealed by immunostaining for β-catenin (red), which labels adherens junctions, and gamma-tubulin (green), which labels the basal bodies of cilia. Stem cell astrocytes contact the ventricle at the center of pinwheels and have a single primary cilium. (c) Acetylated tubulin staining (green) also reveals a network of axons (arrow) present on the surface of the lateral ventricles. **(d)** Migrating neuroblasts form a network of chains that extends throughout the length of the SVZ (red, PSA-NCAM). **(e)** A planar vascular plexus also extends throughout the SVZ (red, CD31). **(f)** ECM structures called fractones (arrow) emanate from the perivascular niche (laminin, green) and frequently terminate in speckles near the ependymal layer.

cells) and the perivascular niche (basal) (Figure 2) [6]. Below we explore how these different niche compartments affect each stage of the stem cell lineage.

The CSF/ependymal niche: a node for systemic signals where flow meets pinwheels

The CSF/ependymal compartment is an important nexus of signaling, cell–cell interactions and fluid dynamics that influence V/SVZ stem cells and their progeny (Figures 2 and 3). The primary source of the CSF is the choroid plexus (CP), a mini-organ floating in the ventricles (Figure 3). The CSF is propelled through the ventricular system by the beating of the motile cilia of ependymal cells, allowing the long-range propagation of local and systemic signals.

The CSF has important support functions in the brain, including physical cushioning, transport of ions and nutrients, and its role as a clearance system. It is also widely used for clinical diagnosis, as its composition is altered during pathological states [7]. Strikingly, proteomic analysis of the CSF in different species from the embryo to adulthood has revealed that the CSF also contains a rich repertoire of signaling molecules [8] whose composition changes over time. In the embryo, CSF promotes the proliferation of neural progenitors, with CSF-borne IGF2 being a key factor [9••]. Moreover, the CSF effect was optimal when age-matched CSF and tissue were used, highlighting the dynamic nature of both this compartment and of the intrinsic state of the responding cells.