

## Editorial

## Regenerative neuroimmunology: The impact of immune and neural stem cell interactions for translation in neurodegeneration and repair



Stem cells are essential for development as well as for regeneration in various adult tissues. In the brain, neural stem cells (NSCs) are being investigated, due to their potential for clinical translation in neurodegenerative and neuroimmunological disorders especially multiple sclerosis (MS). Furthermore, there is an increased recognition that the immune system regulates neural development by modulating neurogenesis, oligodendrogenesis, and synaptic formation (Cunningham et al., 2013). Therefore, understanding the molecular and cellular basis for the interactions between these cells will enhance our ability to harness and manipulate the immune system to improve repair and halt neurodegeneration. The importance of these interactions is highlighted in the search for the next generation regenerative therapies in MS. Hence; working knowledge of these interactions is imperative to realize the goal of regeneration using neuroimmunology principles or *Regenerative Neuroimmunology*.

In Neuroimmunology, there has been a keen interest in understanding the effects of immune cells and molecules secreted by different cells including T, B, astrocyte and microglia on neurons and oligodendrocytes. Understanding the effects of these cells on NSCs biology is an unmet need critical to discover mechanisms of failure of repair in MS and other neurological diseases with a neuroimmunological component that includes stroke, spinal cord injury, and Alzheimer's disease.

The study of interactions of the immune system and NSCs is relatively new. Traditionally, there has been a significant focus on immunological events in the periphery as translational targets for neuroinflammation but not directly within the CNS. The first paper describing the immunological properties of NSCs was published in the *Journal of Neuroimmunology* more than 18 years ago (McLaren et al., 2001). However, beginning in 2003, there was a surge of new discoveries that showed the effects of exogenous NSCs in neuroinflammation models (Pluchino et al., 2003). The effects of inflammation on endogenous NSCs (Monje et al., 2003), followed by mechanistic studies leading to the discovery of the functional expression of several cytokines and chemokines receptors in NSCs and their role in stroke and experimental autoimmune encephalomyelitis (EAE), a model of MS (Imitola et al., 2004a; Imitola et al., 2004b; Odeberg et al., 2005).

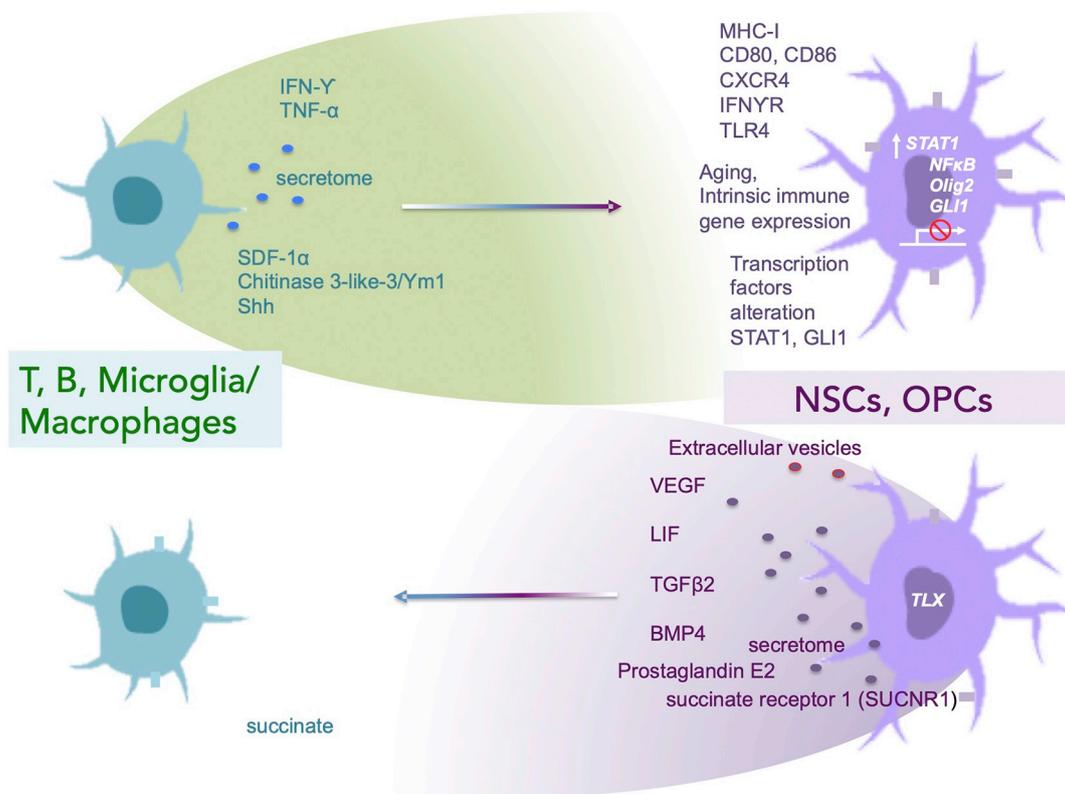
*Stem Cell Neuroimmunology* is now a growing field, since the initial papers describing the disease-associated roles of immune molecules on NSC (Imitola et al., 2004a; Imitola et al., 2004b) and the demonstration that NSCs target the immune system (Pluchino et al., 2005). We have made significant progress understanding the mechanisms of how NSCs modulate the immune system leading to decreased inflammation (Merzaban et al., 2015; Peruzzotti-Jametti et al., 2018; Pluchino et al., 2009) and *vice versa*, how the overactive immune system can lead to NSCs dysfunction *in vivo* (Rasmussen et al., 2011; Wang et al., 2008). In

