

# World Journal of *Stem Cells*

*World J Stem Cells* 2019 September 26; 11(9): 565-721



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: Yan-Xia Xing

Proofing Production Department Director: Yun-Xiaojuan Wu

**NAME OF JOURNAL**

*World Journal of Stem Cells*

**ISSN**

ISSN 1948-0210 (online)

**LAUNCH DATE**

December 31, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Tong Cao, Shengwen Calvin Li, Carlo Ventura

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-0210/editorialboard.htm>

**EDITORIAL OFFICE**

Jin-Lei Wang, Director

**PUBLICATION DATE**

September 26, 2019

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**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Using induced pluripotent stem cells for modeling Parkinson's disease

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**Author contributions:** Minjing Ke and Cheong-Meng Chong contributed equally to this manuscript.

**Supported by** the Macao Science and Technology Development Fund, No. 039/2017/AFJ and 0020/2018/A.

**Conflict-of-interest statement:** The authors have declared no conflicts of interest.

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**Manuscript source:** Invited manuscript

**Received:** February 25, 2019

**Peer-review started:** February 27, 2019

**First decision:** April 11, 2019

**Revised:** July 26, 2019

**Accepted:** August 20, 2019

**Article in press:** August 20, 2019

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### Abstract

Parkinson's disease (PD) is an age-related neurodegenerative disease caused by the progressive loss of dopaminergic (DA) neurons in the substantia nigra. As DA neurons degenerate, PD patients gradually lose their ability of movement. To date no effective therapies are available for the treatment of PD and its pathogenesis remains unknown. Experimental models that appropriately mimic the development of PD are certainly needed for gaining mechanistic insights into PD pathogenesis and identifying new therapeutic targets. Human induced pluripotent stem cells (iPSCs) could provide a promising model for fundamental research and drug screening. In this review, we summarize various iPSCs-based PD models either derived from PD patients through reprogramming technology or established by gene-editing technology, and the promising application of iPSC-based PD models for mechanistic studies and drug testing.

**Key words:** Parkinson's disease; Dopaminergic neurons; Induced pluripotent stem cells; Somatic cell reprogramming; Aging

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**Core tip:** Human induced pluripotent stem cell (iPSC)-derived dopaminergic neurons hold great promise for studying disease mechanisms underlying Parkinson's disease (PD) and testing drug effects. A number of reviews have previously summarized the potential use of patient iPSCs for modeling PD. However, few of them comprehensively discuss the establishment of gene-editing-based iPSCs for PD and their application in research. Our objective is to consolidate the current literature on various iPSC-based PD models either derived from PD patients through reprogramming technology or established by gene-editing technology, and provide new insights into the application of iPSC PD models.



**Published online:** September 26, 2019

**P-Reviewer:** Kujawska M, Li SC, Tarnawski AS

**S-Editor:** Ma RY

**L-Editor:** A

**E-Editor:** Xing YX



**Citation:** Ke M, Chong CM, Su H. Using induced pluripotent stem cells for modeling Parkinson's disease. *World J Stem Cells* 2019; 11(9): 634-649

**URL:** <https://www.wjnet.com/1948-0210/full/v11/i9/634.htm>

**DOI:** <https://dx.doi.org/10.4252/wjsc.v11.i9.634>

## INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease caused by the death of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) and a decrease in dopamine level, which lead to hypokinetic motor symptoms such as shaking, rigidity, slowness of movement, and difficulty in walking<sup>[1,2]</sup>. Although the standard treatments of PD that focus on boosting dopamine or dopamine receptor signaling can reduce symptoms at an early stage of the disease, none is effective at slowing or preventing progression of PD<sup>[3]</sup>.

The onset of PD typically occurs at age > 60 years and its incidence is a global health concern with the increase in the aged population<sup>[4,5]</sup>. Aging is considered to be the most important risk factor for PD<sup>[6,7]</sup>, but multiple genetic and environmental factors are also widely recognized to play critical roles in its development<sup>[8,9]</sup>. PD is generally classified into two forms: sporadic and familial PD. Sporadic PD is usually late onset and accounts for the majority of PD cases<sup>[10]</sup>. Some genetic backgrounds have been reported to increase the incidence of sporadic PD such as cytochrome P450 2D6 and glutathione S-transferase pi 1. However, these are not defined as genetic diseases because they have not been demonstrated to be associated with the development of PD<sup>[11,12]</sup>. In addition, long-term exposure to industrial chemicals and pollutants such as pesticides<sup>[13]</sup>, metals<sup>[14]</sup> and solvents<sup>[15]</sup> is considered to contribute to development of sporadic PD. Familial PD is caused by gene mutations, which accounts for about 10% of PD cases<sup>[16]</sup>, and shares some clinical features with sporadic PD. Currently, 16 familial PD-related genes have been identified. Their classification depends on chromosomal locus, which is named PARK and numbered in chronological order of their identification<sup>[17,18]</sup>. Among these mutations, PARK1/4, PARK3, PARK5, PARK8 and PARK11 are identified as autosomal dominant mutations. Except for PARK1/4, the other autosomal dominant mutations are late-onset PD. Autosomal recessive mutations in PARK2, PARK6, PARK7, PARK9, PARK14 and PARK15 are reported in early-onset PD. Other mutations in vacuolar protein sorting 35 and eukaryotic translation initiation factor 4G1 are identified in large families with dominant late-onset PD but not yet assigned with a PARK locus<sup>[19]</sup>.

