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·Minireview·

Induced pluripotent stem cells and neurodegenerative diseases

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Abstract: Neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease and Amyotrophic Lateral Sclerosis, are characterized by idiopathic neuron loss in different regions of the central nervous system, which contributes to the relevant dysfunctions in the patients. The application of cell replacement therapy using human embryonic stem (hES) cells, though having attracted much attention, has been hampered by the intrinsic ethical problems. It has been demonstrated that adult somatic cells can be reprogrammed into the embryonic state, called induced pluripotent stem (iPS) cells. It is soon realized that iPS cells may be an alternative source for cell replacement therapy, because it raises no ethical problems and using patient-specific iPS cells for autologous transplantation will not lead to immunological rejection. What's more, certain types of neurons derived from patient-specific iPS cells may display disease-relevant phenotypes. Thus, patient-specific iPS cells can provide a unique opportunity to directly investigate the pathological properties of relevant neural cells in individual patient, and to study the vulnerability of neural cells to pathogenic factors *in vitro*, which may help reveal the pathogenesis of many neurodegenerative diseases. In this review, the recent development in cellular treatment of neurodegenerative diseases using iPS cells was summarized, and the potential value of iPS cells in the modeling of neurodegenerative disease was discussed.

Keywords: neurodegenerative disease; induced pluripotent stem cell; stem cell; cell model

1 Introduction

Neurodegenerative diseases, including Parkinson's disease (PD), Alzheimer's disease (AD) and other relative uncommon ones such as Amyotrophic Lateral Sclerosis (ALS), Huntington's disease (HD), Dementia with Lewy Body (LDB), *etc.*, are symptomatically characterized by progressive cognitive, memory, and/or motor dysfunctions that result from age-dependent neuron loss in different regions of the central nervous system (CNS)[1]. Although the present knowledge on neurodegenerative diseases has been greatly expanded, the pathogenesis of most of these diseases remains largely unknown, and treatment of these diseases is still a great challenge. Currently, no disease-modifying therapy is available. Transplantation of stem cell-derived specific neurons to restore the function of affected neurons may serve as an alternative strategy. Among the stem cells, human embryonic stem (hES) cells first identified and cultured by Thomson *et al*. in 1998[2], have been considered to be the most promising source for cell replacement therapy due to their property of unlimited self-renewal and their potential to differentiate into almost all types of somatic cells[3]. The previous preclinical studies have demonstrated functional recovery after trans-

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plantation of progenies of hES cells in animal models of many neurological diseases including PD[4-6], spinal cord injury[7,8], stroke[9,10] and HD[11], indicating the potential therapeutic value of hES cells in treating neurodegenerative diseases. However, the clinical application of hES cells has been hampered due to several problems. One problem involves the ethical debate on obtaining hES cells from human embryo. In many countries, legislations have been settled to prohibit research on hES cells. Another significant problem is associated with immunological rejection after transplantation of specific cells derived from allogeneic hES cells. Although somatic cell nuclear transfer (SCNT) will help obtain stem cells genetically matching the donor organism, which ensures much less immunological incompatibility, SCNT of human somatic cells is difficult to be achieved and also faces the ethical risk of using this technique for human cloning[3,12]. As a result, efforts have been made to find alternative sources of stem cells without these disadvantages. In 2006, Yamanaka *et al*.[13] reported the generation of ES-like pluripotent stem cells from somatic fibroblast cells, which are so-called induced pluripotent stem (iPS) cells. The iPS cells can be generated from adult somatic cells, so the ethical problems are eluded. Besides, cells derived from patient-specific iPS cells have no risk of immunological rejection in cell transplantation. Furthermore, patient-specific iPS cells with disease phenotypes can facilitate exploring the pathogenesis of the disease as well as screening efficient drugs. In this review, the current development and prospects of using iPS cells in cell replacement therapy and disease modeling for neurodegenerative diseases were discussed.

