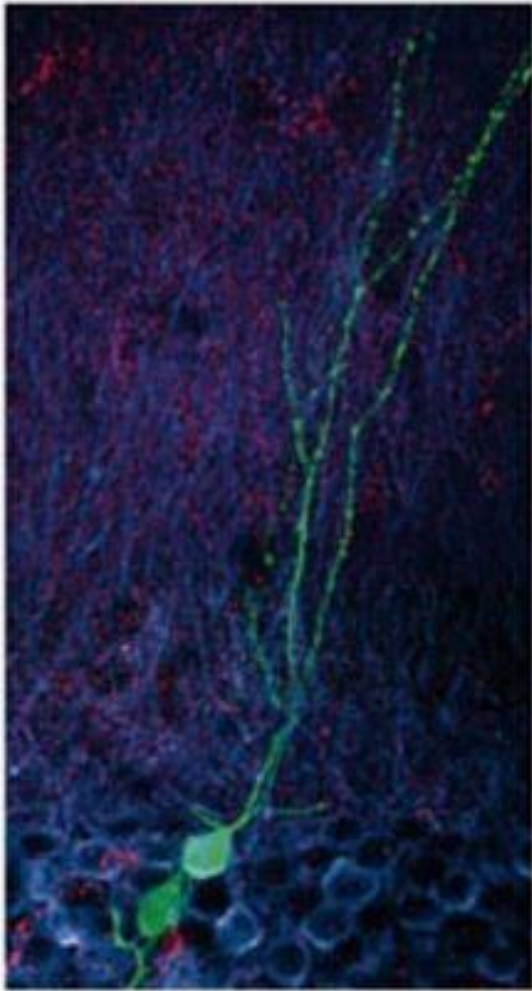


# The Subgranular Zone Niche

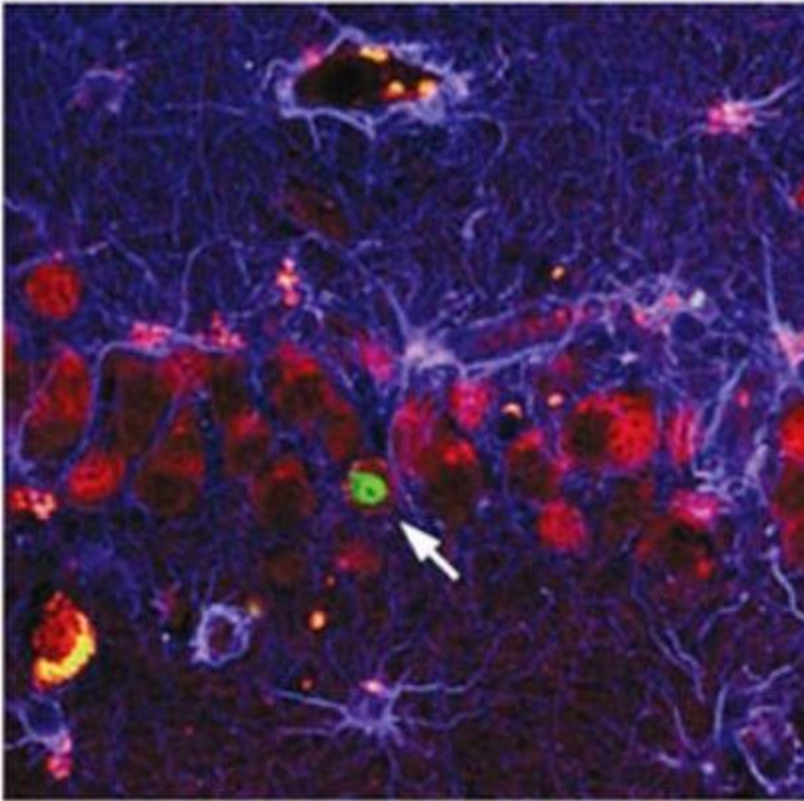
Until recently, it was generally believed that once the mammalian nervous system was mature, no new neurons were “born”—in other words, the neurons formed in utero and during the first few years of life were all we could ever expect to have. The good news from recent studies, however, is that the adult brain is capable of producing new neurons, and environmental stimulation can increase the number of these new neurons.