Previous studies on the pathology of PD have indicated that the deterioration is caused by formation of  $\alpha$ -synuclein immunoreactive inclusion bodies that develop into globular Lewy bodies or Lewy neurites<sup>[20,21]</sup>.  $\alpha$ -synuclein aggregation is recognized as not only a key event in familial PD but also the most consistent marker to define Lewy body pathology in sporadic PD<sup>[22]</sup>. These findings hint that both familial and sporadic PD have similar etiology<sup>[23]</sup>. In addition to abnormal aggregation of  $\alpha$ -synuclein, other pathogenic factors involved in progress of PD have been reported, including mitochondrial dysfunction, oxidative and nitritative stress, neuroinflammation, and impaired autophagy<sup>[24-28]</sup>. However, up to now, the exact etiology and pathogenesis of PD are still unknown. The major barrier to study PD is the lack of brain tissue samples from patients, and current understanding of PD neuronal dysfunction has been largely derived from postmortem and pathological specimens<sup>[29]</sup>. Experimentally modeling PD is conventionally based on biochemical abnormalities in the brains of PD patients, such as oxidative stress and mitochondrial dysfunction. Toxins such as 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), paraquat and rotenone are conventionally used in PD modeling<sup>[30]</sup>. Commonly, 6-OHDA is stereotactically injected into animal brains and the other toxins are injected subcutaneously or intraperitoneally to induce PD models<sup>[31-33]</sup>. These neurotoxins can be taken up by DA neurons via dopamine transporters and cause neuronal damage<sup>[34]</sup>. Their toxicities are possibly due to the inhibition of complex I of the mitochondrial electron transport chain, which leads to depletion of ATP and an increase in reactive oxygen species (ROS), and eventually results in neuronal death<sup>[35]</sup>. Although these toxins can destroy DA neurons in the SNpc, 6-OHDA and MPTP treatment does not yield aggregation of  $\alpha$ -synuclein (Lewy bodies), which is a major pathological marker of PD<sup>[36]</sup>. Typical PD is a type of chronic neurodegeneration. However, 6-OHDA or MPTP causes acute damage, which is not an appropriate model to mimic the pathogenic factors of PD. Chronic exposure to

rotenone in rats leads to aggregation of  $\alpha$ -synuclein, DA neurodegeneration and behavior defects. A major concern about rotenone-induced models is that, in addition to degeneration of nigral DA neurons, rotenone causes pronounced degeneration in basal ganglia and brainstem nuclei<sup>[37]</sup>, and leads to high systemic toxicity<sup>[38]</sup>.

Transgenic mice are alternative models for exploring pathogenic mechanisms of PD-linked genetic factors. Currently, duplication or triplication of the  $\alpha$ -synuclein locus could cause PD symptoms<sup>[39]</sup>, indicating that increasing expression of PD-related genes could be applied to establishment of PD models<sup>[40,41]</sup>. Some PD characteristics can be observed in transgenic mice generated by overexpressing wild-type PD genes or PD gene mutation at age  $\leq 2$  years<sup>[42]</sup>. However, in mammalian models, knockin or knockout mutation of PD-linked genes can only cause a moderate decrease in striatal DA levels accompanied by low locomotor activity in an age-dependent manner, without evident loss of dopaminergic neurons in SNpc<sup>[43]</sup>. Transgenic mouse models may illuminate some pathogenic processes of PD, but cannot fully replicate the phenotypes of human PD because they are insufficient to cause significant nigral degeneration within the animal lifespan<sup>[40]</sup>. The genetic mouse models may not properly represent interaction of genetic factors, aging process, and environmental insults in human PD<sup>[19,44]</sup>. Thus, establishing suitable models to fully represent the characteristics of PD is urgently needed.

Human induced pluripotent stem cells (iPSCs) are generated from somatic cells by reprogramming. The somatic cells reprogramming technology was pioneered by Shinya Yamanaka in 2006 and showed that introduction of four transcription factors (*OCT4*, *SOX2*, *KLF4* and *c-MYC*) could convert somatic cells into PSCs<sup>[45]</sup>. The ability of iPSCs to differentiate into DA neurons overcomes the challenges and shortcomings associated with PD modeling. Two types of iPSC-based PD models are widely used: patient-specific and gene-modifying models. Patient-derived specific disease models have been used in discovering novel biomarkers for diagnosis or candidate drug therapy<sup>[46]</sup>. Genome editing can offset the variation of genetic background among individuals<sup>[47,48]</sup>. In this review, we summarize various iPSC-based PD models either derived from PD patients through reprogramming technology or established by gene-editing technology, and the promising application of iPSC-based PD models for mechanistic studies and drug testing (Figure 1).