2 Generation and biological properties of iPS cells

In 2006, Yamanaka *et al*.[13] selected 24 candidate factors that were hypothesized to play pivotal roles in maintaining ES cell identity, and introduced these factors, either separately or in different combinations, into mouse fibroblasts by retroviral transduction. Later, the reprogrammed cells were kept under ES culture conditions. The expression of *Fbx15* was used for detecting pluripotency of the generated cells. They demonstrate that transduction of 4 selected transcriptional factors *Oct4*, *Sox2*, *Klf4* and *C-myc* in combination, can lead to the generation of colonies expressing *Fbx15*. Further examination shows that cells from these colonies are similar to ES cells in morphology, surface markers, gene expression, proliferation property, as well as teratoma formation. More recently, the same research group have reported that human iPS cells can be induced from adult dermal fibroblasts by the same 4 factors, suggesting that the reprogramming protocol is also applicable for human cells[14]. To date, the generation of iPS cells from different somatic cells with the 4 original factors has been demonstrated by several research groups[15-18], and the iPS cells can be successfully differentiated into cell types of three germ layers including neurons[15,16], smooth muscle cells[17], cardiomyocytes[18], osteoblasts[19], hematopoietic cells[20], *etc.* When injected into blastocysts, mouse iPS cells can produce adult chimeras that are competent for germline transmission[21]. Recently, researchers have achieved the creation of viable mice with iPS cells using tetralpoid complementation test[22,23], which is considered to be the most strict test for pluripotency, indicating the full pluripotency of iPS cells. The mechanism underlying this pluripotency induction remains elusive. Previous studies showed that *Oct3/4* and *Sox2* play critical roles in determining pluripotency, and this effect is absent in differentiated cells, which may be attributed to epigenetic modification in the targeted genes[3,13,24]. Interestingly, 2 research groups have demonstrated that human iPS cells can be generated by introducing an alternative combination of factors including *Oct3/4*, *Sox2*, *Nanog* and *Lin28*[25,26], suggesting that *C-myc* and *Klf4* may be not essential for reprogramming.

3 The role of iPS cells in treating neurodegenerative diseases

Among various neurodegenerative diseases, PD may be the most suitable for cell replacement therapy due to its pathological characteristic, the highly selective dopaminergic neuron loss in the substantial nigra of mid-brain during the entire course of disease, which leads to the apparent

motor symptoms of resting tremor, rigidity, bradykinesia and gait abnormality[27]. Grafting allogenic tissues or cells to restore the dopaminergic function in PD patients has long been attractive. Early studies have demonstrated that implantation of fetal mesencephalic tissue into putamen of PD patients can induce functional improvement in most patients 2 months after operation, and the effects maintain for up to 4–6 years without *L*-dopa medication in following study[28-30]. Positron-emission tomography shows a significant increase in ^{18}F-fluorodopa uptake in relevant brain regions of the transplant recipients, which further confirms the therapeutic effects of transplantation[28]. Recent studies have also found that grafted stem cells from different sources will survive and differentiate into dopaminergic neurons in rodent models of PD and lead to functional improvement within weeks post operation[5,31]. All these studies have provided evidence supporting the cell replacement strategy for PD treatment. Nevertheless, neither fetal mesencephalic tissue nor stem cells are good candidates for transplantation due to their inherent shortcomings such as ethical concerns, limited sources, and immunological rejection.

As described earlier, iPS cells may serve as an alternative source for replacement therapies. After the publication of iPS cell induction by Yamanaka S[13], several studies on the application of iPS cells in PD treatment were reported. In the study of Wering *et al*. in 2008[15], mouse fibroblasts were induced into the pluripotent state, and the iPS cells were demonstrated to be capable of differentiating into neural precursor cells, which later differentiate into neurons, astrocytes and oligodendrocytes. Also, the iPS cells can differentiate into the subtypes of dopaminergic neurons, as assessed by identifying typical markers expressed in dopamine neurons in the midbrain. When the dopamine neurons are transplanted into the striatum of 6-hydroxy dopamine (6-OHDA) lesioned PD rats by surgery, 4 rats out of 5 show marked functional recovery 4 weeks after transplantation[15]. Further histological analysis reveals that a large number of tyrosine hydroxylase (TH)-positive neurons survive in the striatum of the grafted rats, and TH-immunoreactive fibers are found to extend to the host striatum, indicating that the neurons derived from grafted iPS cells are functionally integrated in the host brain[15]. However, a high incidence of tumor formation is observed in the transplanted animals, which may be attributed to the contamination of undifferentiated cells in the graft. To solve this problem, fluorescent-activated cell sorting (FACS) is used to wipe off the undifferentiated cells. Since the stage-specific embryonic antigen-1 (SSEA-1) is thought to be typically expressed in mouse ES cells, FACS was conducted to deplete cell suspension from the SSEA-1-positive cells before transplantation. The results show that 4 animals receiving grafts depleted of SSEA-1-positive cells achieve similar functional improvement as those grafted with nonpurified cell preparations, and no signs of tumor formation is observed for up to 8 weeks[15]. This demonstrates that the iPS cell-derived neurons may have similar therapeutic effect as those derived from other sources of stem cells. Based on this success, the subsequent studies are focused on the therapeutic effects of cells derived from human iPS cells, especially patient-specific iPS cells, which can be used in autologous transplantation.

