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Cellular Organization of the Subventricular Zone in the Adult Human Brain: A Niche of Neural Stem Cells

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1. Introduction

The dogma that the brain is a quiescent organ incapable of postnatal neuron generation was first challenged in the sixties by Joseph Altman (Altman, 1962). He described the presence of thymidine-labeled cells in the subependymal zone located along the ventricular walls, which suggested the presence of dividing neurons in this brain region (Altman and Gopal, 1965; Altman and Das, 1967). A decade after, these findings were confirmed by other group using electron microscopy analyses (Kaplan and Hinds, 1977). Later, further studies described ongoing neurogenesis in female canaries (Goldman and Nottebohm, 1983), lizards (Pérez-Cañellas and García-Verdugo, 1996) and the adult mammalian brain (McDermott and Lantos, 1990; McDermott and Lantos, 1991; Lois and Alvarez-Buylla, 1993; Kornack and Rakic, 1995; Huang et al., 1998; Garcia-Verdugo et al., 2002). This process is mainly confined to the subventricular zone (SVZ) of the forebrain and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus (Reznikov, 1991; Luskin, 1993; Lois and Alvarez-Buylla, 1994). The SVZ is the largest neurogenic niche in the adult brain (Luskin, 1993; Alvarez-Buylla and Garcia-Verdugo, 2002). Within this region resides a subpopulation of astrocytes with stem-cell-like features (Doetsch et al., 1999; Laywell et al., 2000; Imura et al., 2003; Morshead et al., 2003; Garcia et al., 2004). Recently, it has been suggested that the SVZ may be not only a source of neural precursor for brain repair, but also a source of brain tumors (Ignatova et al., 2002; Galli et al., 2004; Sanai et al., 2005; Vescovi et al., 2006). These hypotheses highlight the importance of studying and understanding the organization and regulation of the SVZ precursors. This chapter discusses and analyzes the cytoarchitecture and cellular composition of the human SVZ, as well as, its potential implications on the clinical treatment of neurodegenerative diseases and brain tumors.

2. Human neural stem cells

The gold standard for determining the presence of neural stem cells is the neurosphere assay (Reynolds and Rietze, 2005). This assay consists in plating a suspension of cells under

serum-free, growth-factor-supplemented, non-adherent conditions in-vitro; thus, stem-like cells are able to divide and form multipotent undifferentiated clones called neurospheres (Reynolds and Weiss, 1992). The neurospheres can be serially dissociated and their single-cell clones are able to generate further spheres, while cells not capable of self-renewal eventually die (Reynolds and Rietze, 2005). These neurospheres are multipotent and can generate neurons, astrocytes and/or oligodendrocytes after the removal of mitogens and transfer to adherent plates (Reynolds and Weiss, 1992; Doetsch et al., 2002).

