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Using Induced Pluripotent Stem Cells to Model Neurodegenerative Diseases

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Neurodegenerative diseases are age-related chronic and progressive loss of neurons, such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). In clinical, patients suffered impaired memory and cognitive function, impaired motor coordination and irritability and aggression with neurodegenerative diseases. In the end, patients will gradually lose language and movement function [1]. The burden of neurodegenerative diseases is heavy to patient's families and the whole society. Although many basic and clinical studies have made a lot of efforts to ameliorate the clinical symptoms, it is still far from satisfaction to understand how the interaction of drugs and degenerative neurons is. Many neurodegenerative diseases are caused by genetic mutations, which allow scientists to generate transgenic animals to understand the mechanisms of development and outcome of neurodegenerative disease and therapeutic studies. However, neurons from animals are quite different from human neurons and results in animal trials could not be directly shifted to clinical application.

Recent progress in reprogramming techniques and stem cell biology make it possible to use human induced pluripotent stem cells as a model to study neurodegenerative diseases. In 2006, Kazutoshi Takahashi and Shinya Yamanaka published the pioneer discovery of induction of pluripotent stem cells from mouse embryonic and adult fibroblasts by 4 transcriptional factors, Oct4, Sox2, c-Myc, and Klf4 [2]. In 2007, human induced pluripotent stem cells (iPSCs) were successfully generated from human fibroblasts. Human iPSCs have similar properties with human embryonic stem cells, which have the capacity to be induced to differentiate into all types of cells in the human body [3,4]. The Nobel Prize in Physiology or Medicine in 2012 was awarded to Sir John Gurdon and Shinya Yamanaka due to their discovery that mature somatic cells can be reprogrammed to become pluripotent stem cells. Later on, some groups used similar techniques to generate disease-specific iPSCs. Here, I will focus on iPSCs in modeling neurodegenerative diseases, PD and AD. For extension reading, please see recent review papers [5,6].

Application of iPSCs in Modeling PD

The first PD patient-derived iPSCs were generated from a 57 year old male PD patient's fibroblasts using Yamanaka's factors in 2008 [7]. In 2009, Jaenisch's group generated free of viral iPSCs from five idiopathic PD patients using 3 transcriptional factors, Oct4, Sox2 and Klf4 with Cre-recombinase. Their results also show that PD patient-derived iPSCs can be induced to differentiate into dopaminergic neurons *in vitro*. PD patient-derived iPSCs can differentiate into dopaminergic neurons and integrate with host tissue in the striatum of 6-hydroxydopamine (6-OHDA) lesioned rats [8]. Furthermore, the transplanted iPSCs can reduce motor asymmetry in the rat model of PD [9]. Feng's group results show that dopaminergic neurons derived from human iPSCs with parkin mutation significantly increases oxidative stress. Loss-of-function studies shows that dopaminergic neurons derived from iPSCs with parkin mutation significantly decrease dopamine uptake and significantly increase spontaneous Ca^{2+}-independent dopamine release. Gain-of-function studies show that overexpression of parkin in dopaminergic neurons derived from iPSCs with parkin mutation can rescue all the phenotypes. This paper verified the specific function of parkin in midbrain dopaminergic neurons [10]. PD patient-derived iPSCs were also generated from other mutation patients, such as A53T and E46K point mutation, α-synuclein and LRRK2 mutations.

Application of iPSCs in Modeling AD

AD patient-derived iPSCs were firstly generated from familial AD (FAD) patients with mutations in *PS1* and *PS2* and can be induced to differentiate into neurons. Neurons derived from iPSCs with mutations in *PS1* and *PS2* could increase amyloid β42 secretion, which has been found in patients' brain with mutant presenilins. The production of Aβ40 and Aβ42 is suppressed in the presence of γ-secretase inhibitor, Compound E [11]. Another group generated AD patient-derived iPSCs from two patients with duplication of the Aβ precursor protein gene (APPDp) and two patients with sporadic AD (sAD1 and sAD2). Levels of Aβ40, phospho-tau and active glycogen synthase kinase-3β (aGSK-3β) were significantly higher in iPSC-derived neurons from two APP(Dp) and sAD2 patients than that of controls. Large RAB5-positive early endosomes highly accumulated in the neurons from these two APP(Dp) and sAD2 patients. Interestingly, neurons from these two APP(Dp) and sAD2 patients decreased the level of phospho-Tau and aGSK-3β in the presence of β-secretase inhibitors, but not γ-secretase inhibitors [12].

Using similar techniques, recent studies show that human fibroblasts could be directly programmed into NSCs (iNSCs). Induced NSCs can be induced to differentiate into neurons *in vitro* and *in vivo* [13,14]. NSCs have been used to model neurological diseases more than 10 years. Furthermore, human fibroblasts can be directly programmed into neurons, even subtype specific neurons, such as dopaminergic neurons [15,16]. One report shows that fibroblasts from familial FAD patients with mutations in presenilin-1 and -2 mutations can be directly programmed into neurons [17]. These three types of induced cells, iPSCs, iNSCs and induced neurons, can not only be used for modeling neurodegenerative diseases, but also for cell replacement therapy of neurodegenerative diseases.

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