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REVIEW

THE MULTIFACETED SUBVENTRICULAR ZONE ASTROCYTE: FROM A METABOLIC AND PRO-NEUROGENIC ROLE TO ACTING AS A NEURAL STEM CELL

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Abstract—A few decades ago it was discovered that two regions of the adult brain retain the ability to generate new neurons. These regions include the subgranular zone of the hippocampal dentate gyrus and the ventricular–subventricular zone (V–SVZ) located at the border of the lateral ventricle. In the V–SVZ, it was discovered that neural progenitor cells (NPCs) share many features of mature astrocytes and are often referred as V–SVZ astrocytes. We will first describe the markers, the morphology, and the neurophysiological characteristics of the mouse V–SVZ astrocytes. We will then discuss the fact that V–SVZ astrocytes constitute a mixed population with respect to their neurogenic properties, e.g., quiescent versus activated state, neurogenic fate, and transcription factors expression. Finally, we will describe two functions of V–SVZ astrocytes, their metabolic coupling to blood vessels and their neurogenic-supportive role consisting of providing guidance and survival cues to migrating newborn neurons.

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Key words: subventricular zone, adult neurogenesis, neural stem cells, astrocyte.

Contents

INTRODUCTION

Until recently, it was thought that the generation of neurons in mammals occurred only during the embryonic period. By now it has been clearly demonstrated that new neurons continue to be generated in two regions of the adult brain, the subgranular zone (SGZ) of the dentate gyrus of the hippocampus and the ventricular–subventricular zone (V–SVZ) lining the lateral wall of the lateral ventricle. The neural progenitor cells (NPCs) in the V–SVZ give rise to transit amplifying precursors that themselves give birth to neuroblasts (Doetsch et al., 1999). These neuroblasts migrate tangentially to the olfactory bulb to become interneurons (Luskin, 1993; Lois and Alvarez-Buylla, 1994). The NPCs of the V–SVZ arise during embryonic development and persist into adulthood. In the embryonic brain, a very particular cell type, called radial glia was initially described with the classical Golgi silver impregnation method at the end of nineteenth century (Magini, 1888; Ramon y Cajal, 1995; Retzius, 1894), and found to provide a scaffolding for the migration and placement of newborn neurons (Rakic, 1971). Radial glia were found to possess another critical function, first identified in songbirds, which is their ability to proliferate in the ventricular zone coinciding with sites of neurogenesis (Alvarez-Buylla et al., 1990). This finding was later confirmed and expanded in the embryonic mammalian brain and it is now well-accepted that radial glia act as NPCs and generate the majority of neurons in the embryonic brain (Miyata et al., 2001; Noctor et al., 2001; Malatesta et al., 2003). After birth, most radial glia transform into parenchymal astrocytes throughout the central nervous system (Schmechel and Rakic, 1979; Voigt, 1989; Alves et al., 2002; Merkle et al., 2004), except in the two postnatal neurogenic regions, where radial glia act as NPCs and generate the three main neural cell types, including neurons, oligodendrocytes, and astrocytes

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Abbreviations: BLBP, brain lipid binding protein; GFAP, glial fibrillary acidic protein; NPC, neural progenitor cell; OPC, oligodendrocyte precursor; RMS, rostral migratory stream; Shh, sonic hedgehog; V–SVZ, ventricular–subventricular zone.

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(Kriegstein and Alvarez-Buylla, 2009). These NPCs persist throughout adult life in these two regions, in all mammalian species examined including humans (Bonfanti and Peretto, 2011). The exact fate of NPCs is being more carefully examined using novel labeling methods and lines of transgenic mice based on the concept that not all NPCs are equal in terms of their fate. NPCs in the dorsal V–SVZ were shown to generate oligodendrocyte precursors (OPCs) that migrated radially into the white matter (Marshall and Goldman, 2002; Marshall et al., 2003; Menn et al., 2006). Nevertheless, the generation of neurons predominates over that of oligodendrocytes (Menn et al., 2006) although OPC production is significantly increased following injury, in particular demyelination (Picard-Riera et al., 2002; Aguirre et al., 2007; El Waly et al., 2014)). Importantly, it was elegantly shown that a single NPC exclusively generates OPCs or immature neurons, but not both (Ortega et al., 2013). Here, we do not distinguish between OPC or neuroblast-fated NPCs with respect to their properties.