recent years, emerging technologies including single-cell RNA-seq have shown that neural progenitors *in vivo* acquire an altered immune gene expression (Falcao et al., 2018), and new data points to cellular aging in OPCs induced by the inflammatory microenvironment, as an additional mechanism for repair dysfunction in progressive MS (Nicaise et al., 2019). Finally, microglia have been singled out in the past as negative regulator of neuronal (Imitola et al., 2011; Rasmussen et al., 2007) and NSCs function in MS models (Starossom et al., 2012), but recent studies have shown that microglia can modulate oligodendrogenesis *in vitro* and *in vivo* preventing progression of EAE by secreting Ym1/Chitinase 3-like-3 (Starossom et al., 2019).

This special issue focusing on *Stem Cell Neuroimmunology* outlines the study of the interactions between immunity and NSCs (Fig. 1), by concentrating on the current status of the reciprocal immune-neural stem cells interactions in models of MS, and in manuscripts that cover new information related to the role of immunology in NSCs and progenitor function. We have organized the supplement in topical reviews and original contributions. We selected three reviews of the reciprocal interaction of NSCs with the immune system and *vice-versa*. The first review highlights the responses of endogenous spinal cord-NSCs in response to the inflammatory milieu in EAE, where SC-NSCs migrate into demyelinated lesions and give rise to glia and neurons (Covacu and Brundin, 2016). Another review summarizes the underlying mechanisms of exogenous NSCs in animal models of MS and describes challenges to overcome to move this preclinical work to the bedside (Volpe et al., 2016). The final review focuses on the molecular phenotypes and properties of OPCs in the human brain, in MS lesions and the evidence of the role of immune cells in OPC injury and remyelination (Antel et al., 2018).

We collected five original manuscripts with significant and novel contributions to the field of neuroimmunology with emphasis on NSCs. The first paper studies the effect of cytokines on human NSCs describing the differential effects of interleukin-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interferon- $\gamma$  (IFN- $\gamma$ ) and showing that IFN- $\gamma$  decreases proliferation and neuronal migration in human NSCs. Notably, the authors found an increase in proliferation and inhibition of electrical activity after TNF- $\alpha$  treatment. The data represent novel information regarding the effects of cytokines on proliferation and functional properties of human NSCs (Hagman et al., 2018).

The next paper focuses on the metabolic responses of oligodendrocytes treated with IFN- $\gamma$ ; leading to a reduction in aerobic glycolysis and mitochondrial respiration in these cells. They identified the downstream signaling molecule, SHP-1, as a critical regulator since SHP-1 deficient oligodendrocytes had high constitutive levels of STAT1 and decreased aerobic glycolysis and mitochondrial respiration