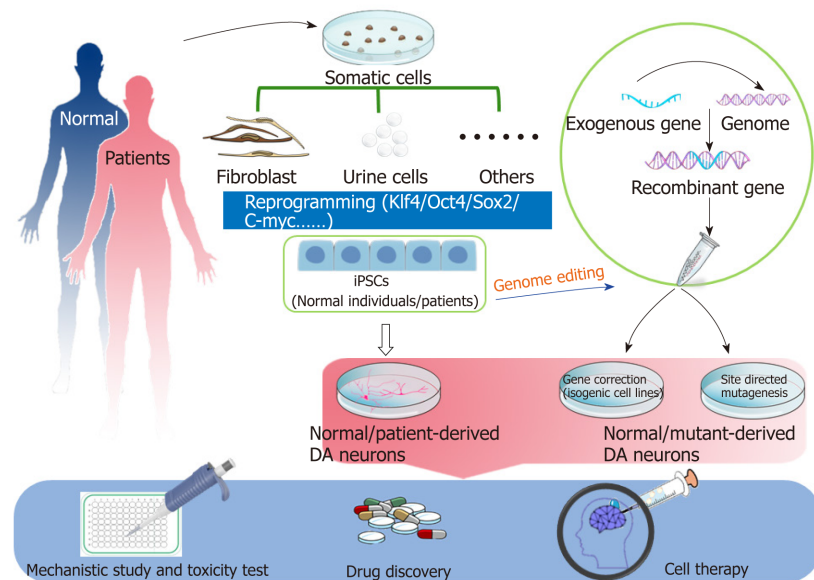
## PATIENT-SPECIFIC iPSCs

It is widely accepted that PD results from a complex interaction of environmental and genetic factors<sup>[49]</sup>. In the hope of copying traits of PD, DA neurons derived from PD-patient-specific iPSCs display the cellular characteristics of PD *in vitro*. Investigators have established iPSC banks of neurodegenerative disease over the past decade. To date, patient-specific iPSCs have been used in a variety of fields including drug discovery, basic research and cytotoxicity testing.

### iPSC models for familial PD

It is well known that sporadic PD occupies  $> 90\%$  of total PD cases, but genetic factors still play an important role in understanding PD etiology. The use of genetic PD iPSCs offers the promise of addressing the contribution of individual genetic factors and functional relevance of underlying molecular pathways in the development of PD. Currently, 16 familial PD-related genes have been identified. Among them, *SNCA*, *LRRK2*, *Parkin*, *PINK1* and *GBA* mutations have mostly been studied in genetic PD iPSCs<sup>[50]</sup> (Table 1). Researchers have made efforts to illustrate the pathological features of DA neurons or other neuronal cells derived from these genetic PD iPSCs. It is generally considered that the fate of these mutated genes is often loss of function that induces aberrant accumulation of inactive proteins<sup>[51]</sup>.

Accumulation of  $\alpha$ -synuclein is a major feature of PD, which is encoded by *SNCA* gene. *SNCA* A53T mutant and triplication *SNCA* are familial PD *SNCA* mutants. In these patients,  $\alpha$ -synuclein level in the midbrain region is three times that in somatic cells, revealing that it is easy to cause accumulation of  $\alpha$ -synuclein in DA neurons. After Soldner *et al*<sup>[52]</sup> successfully generated the first DA neurons from *SNCA* mutant iPSCs, a number of *SNCA* A53T mutant or triplication *SNCA* mutant iPSC lines were generated, and elevated  $\alpha$ -synuclein levels were found in these iPSC-derived DA neurons<sup>[40,53-57]</sup>. Other cellular types such as forebrain cortical neurons, neural precursor cells, and GABAergic neurons were further induced from *SNCA* mutant iPSCs, and endoplasmic reticulum (ER) stress, oxidative stress, or maturation inability but no significant alteration of  $\alpha$ -synuclein protein or mRNA level were detected in these iPSC-derived cells<sup>[56-59]</sup>. These studies show that *SNCA* gene mutations may have great influence on a variety of neuronal subtypes and not just DA neurons.



**Figure 1 Potential applications of induced pluripotent stem cells for study of Parkinson's disease.** Somatic cells are extracted from either normal individuals or patients and then reprogrammed to induced pluripotent stem cells (iPSCs). Gene editing technology enables one to generate knockin mutant Parkinson's disease (PD) iPSCs and isogenic control cell lines. Dopamine (DA) neurons can be successfully differentiated from iPSCs. Both patient-derived and gene-edited iPSCs could be powerful tools for modeling PD for mechanistic studies and drug discovery. Healthy or corrected iPSCs could serve as normal controls and cell sources for cell therapy. iPSCs: Induced pluripotent stem cells; DA: Dopaminergic.

N1437H, R1441C and G2019S mutations of *LRRK2* are known to cause PD. Among them, G2019S is the most common familial PD mutation in *LRRK2*<sup>[60]</sup>. Many studies have pointed out the crucial role of the loss-of-function of *LRRK2* mutant in reducing neurite outgrowth and numbers, and process complexity<sup>[61-65]</sup>. Oxidative stress, mitophagic dysfunction, and DNA damage have been observed in *LRRK2* G2019S iPSC-derived DA neurons. In addition, self-renewal and neuronal differentiation of *LRRK2* G2019 mutant neural stem cells are reported to be impaired, providing evidence on the crucial role of *LRRK2* in neural development<sup>[62]</sup>.

Synergistic effect of *PINK1* and *Parkin* are important to maintain cellular homeostasis such as mitochondrial quality in DA neurons<sup>[66,67]</sup>. It is suggested that overexpression of *Parkin* can largely rescue the defects in *PINK1* mutants through mitochondrial translocation<sup>[66,68]</sup>. *Parkin* improves the uptake of dopamine through enhancing the expression of DAT as well<sup>[69]</sup>. *PINK1* or *Parkin* mutant iPSC-derived DA neurons display abnormal phenotypes such as mitophagy and autophagy impairment, vulnerability to various stresses, and accumulation of peroxisome proliferator-activated receptor- $\gamma$  coactivator 1 $\alpha$  (PGC1 $\alpha$ ), which are consistent with previous studies<sup>[63,70-75]</sup>. These findings support the synergistic effect of *PINK1* and *Parkin*, providing an inspiration for developing therapeutic strategies for PD.

