Dopaminergic precursors differentiated from human blood-derived induced neural stem cells improve symptoms of a mouse Parkinson's disease model

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Abstract

Autologous neural stem cells (NSCs) may offer a promising source for deriving dopaminergic (DA) cells for treatment of Parkinson's disease (PD).

Methods: By using Sendai virus, human peripheral blood mononuclear cells (PBMNCs) were reprogrammed to induced NSCs (iNSCs), which were then

differentiated to dopaminergic neurons *in vitro*. Whole-genome deep sequencing was performed to search for mutations that had accumulated during the reprogramming and expansion processes. To find the optimal differentiation stage of cells for transplantation, DA precursors obtained at various differentiation time points were tested by engraftment into brains of naïve immunodeficient mice. At last, the safety and efficacy of iNSC-derived DA precursors were tested by transplantation into the striatum of immunodeficient PD mouse models.

Results: PBMNC-derived iNSCs showed similar characteristics to fetal NSCs, and were able to specifically differentiate to DA neurons with high efficiency *in vitro*. The sequencing data proved that no harmful SNVs, Indels and CNVs were generated during the reprogramming and expansion processes. DA precursors obtained between differentiation day 10 to 13 *in vitro* were most suitable for transplantation when a balanced graft survival and maturation were taken into account. Two weeks after transplantation of DA precursors into mouse PD models, the motor functions of PD mice started to improve, and continued to improve until the end of the experiments. No graft overgrowth or tumor was observed, and a significant number of A9-specific midbrain DA neurons were surviving in the striatum.

Conclusion: This study confirmed the efficacy of iNSC-derived DA precursors in a mouse PD model, and emphasized the necessity of genomic sequencing and vigorous safety assessment before any clinical translation using iNSCs.