Review

The subventricular zone: new molecular and cellular developments

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The subventricular zone (SVZ), which lines the lateral walls of the lateral ventricle, persists as a neurogenic zone into adulthood and functions as the largest site of neurogenesis in the adult brain. In recent years, with the acceptance of the concept of postembryonic mammalian neurogenesis, neurogenesis in the adult SVZ has been an area of active research. With the rapid accumulation of new information on the SVZ, some of which is contradictory, summarizing existing knowledge on the SVZ and outlining future research directions in this area become important. In this review, we will cover recent molecular and cellular investigations that characterize the SVZ niche, SVZ neurogenesis, and SVZ cell migration within the adult brain.

Key words. Subventricular zone; neurogenesis; neural stem cell.

The germinal subventricular zone

The complex neural circuitry of the brain is generally thought to be restrictive to the addition of new neurons. Logic dictates that addition of new neurons to a fully integrated, functional system would disrupt existing circuits. Therefore, unsurprisingly the brain has little capacity to generate new neurons. However, recent studies have established that the adult brain maintains discrete regions from which new neurons do emanate. These germinal zones appear to be vestiges of the developmental program that initiates brain formation.

The mammalian brain begins as a layer of cells surrounding a fluid-filled ventricle compartment (fig. 1). Actively dividing stem cells reside along the walls of the ventricle in a cellular layer known as the ventricular zone (VZ) and generate neurons. As development proceeds, a second germinal zone – the subventricular zone (SVZ) – forms beneath the ventricular zone (fig. 1) and gives rise to both neurons and glia. Following postnatal development and into adulthood, these proliferative zones diminish until only a thin SVZ remains (fig. 1). The diminished, although still active, SVZ persists into adulthood and functions as the largest site of neurogenesis in the adult brain [1]. Neurogenesis also continues in the dentate gyrus of the hippocampus, but at a lower rate than in the SVZ [2–4].

Historical perspective

The concept of neurogenesis in the adult brain has only recently gained wide acceptance. However, support had slowly been building over the past century. A review of the literature as far back as the beginning of the 1900s reveals that continued mitotic activity in the SVZ of the adult brain has been known for some time. In 1912 [5], and sub-
sequently in 1932 [6], 1938 [7], and 1944 [8], investigators reported a ‘mitotically active subependymal layer’ along the wall of the lateral ventricle of postnatal and adult rodents. With the advent of autoradiography, Smart [9] demonstrated proliferation of SVZ cells in young mice and their transformation into neurons and glia, and Altman, in 1962 [10] and 1963 [11] suggested that neurogenesis may continue in adult rats and cats. However, the fate of these proliferating cells was not always clear; most cells produced in the SVZ during embryonic development were thought to differentiate into neurons, while primarily glial cells were produced in the postnatal and adult mammal [9, 12–16]. The intransigence of the adult brain was revisited in 1983 when Nottebohm and colleagues [17] demonstrated that neuronal replacement occurs in the telencephalon of adult birds. Full acceptance of postembryonic mammalian neurogenesis did not take hold until a decade ago when Marla Luskins [18] described neurogenesis in the anterior portion of the SVZ in postnatal mice and Lois and Alvarez-Buylla [19] demonstrated that adult SVZ cells are capable of proliferation and limited differentiation into both neurons and glia. These findings also suggested the SVZ as the likely source of the neural stem cells identified by Reynolds and Weiss [20].

SVZ niche

Ultrastructural reconstruction of the adult SVZ by electron microscopy (EM) reveals that four major cell types constitute this region [21] (fig. 1). A monolayer of ependymal cells lines the ventricle. Adjacent to the ventricle, and occasionally in contact with it, are astrocytes. Newly generated neuroblasts migrate as tightly apposed chains of cells through the SVZ, eventually congregating in the rostral migratory stream (RMS) that leads to the olfactory bulb. These neuroblast chains are ensheathed by astrocytes (fig. 1). Interspersed among the chains of neuroblasts is an immature cell type best described as a transitory amplifying progenitor (TAP) cell. This TAP cell is the most actively dividing of the SVZ cell types and has an immature phenotype, lacking morphological or immunohistochemical characteristics of either glia or neuroblasts.

Identity of the adult SVZ neural stem cell

Following confirmation of neurogenesis in the adult SVZ, the obvious next step was to identify the stem cell that supports this neurogenesis. The subsequent ensuing search for a self-renewing, multipotent neural stem cell brought conflicting results, due in part to the difficulty identifying a cell that may be quiescent, coupled by a lack of markers to identify neural stem cells. Two claims to the identity of the stem cells that support SVZ neurogenesis have been made. Each identifies a different cell type. Jonas Frisén’s laboratory at the Karolinska Institute in Stockholm presented data that suggested the SVZ neural stem cell was an ependymal cell [22], while Arturo Alvarez-Buylla’s laboratory at Rockefeller University in New York City identified a cell having characteristics of an SVZ astrocyte as the neural stem cell [23]. Because there are already two excellent reviews on the controversy surrounding the identity...