*GBA1* gene mutations are reported to be associated with an increased risk of sporadic PD<sup>[76]</sup>. A number of studies on patient-specific iPSC-derived DA neurons harboring *GBA1* mutations have indicated that  $\beta$ -glucocerebrosidase (*GBA1*) has high correlation with elevated  $\alpha$ -synuclein levels as well as autophagic and lysosomal defects<sup>[77-79]</sup>. Furthermore, calcium homeostasis imbalance, and reduced dopamine storage and uptake are also found in *GBA1* mutant DA neurons<sup>[77-79]</sup>. However, how these above-mentioned phenotypes are triggered by *GBA1* mutant remains to be explored.

### **iPSC models for sporadic PD**

Sporadic PD-derived iPSCs lack known PD mutations. The first case of generation of sporadic PD patient iPSCs was reported by Soldner *et al*<sup>[80]</sup>. They generated iPSCs from skin biopsies obtained from sporadic PD patients by application of modified lentiviruses carrying loxP sites flanking the integrated provirus for improving the efficiency of reprogramming. The advantage of this method was the use of inducible excisable lentivirus, rendering the iPSCs free of reprogramming transgenes. However, the phenotypic analysis of these iPSCs was not performed in that study. Sanchez-Danes *et al*<sup>[71]</sup> generated healthy and sporadic PD iPSCs *via* retroviral delivery of

**Table 1 Patient-derived induced pluripotent stem cell-based modeling of Parkinson's disease**

Gene mutation	Inheritance type	Differentiated cell types	<i>In vitro</i> phenotypes(normalized to normal control / non-isogenic control)	Ref.
A53T SNCA	Familial	DA neurons	Not demonstrated	[52]
Triplication SNCA	Familial	DA neurons	Elevated levels of SNCA mRNA Increased cellular and secreted $\alpha$ -synuclein protein	[40]
Triplication SNCA	Familial	DA neurons	Elevated $\alpha$ -synuclein protein expression Increased expression of oxidative stress-related genes Increased susceptibility to oxidative stress	[53]
SNCA (A53T)/triplication SNCA	Familial	Forebrain cortical neurons	Nitrosative stress Accumulation of ERAD substrates ER stress	[58]
Triplication SNCA	Familial	Neural precursor cells	High vulnerability to stress Increased ROS production	[59]
Triplication SNCA LRRK2 (G2019S)	Familial Familial	Neural precursor cells/DA neurons	Impaired neuronal differentiation and maturation pSer129- $\alpha$ Syn accumulation Increased susceptibility to oxidative stress	[56]
SNCA (A53T)	Familial	DA, GABAergic, and glutamatergic neurons	Protein aggregation (thioflavin S and pSer129- $\alpha$ Syn) Axonal neuropathology Altered expression of synaptic transcripts	[57]
LRRK2 (G2019S)	Familial	DA neurons	Reduced neurite outgrowth Dysregulated autophagy system Increased cell death in response to neurotoxins Elevated $\alpha$ synuclein protein level Dysregulation of genes related to DA neurodegeneration	[61]
LRRK2 (G2019S)	Familial	Neural stem cells	Increased sensitivity to stress Progressive impairment in nuclear envelope organization Defective self-renewal and neuronal differentiation	[62]
PINK1 (Q456X)	Familial	DA and nonDA neurons, and immature cells	Increased vulnerability to stress Dysfunction of mitochondria	[63]
LRRK2 (G2019S)	Familial			[63]
PINK1 (Q456X or R275W)	Familial	DA neurons	Increased neuronal death	[72]
PARK2 (V324A)	Familial		Degenerated dendrites Impaired AKT signaling	[72]
LRRK2 (G2019S) and Sporadic	Familial and Sporadic	DA neurons	Increased apoptosis Reduced neurite numbers and complexity Increased autophagic vacuoles	[81]
SCNA (A53T)	Familial	DA neurons	Elevated $\alpha$ synuclein aggregation and Lewy-body-like deposition Induced nitrosative and oxidative stress Increased vulnerability to mitochondrial toxin-induced cell death	[55]
SCNA (A53T)	Familial	DA neurons	Decreased $\alpha$ synuclein tetramers Increased neurotoxicity	[56]