By using a modified human ES cell differentiation protocol, Cai *et al*.[32] have reported the induction of dopaminergic neurons from a commercially available human iPS cell line. When human iPS cell-derived dopaminergic progenitor cells are transplanted into 6-OHDA-lesioned PD rats, they appear to survive for a long time and develop into real dopaminergic neurons. Meanwhile, Swistowski A *et al*.[33] have also demonstrated that dopaminergic neurons derived from human iPS cells can survive and attenuate behavioural deficits in the same PD models. Nevertheless, these reprogrammed cells in the above-mentioned studies are from healthy people rather than from PD patients. In 2009, Soldner F *et al*.[34] reprogrammed the fibroblasts from 5 idiopathic PD patients, which subsequently differentiated into dopaminergic neurons with approximately the same efficiency as did non-PD iPS cells. However, the biological properties of dopamine neurons derived from PD-specific iPS cells were not further studied in this study. At the same time, it is critical to ensure that neurons derived from patient-specific iPS cells do not possess relevant

disease-phenotypes or vulnerability, which guarantees that the grafted cells will survive long enough and function to restore dopaminergic transmission in the host brain after autologous transplantation. In this regard, Hargus *et al*.[35] differentiated iPS cells from PD patients into dopaminergic (DA) neurons. These DA neurons are demonstrated to survive at a large amount after being transplanted into adult rodent striatum and induce a progressive reduction in motor asymmetry in 6-OHDA–lesioned rats, which serve as an animal model of PD, for up to 16 weeks after transplantation. This indicates that DA neuron derived from PD-specific iPS cells can survive and function without signs of disease in the host brain, at least for a short period of time. Since it is reported that in PD patients receiving fetal mesencephalic dopaminergic neurons transplantation, PD pathology such as Lewy bodies spreads from host brain to grafted tissue 9–13 years after transplantation[36,37], whether the neurons derived from patient-specific iPS cells will undergo degeneration within a short period of time after transplantation needs to be fully reviewed and explored. Life expectancy of PD patients is estimated to be longer than a few years since the day of disease onset, thus the therapeutic effects of cell transplantation must last for a considerable length of time. Further studies are required to determine the long-term survival and functioning of grafted dopamine neurons derived from patient-specific iPS cells.

AD is another common neurodegenerative disease that is estimated to affect over 5 million people in the United States and 17 million worldwide[38]. In early stage, AD patients undergo a significant cholinergic neuron loss in the nucleus basalis of Meynert (NBM), which contributes to the cognitive deficits[39]. Transplanting cholinergic neurons into the affected brain region may be a promising strategy for the treatment of early AD. However, in later stage, neuron loss will inevitably spread to other regions of cortex, and the effects of cellular therapy may be attenuated, which limits the application of cell replacement therapy for AD. Similarly, ALS pathogenesis involves progressive loss of both upper and lower motor neurons and results in lethal diaphragmatic failure within years after disease onset[40]. The application of motor neuron replacement in treating ALS is limited[41], because for this therapy, formation of target muscle innervation needs months to years (in humans), which is longer than the length of the natural course of ALS in most patients. In this regard, iPS cells are an alternative source for AD and ALS therapies. In previous studies[42,43], neural precursors such as neural stem cells (NSCs) rather than differentiated neurons were transplanted into the hippocampus of rodent AD models. The transplanted NSCs are found to survive and migrate to other regions in the host brain, and differentiate into relevant neurons, resulting in functional recovery in animals. Meanwhile, it is suggested that the migration and differentiation of grafted NSCs can be significantly influenced by the microenvironment in the brain. Kwak YD *et al*.[44] have found that over-expression of amyloid precursor protein (APP) will facilitate the differentiation of grafted human NSCs into astrocytes rather than into neurons *in vivo*, indicating that the pathogenic process of AD may have a negative impact on the therapeutic effect of NSC transplantation. On the contrary, neural growth factors (NGFs) are thought to promote survival and differentiation of NSCs. In the report of Wu S *et al*.[43], NSCs stably transduced with *hNGF* gene are shown to survive, integrating into the host brain, and enhance cognitive performance after being grafted into the cerebral cortex of AD rats, which are not observed in NSCs with no genetic modification. In addition, it is reported that NSC transplantation improves the cognitive function in AD models via altering the level of brain-derived neurotrophic factor (BDNF) in the brain[45]. These data suggest that the microenvironmental factors may play pivotal roles in determining the therapeutic effects of grafted cells. Based on these results, future studies should focus on the survival and differentiating capacity of patient-specific iPS cell-derived NSCs in AD or ALS models, and on the employment of the iPS cell-derived NSC recombinant with neurotrophic factors such as NGF, BDNF and glial-derived neurotrophic factor (GDNF), to enhance their therapeutic effects on cognitive/motor functions.

