Induced pluripotent stem cells for modeling and cell therapy of Parkinson’s disease

Neurodegenerative disorders include a variety of hereditary or sporadic diseases involving the chronic, progressive loss on neural tissue. Parkinson’s disease (PD) is the second most common neurodegenerative disease, affecting more than 6 million people worldwide (Wan et al., 2015). Degeneration of nigrostriatal dopaminergic (DA) neurons is the main pathology in PD, although other dopaminergic and non-dopaminergic systems are also affected. Characteristic symptoms are rigidity, hypokinesia, tremor, and postural instability. The loss of DA neurons is accompanied by Lewy bodies and Lewy neuritis, which are mainly formed by protease-susceptible aggregates of alpha-synuclein and Tau protein and might restrain the survival and development of newborn neurons. Etiology of PD remains unclear, however interactions between environmental and genetic factors are believed to cause the loss of nigral DA neurons and ensuing locomotor system. Research indicated that increasing level of iron, oxidative stress, mitochondrial and ubiquitin-proteasome system dysfunction, inflammation, and apoptosis may lead to the progression of PD (Pu et al., 2012; Zhu et al., 2016).

The majority of PD cases are sporadic or idiopathic (80–90%), but a minority of cases (10–20%) are familial and can be linked to particular monogenic mutation associated to PD related genes. Monogenic forms of PD account only for small percentage of PD cases. However, understanding how mutation of PD related genes causes the degeneration of DA neurons is essential for the study of disease mechanism. The most frequent mutation represents G2019S mutation of the leucine rich repeat kinase 2 (LRRK2) gene (Nguyen et al., 2011). Many mouse models and postmortem tissue studies have provided insight into pathogenesis of PD, however, the former consistently fail to recapitulate the cardinal features of PD and the latter are end-stage representations (Marchetto et al., 2011).

There is currently no effective medication to treat PD. Drug therapies only provide relief of symptoms and have unpredictable side effects. Although motor symptoms can be treated relatively well with L-3,4-dihydroxyphenylalanine (L-DOPA), DA agonist, dopamine inhibitor carbipoda, and deep brain stimulation to the nucleus subthalamicus, effective therapies for nonmotor symptoms, such as dementia, are lacking, and disease progression cannot be counteracted. Another possibility to cure PD is fetal tissue transplantation. For example, Korower et al. (2008) published a case report of patient with PD to whom was implanted fetal nigral tissue into the striatum. Study demonstrated that implanted dopamine neurons can survive and reinervate the striatum. However, there are several issues with the use of fetal tissue, such as difficulties in obtaining and ethical concern (Freeman 1997). Stem cell-based therapies for neurodegenerative disorders are particularly attractive, given the limited regenerative capacity of mammalian neurons (Kriks et al., 2011; Han et al., 2015). Clinical trials with transplantation of human fetal ventral midbrain neural stem cells into PD brains have provided proof of principle that neuronal replacement can be effective in some PD patients. However, the ethical issues of human fetal tissue limit its widespread clinical use (Zhu et al., 2016).

The generation of induced pluripotent stem cells (iPSCs) that can be derived from the adult cells of specific patients, has recently revolutionized the field, holding promise that some of the obstacles traditionally associated with stem cells therapy (immune compatibility, ethical issues, purity of cells) could be overcome (Takahashi et al., 2007). Successful reprogramming of somatic cells to a pluripotent state by transient expression of four transcription factors (Oct4, Sox2, Klf4, and c-myc) was achieved for the first time with mouse cells in 2006 (Takahashi and Yamanaka, 2006). However, retroviral insertion can cause genome damage resulting in tumor formation. Since the seminal iPSC work by Dr. Yamanaka and colleagues, the field has rapidly moved forward. In order to retain genome integrity during reprogramming, various techniques have been developed to generate insertion free iPSCs, such as integrative free vectors (piggyBac transposon, plasmid/episomal plasmid vectors, minicircle vectors), and non-integrating methods (direct protein/microRN delivery, small molecules) (Tanabe et al., 2014). However, there still remain safety concerns in the terms of more suitable and harmful endogenous genetic and epigenetic alterations that may occur during reprogramming of iPSCs, since cell growth pathway could be activated and tumor suppressor pathways could be also inhibited after using small molecule cocktail (Oh et al., 2012). The causes of mutations resulting in cellular dysfunction or tumorigenesis are usually retro- or lenti-viral transduction systems using in generation of iPSCs. Moreover, iPSCs can retain gene expression pattern of the cell type of origin. Recently were reported also high variability among iPSC lines including increased levels of aneuploidy, defects in X-chromosome inactivation and presence of point mutations. Thus, in order to use iPSCs for treating human disease, it is necessary to assess the safety of the cells before clinical applications (Marchetto et al., 2011; Cai et al., 2014).

The advent of iPSCs transforms the negative outlook associated with neurodegenerative disease. Reprogramming technology allows researchers to study the development and progression of neurodegeneration in a human system and may enable the discovery of new diagnostics and cell-based therapies. The human neurodevelopmental and neurodegenerative disease can be studied in live neurons in a controlled environment (Figure 1). The major advantage of iPSCs approach is the potential to develop human cell-based disease models of sporadic and genetically complex disease such as PD. Moreover, PD is very interesting model for application of iPSC technology, because protocols for generating DA neurons are relatively robust and reproducible (Soldner et al., 2009; Kriks et al., 2011).

Soldner et al. (2009) derived human iPSCs from skin biopsies obtained from patients with idiopathic PD and developed a robust reprogramming protocol allowing reproducible generation of patient-specific stem cells with efficient removal of transgene sequences. From patient-specific iPSCs were generated of midbrain DA neurons that have the same genetic composition as the patients and share many important properties with the nigral DA neurons (Pu et al., 2012).

One of the first iPSCs model of genetic PD involved a patient triplification in the alpha-synuclein gene was reported by Byers et al. (2011). In the study, DA neurons showed accumulation of alpha-synuclein, overexpression of markers of oxidative stress and enhanced sensitivity to cell toxicity induced by hydrogen peroxide compartment with controls. Tripletion of alpha-synuclein gene causes a fully penetrant, aggressive form of PD with dementia because of alpha-synuclein dysfunction.

Nguyen et al. (2011) described the first biologically relevant cellular phenotype from iPSCs derived neurons from PD patients. In this study, iPSCs were derived from one 60-year-old female PD patient carrying LRRK2 overexpression of markers of oxidative stress and enhanced sensitivity to cell toxicity induced by hydrogen peroxide compartment with controls. Tripletion of alpha-synuclein gene causes a fully penetrant, aggressive form of PD with dementia because of alpha-synuclein dysfunction.

Figure 1 Potential therapeutic applications of PD-iPSCs.

iPSCs can be reprogrammed by different techniques, including viral delivery (retroviruses and adenoviruses), integrative free vectors (piggyBac transposon, plasmid/episomal plasmid vectors, minicircle vectors) and non-integrating methods (direct protein/microRN delivery, small molecules). Obtained iPSCs can be corrected/edited to receive patient-specific cells suitable for clinical application. CRISPR/Cas9: RNA-guided clustered regularly interspaced short palindromic repeats/associated protein 9 nucleas, ZNF: zinc finger nucleas.
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References