<i>PARK2</i> (exon 2–4 deletion or exon 6, 7 deletion)	Familial	DA neurons	Increased oxidative stress, activated NRF2 pathway Abnormal mitochondrial morphology and turnover. Elevated $\alpha$ -synuclein accumulation	[70]
<i>PARK2</i> (exon 3, 5 deletion or exon 3 deletion)	Familial	DA neurons	Increased oxidative stress Reduced dopamine uptake Enhanced spontaneous dopamine release	[71]
<i>PINK1</i> (c.1366C>T; p.Q456X or c.509T>G; p.V170G)	Familial	DA neurons	Impaired recruitment of Parkin to mitochondria Increased mitochondrial copy number PGC1 $\alpha$ upregulation	[74]
<i>PARK2</i> (exon 3, 5 deletion or exon 3 deletion)	Familial	DA neurons	Reduced neurite complexity Diminished microtubule stability	[73]
<i>PARK2</i> (R42P, exon 3 deletion, exon 3, 4 deletion, 255A deletion, R275W or R42P)	Familial	DA neurons	Reduced capacity to differentiate into DA neurons Altered mitochondrial volume fraction	[75]
<i>LRRK2</i> (G2019S) and sporadic type	Familial/sporadic	DA neurons	Elevated oxidative stress response Increased sensitivity to stress-induced cell death	[64]
<i>LRRK2</i> (G2019S) and Sporadic PD	Familial/sporadic	DA neurons	Hypermethylation in gene regulatory regions Reduced expression of transcription factors related to disease	[65]
<i>GBA1</i> (RecNcil/+, L444P/+ or N370S/+) and sporadic type	Familial/sporadic	DA neurons	Reduced dopamine storage and uptake Elevated $\alpha$ -synuclein and glucosylceramide levels Defective autophagic and lysosomal machinery Increased basal and induced calcium levels Enhanced vulnerability to ER stress	[77]
<i>GBA</i> (N370S/+) and sporadic type	Familial/ sporadic	DA neurons	Elevated $\alpha$ -synuclein levels Reduced dopamine levels Induced MAOB expression Disrupted network activity	[78]
<i>GBA1</i> and sporadic	Familial/ sporadic	DA neurons	Decreased dopamine storage and uptake Elevated $\alpha$ -synuclein levels	[79]
SCNA SNP	Sporadic	Neurons	Disease-associated risk variant that regulates SCNA expression	[49]
SCNA (A53T)	Familial	DA neurons	Elevated nitrosative stress SNCA A53T or mitochondrial toxins induce S-nitrosylated (SNO)-MEF2C in DA neurons S-nitrosylation of MEF2C reduces PGC1 $\alpha$ expression and impairs mitochondrial function	[54]

ERAD: Endoplasmic-reticulum-associated degradation; MAOB: Monoamine oxidase B; NRF2: Nuclear factor erythroid 2-related factor 2; SNP: Single-nucleotide polymorphism; TH: Tyrosine hydroxylase.

OCT4, KLF4 and SOX2, and then differentiated them into DA neurons. By comparing with the healthy control group, they found that DA neurons differentiated from sporadic PD-patient-derived iPSCs after long-term culture displayed increased expression of cleaved caspase 3, shortened neurite length, and defective autophagosome clearance<sup>[61]</sup>. Fernández-Santiago *et al.*<sup>[65]</sup> reported genome-wide DNA methylation of DA neurons derived from *LRRK2*-mutant and sporadic PD patients to explore the relationship between DNA methylation and alteration of gene expression and enhancer elements. They found that alterations of epigenetic signature significantly affected DNA methylation in sporadic PD patients. This study provides evidence that it is a common phenomenon that aberrant protein turnover and altered morphology and methylation patterns occur in sporadic PD-patient-derived DA neurons. Piwi-interacting RNA (piRNA) seems to have relevance to aberrant protein

turnover and altered morphology and methylation patterns in sporadic PD-patient-derived DA neurons. piRNA is a complex of piwi protein and RNA, and is a large class of small noncoding RNA molecules expressed in animal cells that are involved in the epigenetic and post-transcriptional silencing of transposons. Schulze *et al*<sup>[82]</sup> have shown that the specific alteration of sin- and line-derived piRNA in DA neurons could be a new mechanism for the causation of PD<sup>[82-84]</sup>.

### ***iPSCs-derived astrocytes in PD modeling***

Astrocytes are the major group of cells in the central nervous system, with a range of functions that provide both structural and metabolic support for neurons. Accumulating evidence suggests that astrocyte dysfunction leads to the pathogenesis of PD, especially familial PD<sup>[85-88]</sup>. As summarized by Booth *et al*<sup>[85]</sup>, mutations in *DJ-1*, *SNCA*, *PLA2G6*, *LRRK2* and *GBA* lead to abnormal glutamate uptake, mitochondrial dysfunction, inflammatory response, water transport defect, and autophagy impairment. Gunhanlar *et al*<sup>[86]</sup> found that in a coculture system of astrocytes and neurons at a consistent ratio (60:40), neuron maturation was distinctly upregulated according to electrophysiological maturity. Accordingly, astrocytes are widely used in implementing cellular modeling approaches to the study of neurodegenerative disorders<sup>[87]</sup>. Similarly, astrocytes could help DA neurons defend against the neurotoxins and attenuate the mitochondrial dysfunction, as observed by Feng *et al*<sup>[88]</sup>. Remarkably, the astrocytes and neuron co-culture system improved the outgrowth of neuron markers, and stabilized the mitochondrial function through downregulation of ROS and increased mitochondrial function<sup>[88]</sup>. On the contrary, astrocytes were also used in inducing PD degeneration phenotypes by Santos *et al*<sup>[89]</sup> and di Domenico *et al*<sup>[90]</sup>. In Santos *et al*'s research, astrocytes were activated and became inflammatory, and were co-cultured with DA neurons<sup>[89]</sup>, while Domenico *et al*<sup>[90]</sup> co-cultured PD-patient-derived astrocytes with normal DA neurons. Normal DA neurons were induced to display apoptosis and multiple system dysfunction after co-culture with dysfunctional astrocytes<sup>[89,90]</sup>. These compelling findings emphasized that astrocytes may substantially participate in PD pathogenesis (Table 2).

