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Editorial: Activation and stimulation of endogenous neural stem/progenitor cells in multiple sclerosis and other neurodegenerative diseases

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Editorial on the Research Topic

[Activation and stimulation of endogenous neural stem/progenitor cells in multiple sclerosis and other neurodegenerative diseases](#)

Neurodegenerative diseases including multiple sclerosis (MS) are characterized by the loss of neurons and glial cells, leading to a decline in cognitive and motor functions (Lassmann, 2018). Despite the recent advances in understanding the signals that stimulate the activity of endogenous neural stem/progenitor cells (NSCs), currently, there is no effective treatment to restore the lack of neural cells in these diseases. In the adult central nervous system (CNS), NSC generation arise at the sub ventricular zone (SVZ) of the lateral ventricles, the sub granular zone (SGZ) of the hippocampus, the fourth ventricle and the central canal of the spinal cord (Picard-Riera et al., 2004). In physiological conditions, adult NSCs self-renew and have pluripotent features giving rise essentially to neurons, with few astrocytes and oligodendrocytes (Obernier and Alvarez-Buylla, 2019). In pathophysiological conditions, adult NSCs are activated and mobilized in response to various injuries and their capacities to undergo neurogenesis or gliogenesis differ according to the location and type of injury. For example, in MS and related animal models, SVZ-derived oligodendrocyte progenitors (SVZ-OPCs) are increased at the expense of neurogenesis, and via unknown signals arising from the lateral ventricles and parenchymal lesions (Nait-Oumesmar et al., 2007; Tepavcevic et al., 2011; Pourabdolhossein et al., 2017). Although the amount adult stem cell niches and their activation are limited, their role is crucial to recover damage in many neurodegenerative disorders (Michailidou et al., 2014; Pourabdolhossein et al., 2017). Therefore, activating and stimulating endogenous adult NSCs may be a promising therapy for neurodegenerative diseases. This Research Topic explored recent advances on the cellular and molecular activation of adult NSCs as a tool for future neurodegenerative disease therapies.

What in the immune microenvironment controls NSC self-renewal is unknown. [Imitola et al.](#) explored the role of STAT1, an IFN- γ transducer, in this process. Overexpressing *Stat1* in SVZ-NSCs reduced the capacity of NSC to self-renew, while deleting *Stat1* gene in purified NSCs enhanced NSC self-renewal, neurogenesis, and oligodendrogenesis. Moreover, using a mouse model of MS they found an up-regulation of STAT1 in NSCs, and an expansion of IFN- γ -expressing T cells rather than interleukin 17 (IL-17)-producing T cells in the cerebrospinal fluid of induced mice. IFN- γ suppressed the proliferation of NSCs more than IL-17 and triggered an abnormal NSC phenotype with increased STAT1 phosphorylation. They also identified a *Stat1*-dependent gene expression profile associated with an increase in the *Sox9* transcription factor, a regulator of self-renewal. By the use of a transcriptional luciferase assay, they unveiled that *Stat1* binds and transcriptionally represses *Sox9*. Thus, *Stat1* serves as an inducible checkpoint for NSC self-renewal, being upregulated during chronic brain inflammation *Stat1* what decreases NSC self-renewal. The relevance of these findings suggests that this pathway could be modulated to prevent progression and loss of repair function in NSCs/neural progenitors in MS.

There are three cell types involved in myelin repair: parenchymal OPCs (pOPCs), which are prevalent in the adult CNS ([Zawadzka et al., 2010](#)); NSC/SVZ-OPCs ([Nait-Oumesmar et al., 1999](#)); and mature oligodendrocytes (OLs) ([Duncan et al., 2018](#)). [Moyon et al.](#) addressed the question of the respective roles of SVZ-OPCs and pOPCs in demyelinating conditions. Using a tamoxifen-inducible-dual reporter mouse line, they explored the contribution of each cell population in response to cuprizone-induced demyelination, confirming that both pOPCs and SVZ-OPCs participate in corpus callosum remyelination. Moreover, they took advantage of the *Myrf*-cKO; Nestin-tdT mouse line to block pOPC differentiation and measure the competition between pOPCs and SVZ-OPCs to remyelinate demyelinated regions. Impeding pOPC differentiation increased NSC-progeny recruitment and differentiation with no regional differences, attesting that OLs derived from pOPCs and SVZ-OPCs are competing for repair in the corpus callosum. These interesting results open the gate to explore signals that control timely cell recruitment, an important step for successful myelin repair.

While the mammalian spinal cord central canal is a well-recognized NSC niche, the identity of the ependymal NSCs is still at debate, and their identification could be of great benefit for NSC-based therapy in spinal cord injuries. Using *Pkd2l1c* as a specific marker of cerebrospinal fluid-contacting neurons (CSF-cNs) as well as *in vivo* and *in vitro* paradigms, [Cao et al.](#) explored the possibility that CSF-cNs are endowed with NSC characteristics. They found that CSF-cNs form clusters in the subependymal layer of the central canal, co-expressing NSC markers *Sox2*, Nestin, and *DCX* *in vivo*, and after purification *in vitro*. *In vivo* delivery of growth factors and spinal cord injury induced CSF-cN proliferation, and their propensity to express the neuroblast marker *Dcx* and GFAP+/Nestin+. These data highlight the possibility that CSF-cNs may serve as potential NSC candidates and be a target of interest to enhance spinal cord repair.

After summarizing the differences in structural and regulatory mechanisms existing between the SVZ and SGC NSC niches,

[Murtaç et al.](#) conducted a very comprehensive review, which highlights how the omics era has fundamentally enhanced our understanding of the nature and function endogenous NSCs in these two structures during development in physiological and pathophysiological conditions. Namely, single-cell transcriptomic approaches, compared to bulk analysis, brought insights into the understanding of NSC heterogeneity and revealed the complex system required to direct neuronal specification during development. While spatial transcriptomic approaches combined with other omics techniques has provided significant knowledge into the spatially restricted neurodevelopmental processes, the integration of transcriptomics and chromatin profiling has proved essential to identify regulatory elements and pathways that control gene expression in different NSC niches. The authors underline that combining these multi-omics approaches with proteomics and metabolomics should further provide a complete picture of the NSC biology and their complex regulatory mechanisms. They also review several omics-based studies, which have explored endogenous NSC in neurodegenerative diseases, and started to unravel insights in disease specific molecular mechanisms, opening the perspective to find treatments that may enhance either neurogenesis or gliogenesis for repair.

In conclusion, the above studies provide valuable insights into the biology of endogenous NSCs and their potential for therapeutic applications in a variety of neurological conditions. Even though activation of endogenous NSC is still in its infancy, additional research based on the ongoing innovating methodologies should overcome the current limitations of this therapeutic approach and provide efficient means for CNS repair.

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