Stem cells in the adult CNS revealed: examining their regulation by myelin basic protein

Neural stem cells (NSCs) are found along the entire neuraxis, through development and into adulthood and old age (Sachewsky et al., 2014; Xu et al., 2016). There are two neurogenic niches in the adult CNS. One is the subgranular zone in the hippocampus and the other is found in the periventricular region throughout the extent of the neuraxis (Barnabé-Heider et al., 2010; Mirzadeh et al., 2010). Herein we focus on the periventricular region where we recently reported and characterized two populations of NSCs: (1) a leukemia inhibitory factor (LIF) responsive “primitive” neural stem cell (pNSC) that expresses low levels of the pluripotency marker Oct4 and (2) an epidermal and fibroblast growth factor responsive definitive neural stem cell (dNSC) that expresses the mature astrocyte marker, glial fibrillary acidic protein (GFAP) (Sachewsky et al., 2014). In the forebrain, the discovery of pNSCs essentially redefined the neural stem cell lineage demonstrating that exceedingly rare pNSCs are found upstream of the more abundant (albeit rare) dNSCs. Interestingly, the non-neurogenic periventricular region of the spinal cord also contains NSCs. Since their original isolation using the in vitro, clonal colony forming “neurosphere” assay, the spinal cord stem cells have been identified as S100β and FoxJ1 expressing cells (Reynolds and Weiss, 1996; Meletis et al., 2008).

The study by Xu et al. (2016) sought to determine whether these same populations in the adult forebrain also existed in the non-neurogenic spinal cord. Indeed, using the same conditions described for forebrain NSC isolation we demonstrated the presence of LIF-responsive pNSCs and GFAP-expressing dNSCs. Similarly, the lineage relationship between these two populations was shown whereby pNSCs can give rise to dNSCs in vitro. Further support for the lineage relationship comes from our recent finding that pNSCs (but not dNSCs) are present as early as embryonic day 10.5 from the embryonic tail bud which gives rise to the caudal spinal cord (Figure 1). Together, these findings reveal the presence of two distinct NSC populations along the entire neuraxis of the developing and mature central nervous system (CNS).

The question why these stem cell populations would persist, even in the non-neurogenic regions of the CNS, can only be speculated upon, but one implication of their persistence is that they could provide a source of cells for tissue regeneration. Indeed, preliminary testing of this hypothesis was conducted by examining the response of these NSC populations to minimal spinal cord injury. We observed injury-induced expansion of the pNSC and dNSC pools and migration of dNSCs towards the lesion site (as previously reported). These findings suggest, in support of the hierarchical relationship between the stem cell populations, that pNSCs may play a role in repopulating the dNSC pool that migrate to the lesion site. These findings do not preclude the possibility that pNSCs also contribute to the lesion site after injury at later times post-injury or in different injury models. Further studies are needed to shed light on this hypothesis.

It is long known that while dNSCs can contribute to tissue regeneration following spinal cord injury, there are inhibitory cues that limit axonal regeneration and impair functional recovery. Proteins from mature myelin such as Nogo, myelin-associated glycoprotein (MAG) and myelin oligodendrocyte glycoprotein (MOG) play a role in the lack of regenerative response (Silver et al., 2014). Hence, while myelin is critical for proper CNS functioning, and myelin formation has been shown to support recovery (Salewski et al., 2015), one of the most interesting findings in the study conducted by Xu et al. (2016) was that myelin is also inhibitory to NSC activation. Exploring the role of myelin basic protein (MBP) in regulating both pNSC and dNSC behavior, revealed that MBP is inhibitory to NSC proliferation. These findings have important implications for the development of both endogenous and exogenous therapeutic strategies to treat spinal cord injury.

Another important consideration when developing...
interventions to promote endogenous repair of the CNS relates to the size of the neural precursor cell pool in these regions, and understanding the role of the stem cell niche in these regionally distinct areas. Notably, we have found that MBP deficient mice have significantly greater numbers of spinal cord NSCs (5–10 times more neurospheres) compared to littermate controls with normal MBP. However, the numbers of forebrain neurospheres is not different in the MBP deficient versus control mice (unpublished observations). We are interested in whether this difference is due to intrinsic differences in the stem cell populations or due to differences in the niche between the brain and the spinal cord.

We hypothesize that niche-specific differences between the spinal cord and the brain may account for this differential response to MBP based on previous work showing that regionally and temporally restricted NSCs can adopt characteristics and behaviours of different NSCs when transplanted or exposed to their corresponding host environment. For example, NSCs from the normally aneurogenic adult spinal cord have been shown to produce neurons when transplanted into the neurogenic niche of the adult dentate gyrus of the hippocampus (Shihabuddin et al., 2000). Similarly, migration capabilities of aged and young neural precursor cells are regulated by the host environment following transplantation (Piccin et al., 2011). These findings indicate that environmental cues dictate NSC behaviour to a greater extent than intrinsic NSC differences.

We conclude from our study that there exist two distinct populations of spinal cord NSCs in the non-neurogenic spinal cord, similar to what is seen in the neurogenic forebrain. Both pNSCs and dNSCs respond to injury and MBP inhibits their proliferation. Further work on regulators of these NSC populations should be explored in order to effectively develop cell therapy strategies for regenerative medicine.

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