## **GENOME-EDITING-BASED iPSCs and ISOGENIC CONTROLS**

Since Yamanaka opened the door for the generation of iPSCs<sup>[45]</sup>, iPSCs differentiation into DA neurons is commonly used for studying PD pathophysiology. Appropriate healthy iPSC-derived cells with higher quality and availability are often used as controls to study the phenotypes of a patient's iPSC-derived cells. However, differences in genetic background are of concern: healthy siblings used as controls share only about 50% of the genome of patients<sup>[91]</sup>. The differences in genetic background lead to higher variations in phenotypic presentation. This critical issue should only be interpreted *via* comparison with isogenic control cells<sup>[92]</sup>. A locus mutation or target gene correction is introduced by editing a specific site in the human genome of iPSCs, which has become a routine procedure in many studies of PD iPSCs. Many genome-editing tools, including zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and CRISPR/Cas9 system are commonly used in editing iPSCs<sup>[93]</sup>. Among them, CRISPR/Cas9 may be the best one in gene editing because of the prospect of flexibility in site selection and affordability, although there are still some concerns about the efficacy and off-target risk<sup>[92]</sup>. The bottleneck in investigating connections between gene function and disease mechanisms is likely to be overcome by these genome-editing technologies.

Many iPSC PD cell lines have been established with genome editing (Table 3). Soldner *et al*<sup>[52]</sup> performed genetic correction in A53T (G209A)  $\alpha$ -synuclein mutation in PD patient-derived iPSCs via ZFN-based gene editing. The G2019S mutation in *LRRK2* is the most common cause of familial PD. Reinhardt *et al*<sup>[94]</sup> performed genetic correction of an *LRRK2* mutation in PD-patient iPSCs *via* ZFN-based gene editing and Cre/LoxP systems, and linked parkinsonian neurodegeneration to extracellular signal-regulated kinase (ERK)-dependent changes in gene expression. They further demonstrated that ERK inhibitor reduces multiple PD-associated phenotypes, including lower neurite outgrowth, autophagy defects, synaptic defects, increased apoptosis, accumulation of tau and  $\alpha$ -synuclein in *LRRK2* G2019S mature DA neurons. Sanders *et al* reported that *LRRK2* G2019S iPSC-derived DA neurons displayed greater levels of mitochondrial DNA damage, whereas this abnormal mitochondrial damage was no longer detected in corrected iPSC-derived neurons by ZFN-mediated genomic correction<sup>[95]</sup>. The mutations and genomic multiplications of the *SNCA* gene ( $\alpha$ -synuclein) account for up to 15% of cases of familial PD<sup>[41,96,97]</sup>.

**Table 2** Induced pluripotent stem cell-derived astrocytes in Parkinson's disease modeling

Cell lines	Differentiated types	Phenotype demonstrated	Ref.
Bone marrow 2-3(BM2-3) hiPSCs	Astrocytes/DA neurons coculture system	Elevated DA neuron identities Stabilization of mitochondrial function Downregulation of mitoROS Increased mitochondrial length (normalized to non-co-culture DA neurons)	[88]
iPSCs and ESCs	Astrocytes/DA neurons coculture system	Non-activated astrocytes co-culture system improved DA neurons survival Non-activated astrocytes co-culture system increased DA neurons neurite lengths (normalized to inflammatory-activated astrocytes coculture system)	[89]
LRRK2 mutant and normal iPSCs	PD Astrocytes/normal DA neurons coculture system	Non-cell-autonomous damage is triggered by impaired autophagy in PD astrocytes Dysfunctional PD astrocytes accumulate and transfer $\alpha$ -synuclein to healthy DA neurons CMA activator drug prevents $\alpha$ -synuclein accumulation and neurodegeneration (normalized to the single culture system)	[90]

iPSCs: Induced pluripotent stem cells; ESCs: Embryonic stem cells; hiPSCs: Human induced pluripotent stem cells; PD: Parkinson's disease; DA: Dopaminergic.

Soldner *et al*<sup>[52]</sup> used CRISPR/Cas9-mediated insertion and exchange of risk-associated enhancer sequences. They identified a common PD-associated risk variant in a noncoding distal enhancer element that regulates expression of *SNCA*. Arias-Fuenzalida *et al*<sup>[98]</sup> induced heterozygous missense A30P and A53T mutations in the *SNCA* gene in healthy iPSCs *via* combined use of CRISPR/Cas9 and fluorescence-activated cell sorting analysis. These edited *SNCA* mutant iPSC-derived neuroepithelial stem cells displayed a significant decrease in maximal respiration, proton leak, basal respiration, ATP production, and nonmitochondrial respiration for the extracellular energy flux. Qing *et al*<sup>[48]</sup> used CRISPR/Cas9 and piggyBac system to establish heterozygous *LRRK2* G2019S mutation in healthy iPSCs. They observed that the number of tyrosine-hydroxylase-positive neurons and their neurite complexity were significantly decreased in *LRRK2* G2019S DA neurons.