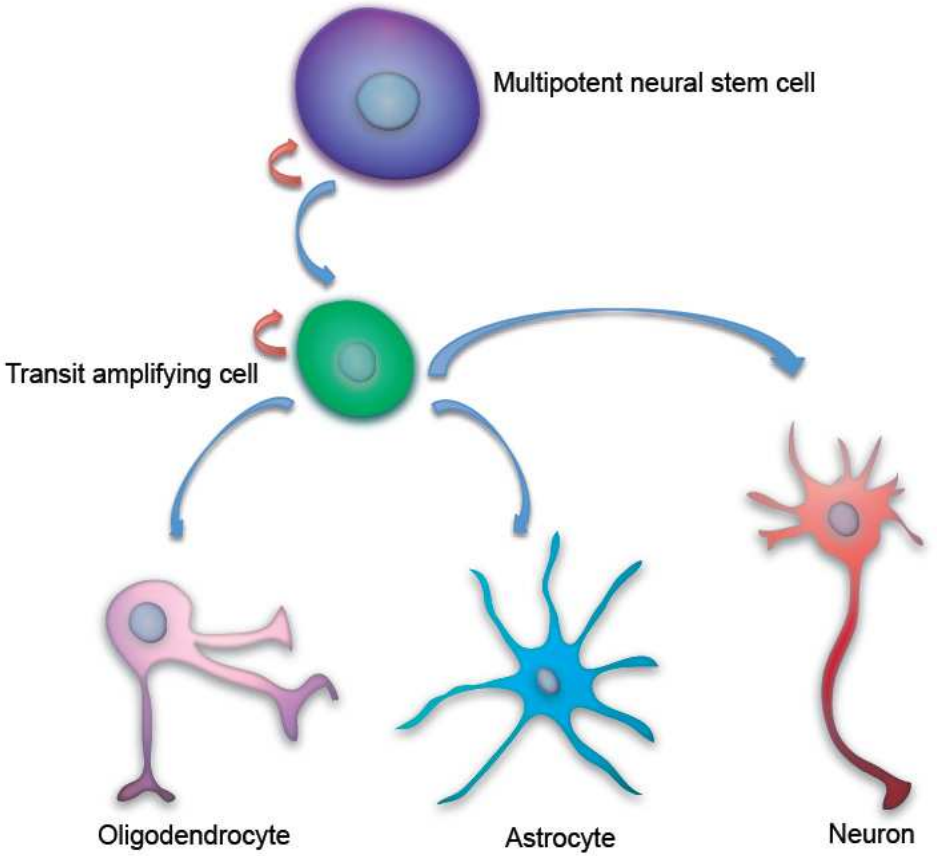

Fig. 1. Neural stem cells and their progeny in the adult SVZ. When a multipotent type B cell (on the top) divides, it generates to a type C cell, also known as transit-amplifying precursors, which can give rise to neurons and glial cells. The petite curved arrows represent the self-renewal capacity of type B and type C cells. *Figure reproduced with permission from: Alvarez-Palazuelos et al. Current Signal Transduction Therapy 2011;6(3) (Alvarez-Palazuelos et al., 2011). Copyright 2011 Bentham Science Publishers.*

Using neurosphere assays, neural stem cells have been isolated in human fetal cells (Chalmers-Redman et al., 1997). These multipotent human cells are also capable of self-renewal when maintained under serum-free conditions (Nunes et al., 2003). In the adult

human brain, neural stem cells can be isolated from the SVZ and SGZ and give rise to neurons, oligodendrocytes and astrocytes in vitro (Figure 1) (Kukekov et al., 1999). Further evidence indicates that SVZ explants isolated from temporal lobectomies in patients with refractory epilepsy are capable of producing neurons in vitro (Kirschenbaum et al., 1994; Pincus et al., 1997). It has been suggested that new neurons are generated in the SGZ of the human hippocampus in vivo (Eriksson et al., 1998). This evidence has been obtained from postmortem brain tissue derived from patients with lung squamous cell carcinomas, who were diagnostically infused with bromodeoxyuridine to label mitotic cells. Nevertheless, despite this promising advances, none of these studies can demonstrate that the adult human brain possess neural stem cells per se, namely with self-renewal and multipotency properties (Vescovi et al., 2006).

2.1 The subventricular zone in the adult mammalian brain

The SVZ is the largest source of new neurons in the adult brain. This neurogenic region is located adjacent to the ependyma at the lateral wall of the lateral ventricles (Figure 2). The epithelial layer is composed by multiciliated non-mitotic ependymal cells, which contribute to the flow of cerebrospinal fluid and appear to play a role in the modulation of the stem cell niche (Lim et al., 2000; Spassky et al., 2005; Sawamoto et al., 2006; Mirzadeh et al., 2008). The SVZ contains a slowly dividing primary progeny (type B cells) and rapidly dividing cell precursors (type C cells) (Figure 2). Type B cells have been identified as the primary neural progenitors i.e., neural stem cells in the adult brain (Doetsch et al., 1999). Interestingly, based on differences in their location and morphology, type B progenitors are a subpopulation of astrocytes that can be categorized into two types: B1 and B2 astrocytes (Doetsch et al., 1997). At the ependymal side of the SVZ, type B1 astocytes are usually closely associated with the ependymal layer through adherens and gap junctions, and frequently extend a short apical process that reaches the ventricle (Mirzadeh et al., 2008). At the parenchymal side of the SVZ, type B1 astrocytes contact the basal lamina and blood vessels that underlie the SVZ (Shen et al., 2004; Mirzadeh et al., 2008). The ventricular end of the apical process of type B1 cells contains a non-motile primary cilium that contacts the cerebrospinal fluid (Mirzadeh et al., 2008). In contrast, type B2 astrocytes are located close to the brain parenchyma (Mirzadeh et al., 2008). It has been suggested that SVZ astrocytes play a dual role in neurogenesis, serving as both neural stem cells per se and supporting cells that promote neurogenesis (Lim and Alvarez-Buylla, 1999; Song et al., 2002).

