A High-Throughput Disease-Specific Phenotype Detection System of Parkinson's Disease

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Disease-specific induced pluripotent stem cells (iPSCs) are widely used for disease modeling and drug discovery. We have established iPSCs from 7 types of familial Parkinson's disease (PD). Notably, each form of familial PD has specific cellular functional abnormalities that induce extensive loss of dopaminergic neurons. To accelerate PD-iPSC research, we sought to establish a 96-well based high-throughput neural differentiation and phenotype detection system. iPSCs were differentiated into dopaminergic neurons on the 96-well plates by a neurosphere-based differentiation protocol (Stem Cell Reports, 2016). Subsequently, several PD-related phenotypes, including impaired mitophagy, which is considered a major phenotype in PARK2 (autosomal recessive juvenile PD, caused by mutations in *PRKN* gene) and PARK6 (autosomal recessive juvenile PD, caused by mutations in *PINK1* gene), cell vulnerability, and α -synuclein accumulation commonly seen in PD, were quantified automatically by using In Cell Analyzer 2200 and In Cell Developer Toolbox (GE Healthcare). We successfully detected the phenotypes characterized in each form of familial PD as compared with healthy controls both quantitatively, and reproducibly. By using this high-throughput assay system, we screened a library of 320 compounds to evaluate phenotypic recovery. We identified several compounds that modify impaired mitophagy observed in PARK2 and PARK6 dopaminergic neurons. Furthermore, we established a small scale iPSC induction method, and completed iPSC induction from over 100 sporadic PD patients. By applying both the high-throughput neural differentiation method and phenotype detection system, we are trying to capture abnormal phenotypes in sporadic PD patients. Thus, this high-throughput phenotype detection system could comprehensively compare phenotypes of each form of familial PD, as well as perform drug screening. This approach is applicable for sporadic cases and other neurodegenerative diseases.

Key words: Parkinson's disease, iPSCs, high-throughput, disease modeling, drug discovery

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