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Human Embryonic Stem Cells Co-Transfected with Tyrosine Hydroxylase and GTP Cyclohydrolase Relieve Symptomatic Motor Behavior in a Rat Model of Parkinson's Disease

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Main strategy for a treatment of Parkinson's disease (PD), due to a progressive degeneration of dopaminergic neurons, is a pharmaceutical supplement of dopamine derivatives or cell replacement therapy. Both of these protocols have pros and cons; former exhibiting a dramatic relief but causing a severe side effects on long-term prescription and latter also having a proven effectiveness but having availability and ethical problems. Embryonic stem (ES) cells have several characteristics suitable for this purpose. To investigate a possibility of using ES cells as a carrier of therapeutic gene(s), human ES (hES, MB03) cells were transfected with cDNAs coding for tyrosine hydroxylase (TH) in pcDNA3.1(+) and the transfectants were selected using neomycin (250 ㎍/㎖). Expression of TH being confirmed, two of the positive clone (MBTH2 & 8) were second transfected with GTP cyclohydrolase 1 (GTPCH 1) in pcDNA3.1(+)-hyg followed by selection with hygromycin-B (150 ㎍/㎖) and RT-PCR confirmation. By immunocytochemistry, these genetically modified but undifferentiated dual drug-resistant cells were found to express few of the neuronal markers, such as NF200, β-tubulin, and MAP2 as well as astroglial marker GFAP. This results suggest that over-production of BH4 by ectopically expressed GTPCH I may be involved in the induction of those markers. Transplantation of the cells into striatum of 6-OHDA- denervated PD animal model relieved symptomatic rotational behaviors of the animals. Immunohistochemical analyses showed the presence of human cells within the striatum of the recipients. These results suggest a possibility of using hES cells as a carrier of therapeutic gene(s).

Key words) *Parkinson's Disease, Cell replacement therapy, hES cell, Genetic modification*