The immediate progeny of type B1 astrocytes is known as transit amplifying progenitors or type C cells, which give rise to migrating neuroblasts (type A cells) (Figure 2)(Kriegstein and Alvarez-Buylla, 2009). These young neurons are surrounded by a glial sheath and migrate anteriorly toward the olfactory bulb (Jankovski and Sotelo, 1996; Lois et al., 1996; Doetsch et al., 1997). The adult SVZ also generates oligodendrocytes, although in much lower numbers than neuroblasts (Menn et al., 2006; Gonzalez-Perez et al., 2009; Gonzalez-Perez and Quinones-Hinojosa, 2010; Gonzalez-Perez et al., 2010b; Gonzalez-Perez and Alvarez-Buylla, 2011). The mechanisms that control the cell proliferation and renewal in the SVZ are not well-known, but increasing evidence indicates that neural stem cells are instructed via cell-cell contacts and extracellular signals from ependymal cells, immunological cells, the extracellular matrix, microglia, the local vasculature, neuronal inputs and the cerebrospinal fluid (Gonzalez-Perez et al., 2010a; Gonzalez-Perez and Alvarez-Buylla, 2011; Ihrie and Alvarez-Buylla, 2011).

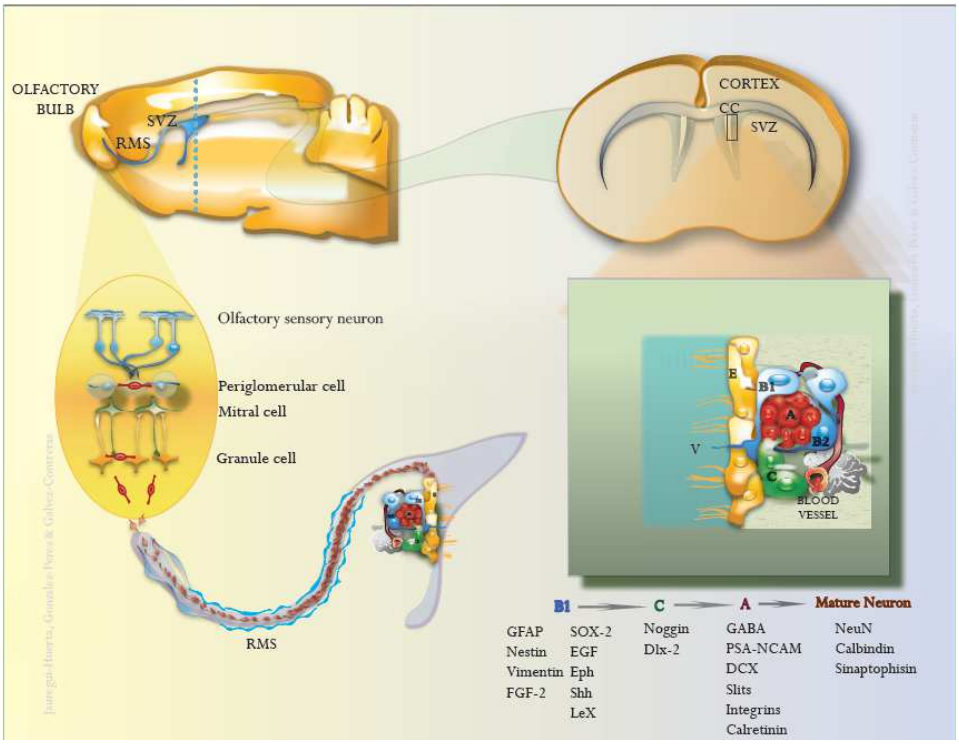

Fig. 2. Schematic representation of the localization and cellular composition of the adult subventricular zone (SVZ) in the rodent brain. Neuroblasts generated in the SVZ niche migrate to the olfactory bulb and, then, differentiate into granular and periglomerular GABAergic interneurons. Cell markers expressed by type B, type C, type A and mature neurons are listed under each cell label. V: Ventricle; E: Ependymal cell; CC: Corpus callosum; RMS: Rostral migratory stream. *Figure reproduced with permission from: Gonzalez-Perez et al. Current Immunology Reviews 2010;6(3):167 (Gonzalez-Perez et al., 2010b). Copyright 2010 Bentham Science Publishers.*