## CHALLENGES IN USING iPSCs TO MODEL PD

### *Efficient generation of DA neurons from human iPSCs*

DA neurons modulate several brain functions such as motor control, reward behavior, and cognition<sup>[99]</sup>. Recapitulation of the *in vivo* developmental profile of a specific cell type provides a powerful strategy for manipulating cell-fate choice during the process of human iPSC differentiation. *In vitro* generation of functional DA neurons is critical in pluripotent cell biology for both experimental and clinical applications. The neural stem/progenitor cell (NSPC) strategy and the floor-plate cell strategy are two useful protocols for generating DA neurons. The NSPC strategy is widely used in neuronal differentiation, in which NSPCs are isolated from rosettes<sup>[100,101]</sup> or induced by defined medium with many supplements<sup>[102]</sup>. The floor-plate strategy was proposed by Hynes *et al* and is based on the fact that the floor plate is a critical signaling center during neural development located along the ventral midline of the embryo<sup>[103]</sup>. Lorens *et al*<sup>[100]</sup> derived the floor-plate cells from human embryonic stem cells (hESCs) using a modified protocol by dual Smad inhibition. The floor-plate cells are predisposed to differentiate into mature ventral midbrain DA neurons with a higher efficiency than rosette-based neurons<sup>[101]</sup>. The floor-plate-derived midbrain DA neurons are able to control dopamine release and selective dopamine reuptake, as well as other features such as synaptic transmission. Importantly, PD patient iPSC-derived DA neurons show cellular PD phenotypes such as increased accumulation of mitochondrial ROS and cytoplasmic  $\alpha$ -synuclein, mitochondrial DNA damage, shortened neurites, and impaired autophagy<sup>[80,104,105]</sup>.

### *Disease phenotypes in modeling late-onset PD*

**Table 3** Pluripotent stem cell-based genome-editing Parkinson's disease models

Gene mutation	Editing system	Cell line	Phenotype demonstrated	Application	Ref.
SNCA A30P	CRISPR/CAS 9	hiPSC	Not demonstrated	Locus mutation	[48]
LRRK2 G2019S	ZFN	hiPSC	Not demonstrated	Gene correction	[95]
LRRK2 G2019S	CRISPR/CAS 9	hiPSC	Synaptic defect, fraction of TH+/S129P- $\alpha$ S+ neurons was significantly reduced	Locus mutation	[48]
SNCA E46K	ZFN	hESC	Not demonstrated	Locus mutation	[53]
SNCA A53T	ZFN	hiPSC	Not demonstrated	Gene correction	[52]
SNCA A30P/A53T	CRISPR/CAS 9	hiPSC	Not demonstrated	Locus mutation	[98]
SNCA (rs356165 A/G)	CRISPR/CAS 9	hiPSC	Not demonstrated	Locus mutation	[49]
LRRK2 G2019S	ZFN	hiPSC	Basic phenotypes: autophagy defects, synaptic defects, increased apoptosis, accumulation of $\tau$ and $\alpha$ -synuclein. Phenotypes were alleviated after genetic correction	Gene correction	[94]

hiPSC: Human induced pluripotent stem cell.

Aging is a crucial risk factor for all late-onset neurodegenerative diseases. One important challenge found in iPSC-based PD models is to appropriately reproduce the late-onset characteristics. Reprogramming somatic cells to iPSCs resets their identity back to an embryonic state. The ability of iPSCs to undergo unlimited division while maintaining genomic integrity provides a way to overcome the senescence barrier. Even if these iPSCs differentiate into mature DA neurons, it still needs a lot of time to culture for mimicking aging DA neurons, presenting a significant hurdle for modeling PD. Thus, how to induce aging in iPSC-derived DA neurons is an important issue. Justine *et al*<sup>[72]</sup> compared young and aged human fibroblasts; they found a predominant difference in progerin level between adolescent and aged cells. They further demonstrated that overexpression of progerin in PD iPSC-derived DA neurons *in vitro* or *in vivo* promoted cell aging for modeling late-onset PD features such as pronounced dendrite degeneration, progressive loss of tyrosine hydroxylase expression, and enlarged mitochondria or Lewy body inclusions<sup>[72]</sup>. Thus, progerin expression could accelerate aging in iPSC-derived DA neurons for inducing PD pathogenic phenotypes, and introducing progerin expression could be a useful strategy to manifest disease phenotypes in iPSC-based late-onset PD models. However, it should be noted that neurons are fragile for undertaking the delivery of exogenous genes. The low efficiency of transfection in neurons remains a big challenge for widespread and convenient application of progerin expression to model iPSC-based late-onset neurodegenerative diseases.

Previous studies have indicated that chronic treatment with anticancer drug hydroxyurea (HU) could induce cellular senescence in human fibroblasts<sup>[106]</sup> and mouse neural stem cells<sup>[107]</sup> via induction of genes related to DNA damage and repair, mitochondrial dysfunction, and ROS increase. In our recent study<sup>[108]</sup>, we found that HU induced disease phenotypes of sporadic PD-patient-specific iPSC-derived DA neurons. HU treatment significantly reduced neurite outgrowth, expression of p-Akt and its downstream targets (p-4EBP1 and p-ULK1), as well as increased the level of cleaved caspase 3 in iPSC-derived DA neurons from sporadic PD patients. Transcriptome analysis and Western blotting indicate that HU alters the expression of genes and proteins related to the ER stress pathway in healthy iPSC-derived DA neurons. It reveals that ER stress might contribute to HU-induced aging in iPSC-derived DA neurons from sporadic PD patients. Our study also found that the midbrain characteristics decline after iPSC-derived DA neurons are treated with HU, which is similar to the characterization of PD. Thus, increasing chemically induced ER stress could be an alternative approach to accelerating aging of iPSC-derived DA neurons from PD patients for manifestation of PD cellular phenotypes.

