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ES cell therapy for experimental Parkinsonism

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Pluripotent, embryonic stem (ES) cells can be propagated indefinitely in vitro and induced to differentiate into various cell types. These unique properties enable ES cells to be used as an appropriate tool for studying specific cellular development as well as a potentially unlimited source for cell replacement therapy.

Parkinsons disease is a neurodegenerative disorder characterized by progressive loss of midbrain dopamine neurons. Graft of human fetal ventral mesencephalon can survive and reduce motor symptoms after transplantation into the striatum of Parkinsons patients. Although the fetal tissue transplantation is promising for treating Parkinsons disease, there are problems of limited availability of fetal tissue and ethical controversy in its use. In this regard, dopaminergic differentiation from ES cells is of great interest to overcome the limitations in the use of fetal tissue. Several methods including lineage selection method (Lee et al., 2000), and co-culture with stromal cells (Kawasaki et al., 2000) have been introduced to differentiate ES cells into midbrain dopaminergic neurons. Although midbrain dopaminergic neurons functions in vitro or in vivo on transplanted striatum (Kim et al., 2002) could be enriched using these protocols, there is still a definite need to improve the efficiency of the dopaminergic differentiation, with which eliminates the possibility of unwanted side effects caused by inappropriate cells included along with the midbrain dopamine neurons, especially undifferentiated ES cells, when the mixture of differentiated ES cells were grafted into Parkinson patients. In addition to the safety problems of ES cell therapy, the long-term survival and efficacy of donor cells also need to be guaranteed for the desirable cell therapy for Parkinsons disease. One possible strategy to make ES cells as an adequate cell source might be to manipulate specific genes involving development, survival or functional efficacies of dopamine neurons.

We, here, demonstrate that Bcl-XL , a Bcl-2 family anti-apoptotic protein, markedly enhanced ES cell-derived neuronal differentiation, particularly into DA neurons which are more resistant to Parkinsonian toxin MPP+, compared to DA neurons derived from naïve ES cells. Upon grafting into the striatum of Parkinsonian rats, Bcl-XL overexpressing ES (Bcl-ES) cells differentiated into DA cells morphologically more mature with long and extensive neurite outgrowth, and restored more efficiently Parkinsons motor behavior.