2.2 Cell type markers of the SVZ progenitors

As mentioned above, type B1 cells have astrocytic morphology and ultrastructure and express molecular markers that have been usually associated with astroglia, such as: the glial fibrillary acidic protein (GFAP), nestin, vimentin, connexin 30, the astrocyte-specific glutamate transporter (GLAST) and the brain-lipid-binding protein (BLBP) (Doetsch et al., 1999; Hartfuss et al., 2001; Kriegstein and Alvarez-Buylla, 2009). Type B1 astrocytes also express the cell surface carbohydrate Lewis X (LeX)/CD15/SSEA-, which has been proposed as a marker of neural stem cells in the SVZ (Capela and Temple, 2002). In addition, type B1 cells express prominin-1, also known as CD133, a protein commonly used as a stem-cell marker (Coskun et al., 2008; Shmelkov et al., 2008; Beckervordersandforth et al., 2010). However, prominin-1 expression at the apical endings of type B1 cells appears to be dynamically regulated (Mirzadeh et al., 2008). Therefore, given that Type B1 cells have

many astroglial characteristics, finding potential markers to distinguish the B1 cell progeny from other non-multipotent astrocytes would be very useful in future studies. Some markers generally used to identify type-C cells are the epidermal growth factor receptor (EGFR), Dlx2 and Ascl1 (also known as Mash1) transcription factors (Doetsch et al., 2002; Parras et al., 2004), while doublecortin and the polysialylated neural cell adhesion molecule are useful to identify A-cell progeny (SVZ neuroblasts) (Lois and Alvarez-Buylla, 1994; Rousselot et al., 1995; Francis et al., 1999). Ependymal cells express S100beta and CD24 (Raponi et al., 2007; Mirzadeh et al., 2008).

Longitudinal analysis of molecular markers within the SVZ progenitor cells indicates that many of these proteins are expressed at particular points along the cell differentiation of neural stem cells. For instance, while GFAP expression is restricted to B cell progeny, GLAST and the orphan nuclear receptor Tlx is also present in a subpopulation of type C cells (Pastrana et al., 2009). Similarly, EGFR and Mash1are expressed in a limited number of type B cells, and they possibly may be useful to label ''activated'' type B cells (Doetsch et al., 2002; Gonzalez-Perez et al., 2010a; Gonzalez-Perez and Alvarez-Buylla, 2011). In addition, nestin expression that was thought to be exclusive to adult neural stem cells has been found broadly expressed within the brain (Hendrickson et al., 2011). Taken together, this evidence indicates that marker for stem and/or progenitor cells are likely to identify overlapping, but not identical subpopulations of SVZ cells. Therefore, researchers should be cautious when assigning biological characteristics to a subset of SVZ cells (Chojnacki et al., 2009).

