Therapeutic Effects of Human Neural Progenitor Cells Derived from Placental Fibroblasts Induced by Small Molecule Compounds Under Normoxia on Parkinson's Disease Rat Models

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Abstract

Neural precursor cells (NPCs) can self-proliferate and have multi-directional differentiation potential, and chemically induced neural precursor cells (ciNPCs) derived from somatic cells have great potential for the treatment of neurological diseases. However, the single source and low number of endogenous neural precursor cells currently available for transplantation remains a major challenge in the effective treatment of central nervous system injury. Here, we present an effective method for reprogramming human fibroblasts into ciNPCs using a chemical cocktail of valproic acid, CHIR99021, and Repsox (VCR) under normoxia. In the two-step reprogramming of human placental fibroblasts (HPFs), intermediate compact cell colonies were first chemically induced in KSR medium containing VCR for 10 days under different oxygen conditions, followed by lineage-specific induction. Cells at each stage were analyzed by genome sequencing. A partial Parkinson's disease rat model was established using 6-OHDA with a brain stereotaxic apparatus. Two weeks post-lesion, successful modeling was confirmed by apomorphine-induced rotation. ciNPCs were labeled with CM-DiI and transplanted into the MFB region of the brain. At 2, 4, 8, and 12 weeks post-transplantation, motor behaviors were assessed to evaluate functional recovery. At 4, 8, and 20 weeks, brains were perfused and collected to examine ciNPC survival, migration, and differentiation in the PD microenvironment. After 10 days of induction with the VCR combination under varying oxygen conditions, the cells formed neurospheres following two days of suspension culture in low-adherence plates. Most of these cells stained positive for alkaline phosphatase and exhibited high expression of NPC-specific markers, as well as the astrocyte marker GFAP and the neuron-specific marker Tuj1. Following transplantation, ciNPCs survived and functioned in the MFB region of Parkinson's model rats for over 20 weeks and significantly improved motor behavioral deficits. Moreover, the grafted ciNPCs demonstrated long-term survival, migrated over long distances, and differentiated into various neural cell types in vivo. Our findings suggest that this chemical reprogramming approach, which generates ciNPCs directly from human fibroblasts without introducing exogenous genes, may provide a novel donor cell source for stem cell-based therapy in Parkinson's disease.

Keywords

Small Molecule Compounds, Neural Progenitor Cells, Cell Reprogramming, Parkinson's Disease, Cell Transplantation, Normoxia