



The ventricular-subventricular zone: a source of oligodendrocytes in the adult brain

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Demyelinating diseases are characterized by an extensive loss of oligodendrocytes and myelin sheaths from axolemma, which commonly result in disability in young adults. To date, there is no effective treatment against these neurological disorders. In the adult brain, there are neural stem cells (NSCs) that reside within a niche denominated ventricular-subventricular zone (V-SVZ) in the lateral wall of the cerebral ventricles. These NSCs give rise to neurons and oligodendrocytes that help preserve cellular homeostasis (Kriegstein and Alvarez-Buylla, 2009). Growing evidence indicates that V-SVZ progenitor cells may represent an endogenous source of oligodendrocytes that can be useful to treat demyelinating diseases.

The e-Book “*The ventricular-subventricular zone as a source of oligodendrocytes in the adult brain*” has collected the most recent evidence regarding the mechanisms that modulate the proliferation, migration, quiescence, cell-fate choices and survival of oligodendrocyte precursors generated in the V-SVZ. This e-Book begins with an excellent study performed by the members of the Nada Zecevic’s laboratory. They analyzed the effects of Sonic hedgehog (Shh) signaling on proliferation and specification of human cortical Olig2+ progenitors *in vitro*. They demonstrated that Shh increased the number of oligodendrocyte progenitors (OPCs). However, inhibition of endogenous Shh did not reduce the density of Olig2+ cells, which suggest an additional Shh-independent mechanism for oligodendrocyte generation (Ortega et al., 2013).

In the adult V-SVZ, the activation of NMDA receptors (NMDAR) increases the oligodendrocyte differentiation. Using the reporter gene luciferase, Carlos Matute et al. (Chapter 2) found that the activation of NMDAR stimulates PKC, which precedes the activation of NADPH oxidase (NOX) (Cavaliere et al., 2013). Hence, the authors propose that NOX2 is involved in the transduction of the signal from NMDAR through PKC activation. This work also suggests that signaling through the cascade NMDAR–PKC–NOX2 generates ROS that, in turn, activate the PI3/mTOR pathway and drives oligodendrogenesis.

Tyrosine kinase (Trk) receptors play a key role in regulating the function of V-SVZ NSCs. Particularly, V-SVZ neural progenitor cells express the epidermal growth factor receptor (EGFR). EGF strongly stimulates proliferation, survival, migration and differentiation into the oligodendrocyte lineage (Gonzalez-Perez and Alvarez-Buylla, 2011). In the chapter 3, Galvez-Contreras and colleagues compiled the current data regarding the role of EGFR and ErbB family signaling on V-SVZ NSCs and explained

the downstream cascades involved in oligodendrogenesis (Galvez-Contreras et al., 2013). The authors also proposed a hypothetical model to support the EGF-induced oligodendrogenesis, which involves homodimerization between ErbB1 and ErbB3, which probably activate the PI3K or the STAT pathways. In consequence AKT is activated and the expression of Olig-2 is induced, which determines oligodendroglial specification.

Endocannabinoids have been involved in oligodendrogenesis. As reported by the Dr. Malva’s group (chapter 4), hemopressin, a modulator of cannabinoid receptor-1, can increase the oligodendroglial differentiation in V-SVZ progenitor cells (Xapelli et al., 2014). Their results suggest that hemopressin may be of potential interest to treat demyelinating diseases.

Erythropoietin (EPO) promotes the V-SVZ-derived neurogenesis and oligodendrogenesis. Sawamoto and coworkers recently demonstrated that the EPO derivative asialo-EPO promotes the differentiation of V-SVZ-derived OPCs into myelin-forming mature oligodendrocytes in the injured white matter of neonatal mice without causing erythropoiesis (Kaneko et al., 2013). These findings and the therapeutic proposal are discussed in the chapter 5 of this book.

In the chapter 6, the group of Prof. Dietzel found that the addition of equiosmolar supplements of mannitol or NaCl associated with microglia cells can influence the proliferation of OPCs (Kleinsimlinghaus et al., 2013). Interestingly, a maximal yield of OPCs is obtained by combining a cell culture medium with osmolality >280 mOsm and low density of microglia cells.

Aging progressively decline in the proliferative capacity of V-SVZ progenitor cells that subsequently affects the incorporation of new cells in the olfactory bulb. In the chapter 7, Quiñones-Hinojosa’s group presents the effects of aging across the V-SVZ–OB system. They surprisingly found that neurogenesis decline with aging, but oligodendrogenesis in the rostral migratory stream is not compromised (Capilla-Gonzalez et al., 2013).

In the chapter 8, Ken Arai and colleagues (Maki et al., 2013) summarized the recent studies on extrinsic (extracellular matrix, cerebrospinal fluid, vasculature) and intrinsic (transcription factors or epigenetic modifiers) factors, which mediate oligodendrocyte generation from the V-SVZ progenitor cells. These factors appear to decrease by aging and compromise the efficiency of remyelination into the brain. In the chapter 9, significant questions and hypotheses regarding this topic are analyzed by Agathou et al. (2013). In the last chapter, Zhang et al. compiled evidence

that indicates that a pathological condition as stroke can increase oligodendrogenesis in the white matter and V-SVZ during brain repair (Zhang et al., 2013), which support the notion that many inflammatory cytokines regulate the V-SVZ cells (Gonzalez-Perez et al., 2012).

In summary, growing evidence indicates that V-SVZ NSCs are good candidates to establish stem cell-based therapies in demyelinating disorders. Nevertheless, chemical mediators and signaling pathways involved in all these processes are to be completely elucidated. Understanding the mechanisms that regulate the V-SVZ progenitor cells may help develop therapeutic approaches to treat demyelinating diseases.

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