In the V–SVZ, It was found that NPCs share many features of mature astrocytes including morphological and biophysical characteristics as well as antigens such as glial fibrillary acidic protein (GFAP) (Doetsch et al., 1997, 1999; Liu et al., 2006). Here, we will focus on describing specific properties of the V–SVZ NPCs, referred to as V–SVZ astrocytes. We will first describe the unique set of markers, the morphology, and the neurophysiological characteristics of V–SVZ astrocytes. We will discuss the fact that although the population of V–SVZ astrocytes seems homogenous with respect to their neurophysiological properties (electrophysiological, coupling, neurotransmitter receptors, and transporters expression) they differ with respect to their neurogenic properties, e.g., stages of the cell cycle, quiescence versus activation state, neurogenic fate, and transcription factor expression. Finally, we will describe two functions of V–SVZ astrocytes, their coupling to blood vessels and their neurogenic supportive role consisting of providing guidance and survival cues to migrating newborn neurons.

MORPHOLOGICAL AND ANTIGENIC PROPERTIES DEFINING V–SVZ ASTROCYTES

Two main populations of GFAP-positive cells and a third more discrete population were observed in the V–SVZ (Jankovski and Sotelo, 1996; Doetsch et al., 1997) (Fig. 1). The two main populations were called type B1 and B2 cells (Doetsch et al., 1997), both of them exhibiting characteristics of astrocytes. B1 cells were initially described morphologically with a simple fusiform cell body, only 2 to 3 processes with few branches (Jankovski and Sotelo, 1996). These cells were identified as the NPCs of the V–SVZ (Doetsch et al., 1999). Type B1 slowly divide to give birth to highly proliferative transit amplifying precursors (Type C cells) that themselves give birth to neuroblasts (Type A cells), which migrate to the olfactory bulb to become interneurons (Doetsch et al., 1999). Both type B cells directly contact neuroblasts and form a glial sheath around chains of newborn neurons as they migrate toward the olfactory bulb (Lois et al., 1996; Doetsch et al., 1997). Through improvement in labeling technique, the morphology of type B1 cells has been found to be more specialized and complex than initially described. In particular, the cell bodies of B1 cells are located beneath the ependymal layer and their apical process is frequently intercalated between ependymal cells (Doetsch et al., 1999; Mirzadeh et al., 2008) while their basal process projects across the V–SVZ thickness and terminates on blood vessels, in particular capillaries (Mirzadeh et al., 2008; Shen et al., 2008; Tavazoie et al., 2008; Lacar et al., 2011). The basal processes are of variable lengths depending on the proximity of the vessels to the ependyma and confer a radial glia-like morphology to NPCs (Mirzadeh et al., 2008; Lacar et al., 2011) (Fig. 1). B1 cells have fewer processes than typical stellate astrocytes. Nevertheless by examining the very fine morphology of individually labeled B1 cells, it became apparent that the complexity of their morphology has been underestimated. They possess a high density of short and thin projections extending from their apical and basal processes (Fig. 1) (Mirzadeh et al., 2008; Lacar et al., 2011, 2012). The function, the molecular composition, and the presence of receptors on these thin processes are unknown, but they may allow B1 cells to better sense cues in their microenvironment.

The second population of astrocytes, the type B2 cells, also called niche astrocytes, displays a stellate appearance resembling that of parenchymal astrocytes (Mirzadeh et al., 2008; Lacar et al., 2011)(Fig. 1). They are mostly located at the periphery of the V–SVZ creating a physical boundary between the SVZ and the striatum (Liu et al., 2005) and are probably non-neurogenic. They do not contact the ventricle but interact with blood vessels (Mirzadeh et al., 2008; Lacar et al., 2011). A third very small population of astrocytes was observed in the V–SVZ of 4-week-old animals and represent only very few cells (Platel et al., 2009). These astrocytes are S100B positive (Platel et al., 2009), but surprisingly have not been observed in *s100b*-GFP mice (Raponi et al., 2007). In human (h) *Gfap*-GFP mice, few S100B-positive cells are GFP-positive while the others are GFP-negative (Platel et al., 2009). Approximately half of these S100+ cells are also NG2 positive. These cells present a relatively immature stellate appearance and don't have a specific location along the V–SVZ, but are never in contact with the ventricle (Platel et al., 2009). This population may represent astrocytes or NG2 cells born in the V–SVZ. Their function and potential migration pattern remain unknown.

Type B cells have been reported to express several markers associated with astrocytes or radial glia, like GFAP (Jankovski and Sotelo, 1996; Doetsch et al., 1997), nestin, vimentin (Doetsch et al., 1997), the glutamate transporter GLAST (Braun et al., 2003; Bolteus and Bordey, 2004), and brain lipid binding protein (BLBP) (Platel et al., 2009; Giachino et al., 2014) (Table 1). Therefore, type B cells are also frequently referred to as V–SVZ astrocytes. Additional markers expressed in other cell types outside of the neurogenic region have been identified in V–SVZ astrocytes and further divide this