## POTENTIAL APPLICATION OF iPSCs IN PD

***iPSCs-based mechanistic studies for exploring clinical therapeutic strategies***

Due to the ability of human iPSCs to differentiate into human DA neurons and astrocytes, human iPSCs are a promising model for studying the pathogenesis of PD. Compared with neurotoxin-induced injuries, human iPSC-derived DA neurons from sporadic or familial PD patients could give help us to understand the progressive changes of PD neuronal phenotypes as culture time increases<sup>[50,109]</sup>. Through this PD iPSCs model, we can verify the possible mechanisms of pathogenesis suggested in previous studies in other cell or animal models. Most importantly, studying these PD-iPSC-derived DA neurons could explain how the clinical degenerative features of human DA neurons occur<sup>[110,111]</sup>. At least the changes in some human familial- PD-iPSC-derived neurons can represent the middle or final stage of PD because this iPSC-derived DA neuronal death occurs with  $\alpha$ -synuclein accumulation, which is consistent with the observation in PD patients. Compared with familial PD, the etiology of sporadic PD is still a major challenge because of the multifactorial etiopathogenesis of sporadic PD. Since sporadic PD is complicated, the changes in neuronal phenotype cannot reflect the pathogenic alteration in the whole brain or other systems of sporadic PD patients<sup>[112,113]</sup>.

***iPSCs as a powerful and convincing drug discovery tool in PD***

Current PD therapies help patients relieve motor symptoms, but do not effectively prevent, slow or halt the progression of PD, particularly in the loss of DA neurons<sup>[114]</sup>. Neurotoxin-based neurons or animal models are commonly used for anti-PD drug screening. Many drugs based on these artificial models have been developed but do not significantly prevent PD progression<sup>[115]</sup>. One reasonable explanation is that these neurotoxins that usually cause strong injuries in DA neurons cannot mimic the progressive death of human DA neurons in PD. In addition, DA neurons from animals are distinct from human DA neurons. In PD-iPSC-derived DA neurons, the typical PD features such as accumulation of  $\alpha$ -synuclein, progressive degeneration, and death could be observed. These robust and reproducible PD phenotypes are amenable to screening potential compounds. Thus, PD-iPSC-derived DA neurons are more suitable for screening anti-PD drugs than artificial models are.

***iPSC-based research enhanced development of cell therapy***

The inspiring success in PD treatment was achieved through allograft of human fetal midbrain cell suspensions in 1980<sup>[116]</sup>. In addition, in MPTP-treated monkey brains, monkey ESC-derived neural progenitor cells differentiated into DA neurons and cells integrated well in the striatum, thereby PD-related motor symptoms improved<sup>[117]</sup>. Compared with ESCs, iPSCs have more potential in cell replacement therapies for PD because they can be generated from patients' own cells and differentiate into DA neural progenitor cells that specifically develop into DA neurons<sup>[118]</sup>. iPSCs have the advantage of eliminating immune rejection concerns as they are obtained from the host. The generation of iPSCs from a patient's own somatic cells would potentially allow for a plentiful source of cells for autotransplantation. In addition, using iPSCs rather than ESCs means that this treatment would be potentially available in some countries that ban the application of ESCs, including Italy, Ireland, and most African and South American countries<sup>[119,120]</sup>. For familial PD patients, the corrected iPSCs are also a reasonable source for the transplantation of normal DA neurons to reduce motor symptoms. Recently, scientists from Japan have started a clinical trial<sup>[121]</sup> (ClinicalTrials.gov NCT02452723) to treat PD with human iPSCs. All these suggest that the transplant of human iPSCs-derived DA neurons will be a promising therapeutic strategy and customized treatment is practical due to individual differences.

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**CONCLUSION**

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In this review, we have summarized iPSC-based PD models from patient-specific as well as genome-editing-based iPSCs. Patient-specific iPSCs that harbor the disease-associated genotype have provided extensive insights into pathogenic mechanisms of PD. However, given inherent genetic heterogeneity between individuals, it is understandable that disease phenotypes could be confounded by use of patient-specific iPSCs with different genetic backgrounds. The use of gene-targeting strategies based on ZFNs, TALENs or CRISPR/Cas9 to induce or correct a particular genetic mutation, has become indispensable in developing isogenic lines with and without a disease genotype. However, although great advances have been made in gene editing, high off-target risk and low efficacy still make it difficult and time-consuming in generating genome-editing-based iPSCs. Thus, improving the efficiency and precision



of gene editing is important for generating more isogenic PD-specific iPSCs and control cell lines. How to reliably establish iPSC-based models for late-onset PD remains to be resolved. Inducing an aged state by long-term culture, overexpression of an aging protein, or small molecules is encouraged in most iPSC-based age-related PD models. Finally, iPSCs cannot mimic motor symptoms and some nonmotor symptoms such as depression, agrypnia, hyposmia and impairment of cognition. Thus, how to bridge the gap between animal and cell studies should be addressed in the future.

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