In these experiments, researchers injected adult mice, rats, and marmosets with bromodeoxyuridine (BrdU), a nucleoside that resembles thymidine. BrdU is incorporated into a cell’s DNA only if the cell is undergoing DNA replication; therefore, any cell labeled with BrdU must have been undergoing DNA synthesis during the time it was exposed to BrdU. This labeling technique revealed that adult mice produce thousands of new neurons each day. Moreover, these new brain cells integrated with other cells of the brain, had normal neuronal morphology, and exhibited action potentials (Figure 1; van Praag et al. 2002). These new cells turn out to be radial glial cells similar to the cells that produced the brain during embryogenesis, and like the original radial glial stem cells, they are self-renewing and multipotent (i.e., capable of forming both neurons and glia; Bonagudi et al. 2011).



**Figure 1** Newly generated adult mouse neurons (green cells) have a normal morphology and receive synaptic inputs. The red spots are synaptophysin, a protein found on the dendrites at the synapses of axons from other neurons. (B) In the adult mouse hippocampus, the soma of neural stem cells (green) reside below their progeny, the granule neurons (red). The long axons of the stem cells can be seen extending through this region of neurons. (From Van Praag et al. 2002.)

Injecting humans with BrdU is usually unethical, since large doses of BrdU are often lethal. However, in certain cancer patients, the progress of chemotherapy is monitored by transfusing the patient with a small amount of BrdU. Gage and colleagues took postmortem samples from the brains of five such patients who died between 16 and 781 days after the BrdU infusion (see Eriksson et al. 1998). In all five subjects, they saw labeled (new) neurons in the granular cell layer of the hippocampal dentate gyrus (a part of the brain where memories may be formed). The BrdU-labeled cells also stained for neuron-specific markers (Figure 2). Thus, although the rate of new neuron formation in adulthood may be relatively low, the human brain is not an anatomical fait accompli at birth, or even after childhood.



**Figure 2** A newly generated neuron (arrow) in the adult human brain (specifically, in the dentate gyrus of the hippocampus). The red fluorescence is from an antibody that stains only neural cells. Yellow indicates the overlap of red and green. Glial cells are stained purple. (From Eriksson et al. 1998, photograph courtesy of F. H. Gage.)

Production of neurons in adults appears to be limited to (1) the subventricular zone (adjacent to the ventricular zone) along the walls of the lateral ventricles and (2) certain regions of the hippocampus (Kempermann et al. 1997a,b; Kornack and Rakic 1999; van Praag et al. 1999; Ihrie and Alvarez-Buylla 2011). In the subventricular zone, the type of neuron produced is determined by the paracrine factors that are secreted by other cells in the neighborhood. Sonic hedgehog, produced by a small group of neurons in the ventral forebrain, is an especially important paracrine factor in producing ventral neuronal types (such as those whose defects cause Parkinson disease). If these Shh-secreting neurons are ablated, no new ventral neurons form; and if Shh is ectopically placed near the dorsal portions of the subventricular zone, those new neuroblasts are transformed into ventral neuroblasts (Ihrie et al. 2011).

Adult neural stem cells represent only about 0.3% of the ventricle wall cell population, but they can be distinguished from more differentiated cells by their cell surface proteins<sup>1</sup> (Rietze et al. 2001). In the adult mouse, thousands of new neuroblasts are generated each day, migrating from the lateral subventricular zone to the olfactory bulb, where they differentiate into several different types of neurons. Recent evidence suggests that these stem cells are not multipotent (becoming specified only when they reach the olfactory bulb) but instead are a population of heterogeneous neuroblasts that are already committed to becoming certain neuronal types (Merkle et al. 2007). These adult neural stem cells proliferate in response to exercise, learning, and stress (Zhang et al. 2008).

Before they become neurons, neural stem cells are characterized by the expression of the NRSE translational inhibitor that prevents neuronal differentiation by binding to a silencer region of DNA

(see Chapter 3). When neural stem cells begin to differentiate, they synthesize a small, double-stranded RNA that has the same sequence as the silencer and which might bind NRSE and thereby permit neuronal differentiation (Kuwabara et al. 2004). The use of cultured neuronal stem cells to regenerate or repair parts of the adult brain will be considered in Chapter 18.

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<sup>i</sup> These neural stem cells may have particular physiological roles as well. During pregnancy, the hormone prolactin stimulates production of neuronal progenitor cells in the subventricular zone of the adult mouse forebrain. These progenitor cells migrate to produce olfactory neurons that may be important for maternal behavior of rearing offspring (Shingo et al. 2003).