

Modeling Parkinson's Disease with Human Induced Pluripotent Stem Cells

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Introduction

Pluripotent stem cells (PSCs) and multipotent neural stem cells (NSCs) offer great in vitro tools to study the process of neurodevelopment and neural cell specification [1-11]. With the discovery of human induced pluripotent stem cells (iPSCs) [12], it is possible to model human neural system diseases in a dish. Recent studies have shown the progress on modeling neurodegenerative disorders using human iPSCs [13-18]. Here this editorial briefly summarizes and discusses the advances on modeling Parkinson's disease (PD) using human iPSCs.

Human iPSCs have been successfully generated from sporadic [19-21] and familial PD patients with mutations [6-14,19]. Deficits were found in PD iPSC-derived NSCs [20], neurons [21] and dopaminergic neurons [16-23]. LRRK2 (G2019S) mutant iPSC-derived NSCs show increased susceptibility to proteasomal stress as well as passage-dependent deficiencies in nuclear-envelope organization, clonal expansion and neuronal differentiation [21]. PARK2 mutant iPSC-derived neurons showed increased oxidative stress, enhanced activity of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, abnormal mitochondrial morphology, impaired mitochondrial homeostasis, and the accumulation of α -synuclein [20]. Since PD is mainly caused by the death of dopamine-generating cells in the substantia nigra, the phenotypes from midbrain dopaminergic neurons are more valuable for modeling this disease. SNCA triplication mutant iPSC-derived midbrain dopaminergic neurons show higher SNCA mRNA level and α -synuclein protein level [24]. Patient iPSC-derived A53T α -synuclein mutant A9 dopaminergic neurons form α -synuclein protein aggregates and show the inhibition of MEF2C-PGC1 α pathway, which contributes to mitochondrial dysfunction and apoptotic cell death [25]. Parkin mutant iPSC-derived dopaminergic neurons show lower PINK1 mRNA level, impaired recruitment of Parkin protein to the depolarized mitochondria, decreased clearance rate of depolarized mitochondria, increased transcription of monoamine oxidases and oxidative stress, reduced DA uptake and increased spontaneous DA release [19,25]. LRRK2 (G2019S) mutant iPSC-derived dopaminergic neurons show increased expression of key oxidative stress-response genes and α -synuclein protein, dysregulation of CPNE8, MAP7, UHRF2, ANXA1 and CADPS2, increased ERK phosphorylation, more sensitive to stress, and morphological alterations [24-26].

With the development of PD studies and pre-clinical cell therapeutic exploration using iPSCs [5,20,27-33], more efficient and effective treatments for PD are expected in the near future.

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