2.3 The cell composition and architecture of the human subventricular zone

The human SVZ is located within the lateral wall of the lateral ventricles and consist of four layers with very particular cell compositions (Figure 3) (Quinones-Hinojosa et al., 2006). The layer adjacent to the lateral ventricle (Layer I) is formed by a monolayer of multiciliated ependymal cells with basal cytoplasm expansions that are either tangential or perpendicular to the ventricular surface. The Layer II or hypocellular layer is comprised of some of ependymal cytoplasm expansions interconnected with a number of astrocyte processes and very rare astrocytic and neuronal cell bodies (Figure 3) (Quinones-Hinojosa et al., 2006). The biological relevance of this hypocellular gap, is unknown, but it may be a remnant of the brain development at embryonic stages, because from this region a number of new neurons born and migrate radially and tangentially toward cortical and subcortical structures (Guerrero-Cazares et al., 2011). Other hypotheses suggest that the astrocytic and ependymal interconnections within this layer regulate neuronal functions or preserve metabolic homeostasis in the SVZ (Ihrie and Alvarez-Buylla, 2011; Ihrie et al., 2011). Abutting the hypocellular layer is a ribbon of astrocyte somata (Layer III) (Figure 3), which shows some proliferative activity as indicated by postmortem Ki67 expression (Sanai et al., 2004; Quinones-Hinojosa et al., 2006). It is believed that a subpopulation of astrocytes within this ribbon can proliferate in vivo, as well as form multipotent neurospheres (Sanai et al., 2004; Quinones-Hinojosa et al., 2007). Based on differences in their location and morphology by electron microscopy, the SVZ astrocytes can be subdivided into three types (Quinones-Hinojosa et al., 2006): The small astrocytes that are predominantly found in the hypocellular layer, and possess long, tangential cytoplasm processes. These astrocytes contain scarce cytoplasm, very dense bundles of intermediate filaments and sparse organelles. The second type of astroglia is the large astrocyte that has large cytoplasm expansions, abundant

organelles and is found at the interface between Layer II and III and within the ribbon itself. This type of astrocyte is primarily found in the medial wall at the level of the body of the lateral ventricle. The third type of astrocyte is also large, but it possesses few organelles and is primarily found in the ventral temporal horn overlying the hippocampus. To date, the physiological relevance n of these three types of astrocytes is unknown differences, but in vitro evidence sugests that neural stem cells may belong to one of these astrocytic subtypes (Sanai et al., 2004). On the other hand, small clusters of displaced ependymal ells can be occasionally found embedded within this ribbon. This type of cells has abundant cilia, junctional complexes and microvilli (Figure 3). Finally, a few oligodendrocytes that do not appear to be myelinating axons are also seen in the Layer III (Figure 3). The deepest layer, the Layer IV is comprised of a number of myelin tracts and is considered a transition zone between the astrocytic ribbon and the brain parenchyma (Quinones-Hinojosa et al., 2007).

