Human IPSC-derived Neural stem cells and their progeny: a relevant model for pharmacological studies

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Neural stem cells (NSC) reside in specific regions, called niches, of the adult brain. The most studied niches are the subventricular zone adjacent the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus. NSC are multipotent stem cells with the capacity of self-renewal and differentiation in neurons, astrocytes and oligodendrocytes. This capacity is regulated by intrinsic and extrinsic factors and, interestingly, also by drugs. For example several psychoactive drugs, including antidepressants and mood stabilizers, are well known to positively modulate neuronal differentiation of adult hippocampal NSC (Valente et al., 2012; Cuccurazzu et al., 2013; Bortolotto et al., 2014). On the contrary, opiates negatively affect adult hippocampal NSC (Meneghini et al., 2014) NSC are critical in the adult brain because they regulate tissue homeostasis. In hippocampus, NSC derived neurons are very important for spatial learning, patter discrimination and mood regulation. Reduced capacity for NSC self-renewal due to senescence may also contribute to aging and potentially to several neurodegenerative and neuropsychiatric diseases. The vast majority of studies on the biology of adult NSC have been performed on murine models. In the past we have developed a protocol for isolation of NSC from 3-4 month-old C57BL/6 mouse hippocampus. Murine NSC are maintained in suspension as neurospheres for 5 days in a medium supplemented with growth factors and under these conditions they stably express markers such as nestin and SOX2. For their differentiation, we seed single NSC in adhesion onto laminin and in a medium without growth factor for at least 24 hours, allowing cells to give rise to neurons (MAP2+ cells), astrocytes (GFAP+ cells) and oligodendrocyte precursors (NG2+ cells). Murine models are very useful in pharmacological research especially since their genome can be manipulated in transgenic and knock out/knock in animals. On the other hand, it is crucial to compare results obtained in murine cells with human models and, of course, the availability of adult NSC and their progeny from human brain is very limited. In such respect the use of induced pluripotent stem cells (iPSC) which allow the generation of human NSC and their neuronal and non neuronal progeny represents an important opportunity. We currently work with human iPSC reprogrammed from both fibroblasts and hematopoietic CD34 positive cells. Such iPSC can be differentiated in cells belonging to three embryonic layers: mesoderm, ectoderm and endoderm. Our current specific aim is to put in place a reproducible protocol to generate long-term and self-renewing iPSC-derived human NSC. These cells will be then studied in their proliferation capacity, in their differentiation potential to neuronal and glial lineages and in their response to clinically relevant psychoactive drugs in comparison with their murine counterpart. 1. Valente MM et al. Î±2δ ligands act as positive modulators of adult hippocampal neurogenesis and prevent depression-like behavior induced by chronic restraint stress. Mol Pharmacol. 2012 Aug;82(2):271-80.PubMed PMID: 22572885. 2. Cuccurazzu B et al. Upregulation of mGlu2 receptors via NF-κB p65 acetylation is involved in the Proneurogenic and antidepressant effects of acetyl-L-carnitine. Neuropsychopharmacology. 2013 Oct;38(11):2220-30. PubMed Central PMCID: PMC3773672. 3. Bortolotto V et al. NF-κB mediated regulationof adult hippocampal neurogenesis: relevance to mood disorders and antidepressant activity. Biomed Res Int. 2014;2014:612798. doi: 10.1155/2014/612798. PubMed Central PMCID: PMC3942292. 4. Meneghini V et al. A novel role for the Receptor for Advanced Glycation End-products in neural progenitor cells derived from adult SubVentricular Zone. Mol Cell Neurosci. 2010 Oct;45(2):139-50.PubMed PMID: 20600932.