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Stem Cell Research 2018-Regionally-Derived Second-Trimester Primary fNSCs Have Different Neurogenic Capacity for Neuronal Differentiation- Yiping Fan- KK Women's and Children's Hospital

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Introduction

Parkinson Disease (PD) is a debilitating neurodegenerative disease that affects more than a million Americans. It is estimated there will be an increase from 4.1 million PD patients in 2005 to 8.7 million by the year 2030, making it particularly important to find a longterm effective therapy for it. It is characterized by a loss of the midbrain dopaminergic (DA) neurons, resulting in a characteristic movement disorder. Studies involving grafting of fetal DA neurons have yielded positive repair in a non-human primate [2,3] and clinical transplantation of fetal ventral mesencephalic tissues rich in DA neuron progenitors in Parkinsonian patients has also shown favorable results up to 18 years post-transplantation, with no further treatment with levodopa. Since 2015, TRANSEURO, a trial in Europe have engrafted at least eleven patients with human fetal mesencephalic allografts although the lack of adequate samples have resulted in only 20 out of the intended 90 surgeries actually being realized. In addition, dopaminergic cell therapy is potentially useful as the disease progression occurs over a long time, with grafted neurons unaffected even after a decade. However, dyskinesis have been encountered by some of the graft recipients, highlighting the lack of control of the grafts. In addition, the use of fetal mesencephalic tissue has been encumbered by the need for multiple fetal samples per transplantation, the limited duration of storage before transplantation, and ongoing ethical, safety and quality concerns have curtailed its implementation as a mainstream treatment for Parkinsons disease (PD). Nonetheless, PD remains one of the primary targets for cell regenerative therapies as only a limited number of neurons degenerate in a specific brain region, the substantia nigra, with a unique biochemical deficit. There is a need to find a well-defined neural cell population to address the efficacy and safety for clinical purposes such as Neural Stem Cells (NSCs), which will be more controlled and homogenous than fetal neural tissue allografts. Induced pluripotent stem cell (iPSCs) has also been suggested as a viable cell source, with efficient directed differentiation shown, and engraftment into animal models of PD. However, the use of pluripotent stem cells has been beset by risks of tumor formation and integration events. While purification of desired cells can be done to reduce tumorigenicity, this technology is still relatively new and requires further testing. Moreover, the genetic component for PD will remain with the use of autologous iPSCs, although emerging technological tools through CRISPR/cas9 editing may be able to efficiently circumvent that. NSCs have been proposed to be an alternative cell source as they can be generated in large quantities in suspension bioreactors under standardized conditions. Cryopreservation also permits the longterm storage of NSCs with a post-thaw ability of 70-95% and no reduction in neuronal differentiation capacity. Finally, longterm expanded NSCs have been shown to be non-tumorigenic after transplantation in the murine striatum. In addition to its potential in neuronal replacement therapy, NSCs have been shown to rescue dysfunctional endogenous neurons through chaperon and trophic effects and may serve as cellular gene delivery vehicles for growth factors such as Glial-Derived Neurotrophic Factor (GDNF), leading to functional improvements. While adult NSCs has only been found in the sub-ventricular zone (SVZ) and hippocampus, NSCs can be derived from virtually every part of the developing central nervous system in the first half of pregnancy [25-31]. Human fetal NSCs (hfNSCs) possess unique regional and temporal identities which are postulated to

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develop during early embryogenesis due to graded morphogen levels and the differential expression of regulatory genes found in the developing brain. Subpopulations of NSCs, with a distinct expression of transcription factors, can also be found in the telencephalon. Weiss et al. Provided pioneering evidence of the different mitogenic requirements of adult spinal cord versus forebrain NSCs in culture. Mukhida et al. reported that telencephalon-derived hfNSCs exhibited significantly higher cell-fold expansion rates and larger neurosphere diameters than ventral mesencephalon (VM)-isolated fNSCs [36]. hfNSCs derived from more rostral regions of the CNS were shown to display faster proliferation rates. Short and longterm cultures revealed that forebrain NSCs were consistently more neurogenic than midbrain and hindbrain NSCs. Extended cultures generally exhibited reduced neurogenesis and increased astrocyte production except for cerebellar NSCs, which differentiated into significantly more neurons. This suggests a developmental timing whereby a maturing brain generally produces more astrocytes , which is concordant with what is known about the timing at which neurogenesis and astrogliogenesis take place. More recently, we have reported that the regionally derived NSCs from a fetus between 14 and 23 weeks exhibit different efficiencies in neurosphere initiation and neuronal/glial differentiation. We have also shown pre-differentiated GABA neurons from hfNSCs are more efficacious in engraftment and bringing about functional recovery after transient ischemic stroke. NSC differentiation has been shown to be regulated by intrinsic genetic programming. An inductive signal produced by floor plate cells, the amino-terminal product of Sonic hedgehog auto-proteolysis, Shh-N, can determine DA neuron differentiation in vitro and in vivo through a contact-dependent manner [42]. Exogenous factors present in the differentiation medium, such as interleukin-1, can similarly influence DA neuron induction. We hypothesize that regionallyderived second-trimester primary hfNSCs have different neurogenic capacity for DA neuronal differentiation due to differences in intrinsic genetic programming. Our objectives are to define the optimal DA neuronal differentiation conditions for the different regionally-derived hfNSCs. Understanding these keys may facilitate the choice of hfNSCs for different clinical scenarios such as neurodegenerative or traumatic brain injuries.

Conclusion

Current treatment modalities for PD have been hampered by limited efficacy and the eventual exhaustion of DA neurons in the nigra-striatal tract. While first-trimester neural tissues have been studied as a source for TH+ neurons, they are limited by the small cell numbers. Here we provide evidence for the differential neurogenic potential of regionally-derived NSCs and their putative genetic programming in the developing second trimester CNS. In turn, this may have implications for their utility as neural cell replacement sources for PD and other neurodegenerative disorders.

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