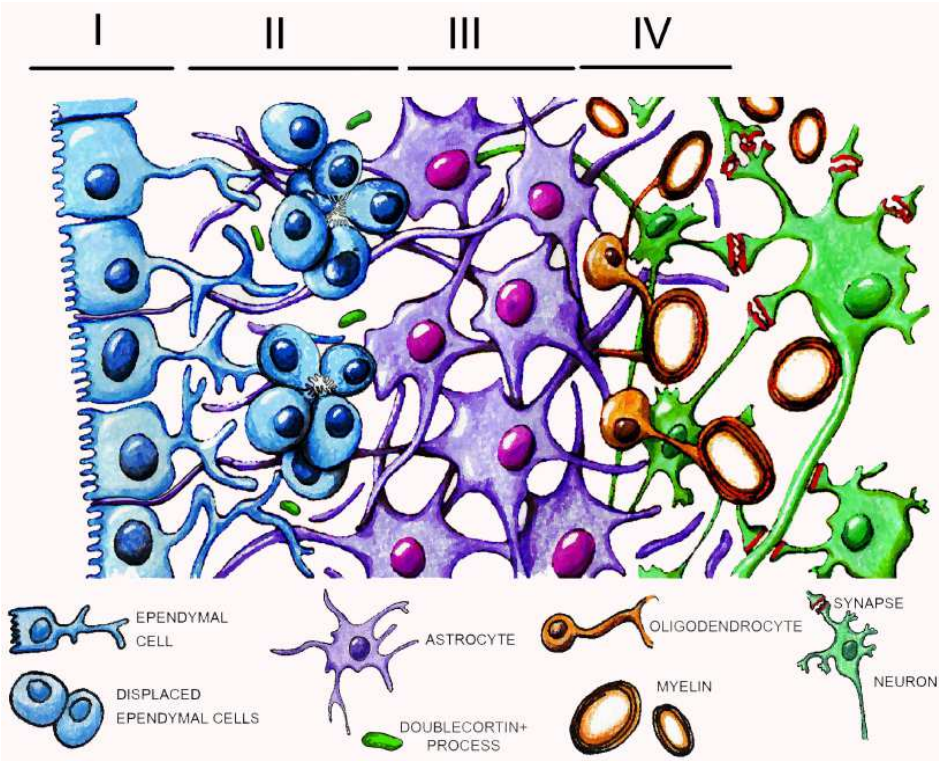

Fig. 3. Cellular organization within the human SVZ. The human SVZ displays unique characteristics as compared to the rodent or primate SVZ. Briefly, layer II devoid of cell bodies, type B cells (astrocytes) are organized as a ribbon of GFAP+ cells, which is not in close contact with the ependymal layer, no chains of migrating neuroblasts are found along the ventricular wall, and very few neuronal cell bodies as well as proliferating cells can be found within the human SVZ. *Figure reproduced with permission from: Alvarez-Palazuelos et al. Current Signal Transduction Therapy 2011;6(3) (Alvarez-Palazuelos et al., 2011). Copyright 2011 Bentham Science Publishers.*

As described above, many features of the human SVZ (Figure 3) are dissimilar to the well-studied rodent SVZ (Figure 2). Some of these fundamental differences are: First, the presence of a layer devoid of cell bodies (Layer II), which contrast with findings reported in the lizard, rodent, feline, canine or primate SVZ that show that all of them have type B cells in close contact to ependymal cells (Doetsch et al., 1997). The second dissimilarity is that the human SVZ lacks chains of migrating neuroblasts (Sanai et al., 2004; Quinones-Hinojosa et al., 2006; Sanai et al., 2007; Wang et al., 2011). Although some authors have suggested that other regions might have migrating cells in the human brain (Bernier et al., 2000; Curtis et al., 2007). Third, the number of proliferating cells (Ki-67 or PCNA expressing cells) in the human SVZ is significantly less than that reported in the rodent SVZ (Sanai et al., 2004; Quinones-Hinojosa et al., 2006; Sanai et al., 2007). Finally, the human SVZ has also very few neuronal cell bodies as compared to other species (Doetsch et al., 1997; Sanai et al., 2004; Quinones-Hinojosa et al., 2006; Sanai et al., 2007). In summary, all these obvious differences between the cell compositions of the human versus the rodent SVZ may also indicate functional differences that need to be studied in detail.

3. Conclusion

Until the end of the twenty century, the brain was perceived as a quiescent organ, with only glia able to have postnatal mitosis. This view was challenged with the isolation of neural stem cells within the adult brain. These multipotent and self-renewing cells are primary located within two germinal niches, the SVZ and SGZ of the hippocampus. The SVZ is the largest source of new cells in adult mammals; thus, a detailed understanding of this neurogenic region may have fundamental medical implications. Nevertheless, a number of questions remain to be elucidated, including the understanding of the role of SVZ neurogenesis in physiological processes such as learning, memory and cell migration. Moreover, SVZ neural stem cells might have some medical uses for a number of neurological disorders including Alzheimer's disease, multiple sclerosis, ischemia, Parkinson's disease, schizophrenia, depression and others. In contrast, since genetic alterations can be acquired through our life time, some groups have proposed that the SVZ may also represent a source of cells for the development of malignant brain tumors but, so far, there is no concluding evidence to support this hypothesis. In summary, the study of neural stem cells in the human SVZ, which is distinct region from those of other animal species, is a vital step with potential medical implications. Therefore new research on the human brain tissue is very important to elucidate these questions.

4. Acknowledgment

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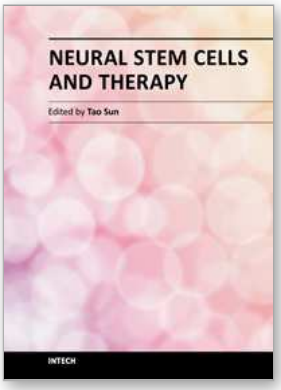

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This book is a collective work of international experts in the neural stem cell field. The book incorporates the characterization of embryonic and adult neural stem cells in both invertebrates and vertebrates. It highlights the history and the most advanced discoveries in neural stem cells, and summarizes the mechanisms of neural stem cell development. In particular, this book provides strategies and discusses the challenges of utilizing neural stem cells for therapy of neurological disorders and brain and spinal cord injuries. It is suitable for general readers, students, doctors and researchers who are interested in understanding the principles of and new discoveries in neural stem cells and therapy.

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