**Fig. 1.** Model for NSCs and immune cells crosstalk in Neuroinflammation. Immune cells, especially T cells and microglia, establish reciprocal interactions with NSCs and OPCs. *Top Panel:* Activated microglia and T cells can provide a microenvironment that is conducive to the maintenance of NSCs function during homeostatic conditions since deletion of IFN- $\gamma$  leads to increase in NSCs in the SVZ (Li et al., 2010). But the increased expression of IFN- $\gamma$  and TNF- $\alpha$  in MS models is deleterious (Imitola et al., 2004a; Pluchino et al., 2008; Rasmussen et al., 2011) suggesting that massive release of these cytokines by immune cells may overwhelm this homeostatic system. In addition, secretion of chemokines like SDF-1 $\alpha$  in MS models and stroke can mobilize CXCR4 expressing NSCs to migrate to areas where they are needed (Imitola et al., 2004b). By contrast, activated macrophages and microglia can affect NSCs function and neurogenesis in acute (Monje et al., 2003) and chronic disease (Starossom et al., 2012). Notably, microglia can secrete Chi3l3 that increases oligodendrogenesis in NSCs (Starossom et al., 2019). A closer look at the molecular changes in NSCs and OPCs by inflammation indicate that they accumulate direct transcriptional changes and altered molecular programs during Neuroinflammation like NPCs aging (Nicaise et al., 2019), an abnormal intrinsic immune gene expression (Falcao et al., 2018) and alteration of transcription factors GLI1, (Wang et al., 2008), and STAT1 (Pereira et al., 2015). (De Feo et al., 2017). *Bottom Panel:* NSCs, when injected in models of MS, leads to decreased inflammation by multiple mechanisms targeting T cells and macrophages/monocytes and microglia. Mechanistically, Leukemia inhibitory factor can reduce the activation of Th17 cells and exert neuroprotection (Cao et al., 2011; Laterza et al., 2013). Furthermore, a series of molecules secreted by NSCs such as VEGF (Mosher et al., 2012), extracellular vesicles (Morton et al., 2018), TLX (Kozareva et al., 2017) TGF $\beta$ 2 (De Feo et al., 2017) and PGE2, activated by the release of succinate by macrophages, (Peruzzotti-Jametti et al., 2018) can modulate immune cells, especially microglia and monocytes.

compared to controls. This data is relevant because it offers an in-depth analysis of glycolysis and mitochondrial respiration in oligodendrocyte metabolism after inflammatory cytokine exposure (Minchenberg and Massa, 2017). This data indicates that the metabolism is another target by which inflammation may render these cells dysfunctional in MS and suggest that cellular phenotypes associated with the metabolic activity may be additional targets for repair (Hollingsworth et al., 2017).

The next original paper focuses on the innate immunity of NSCs. Traditionally, the focus of innate immunity involves the functions of microglia and macrophages, and in this paper, the authors showed that LPS activates nuclear factor- $\kappa$ B (NF- $\kappa$ B) in TLR4-expressing NSCs of mice. They showed that inhibition of TLR4 augmented hyperthermia and inhibited NF- $\kappa$ B activation in circumventricular NSCs of LPS-treated animals. Finally, administration of high-dose TLR4 inhibitors induced hyperthermia and molecular activation of NSCs and hypothalamic neurons, indicating that TLR4 functions as a central regulator for thermogenesis in NSCs (Muneoka et al., 2018).

The next paper focuses on the study of microglia in the circumventricular organs (CVOs). The authors observed that microglia displayed activated morphology compared to other brain regions. They discovered that microglia in CVOs showed increased expression of

CD16 and CD86, CD206 and Ym1/Chitinase 3-like 3 indicating activation in the absence of pathology (Takagi et al., 2017). This paper adds to the existing body of literature showing the presence of microglia in the niche areas and their interactions with resident NSCs in models of injury (Monje et al., 2003; Rasmussen et al., 2011).

The last paper focuses on the role of intrinsic molecules on NSCs and how they may modulate the immune microenvironment. The authors showed that the lack of the orphan nuclear receptor TLX in NSCs, a key regulator of hippocampal neurogenesis, resulted in microglial activation and was associated with a decrease in survival and function of newborn cells in the hippocampus (Kozareva et al., 2017), suggesting that intrinsic molecules acting on NSCs may regulate the immune microenvironment.

Taken together these eight manuscripts represent new advances in the field of *Stem Cell Neuroimmunology*, and will generate future hypotheses and mechanistic studies regarding the reciprocal interaction between NSCs and the immune system. While it is impossible to cover all aspects related to *Stem Cell Neuroimmunology* or to include all the work in the area, I am confident that we have compiled a selection of informative articles for a broad audience of clinical and basic neuroimmunologists aiming to spark interest in this growing field.

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