Despite the great value of iPS cells in cellular treatment of neurodegenerative diseases, some potential safety

risks should be fully considered before its clinical application. The high frequency of tumor formation after cell transplantation may be the most important one[3,39,46]. Since most iPS cells are reprogrammed by retrovirus transduction, during which exogenous genes integrate into the host genome, the host oncogenes such as *C-myc* and *Klf4* may be reactivated. In addition, the random transgene integration may possibly result in mutations of the host gene. Both mutation in the host gene and reactivation of oncogenes will significantly increase the risk of tumor formation after transplantation. Although some strategies not involving gene integration can be used for induction of pluripotency, most of these methods are demonstrated to have a low efficiency. Further investigations are needed to develop new effective reprogramming strategies with a promising safety.

4 iPS cells for disease modeling

One problem that hampers the study on neurodegenerative diseases is the lack of disease model. It is considered that most neurodegenerative diseases are caused by both genetic and environmental factors[39,40,47]. For an affected individual, more than one dozen gene sites may be involved in disease onset, concerning the genetic factor alone. The well-established transgenic models with identified gene mutations are able to model the pathogenesis of only 5%–10% neurodegenerative patients who have an obvious family history, while the pathogenesis of the rest majority of sporadic patients cannot be explained, because it is impossible to replicate the entire genetic background of the patients *in vitro*, which may serve to increase the disease risk for sporadic patients. The generation of patient-specific iPS cells offers an opportunity to explore the biological properties of the affected neurons directly from the patients *in vitro*, and provides an alternative strategy for disease modeling. In 2008, Dimos JT *et al*.[16] reported the generation of iPS cells from the skin fibroblasts of an 82-year-old familial ALS patients. These patient-specific iPS cells are successfully directed to differentiate into motor neurons that display no disease phenotype. This result indicates that the onset of familial ALS may be triggered by some endogenous or exogenous factors during aging. In this regard, it would be interesting to expose the disease-relevant neurons from patient-specific iPS cells to estimate the pathogenic factors and find out the interactions between genetic and exogenous factors that are involved in the pathogenesis of neurodegenerative diseases. For instance, in the study of AD, by comparing the vulnerability of cholinergic neurons derived from patient-specific iPS cells with that of normal controls, to the pathogenic conditions such as Aβ toxicity, hypoxia, oxidative stress, or certain metal ions, the involvement of the genetic background in the pathogenesis of sporadic AD can be investigated, and the critical pathogenic factors contributing to neuronal apoptosis can be identified. The same strategy can be used in studying the etiology of PD and ALS. Furthermore, once the phenotype-specific cells are generated by the forgoing strategy, they can be effectively used for drug screening. Recently, Moretti A *et al*.[18] have generated patient-specific iPS cells from dermal fibroblasts of patients with familial long-QT syndrome type 1, and directly differentiated them into functional cardic myocytes with disease phenotype. Further examination demonstrated that the phenotype-specific cardiac myocytes have an increased susceptibility to catecholamine-induced tachyarrhythmia, and beta-blockade can attenuate this phenotype. The result suggests that it is possible to directly investigate the therapeutic effects of certain drugs on the patient-specific cells *in vitro*. The current absence of effective disease-modifying therapy for most neurodegenerative diseases may be attributed to the lack of promising disease models for drug development. The generation of patient-specific iPS cells would provide an alternative strategy for high-throughout drug screening and help discover novel medications.

5 Conclusion

The generation of iPS cells has so far attracted much attention. There are at least 3 remarkable advantages of iPS cell application in this field, compared with ES cell application. Firstly, fibroblasts can be obtained from various tissues in adult body, which ensures a steady source of iPS cells. Secondly, autologous transplantation using patient-

specific iPS cells will not lead to immunological rejection that may cause serious side-effects in heterogenous transplantation recipients. Thirdly, the generation of iPS cells does not raise any ethical concerns such as destruction of human embryos and human cloning. Undoubtedly, treatment of neurodegenerative diseases will particularly benefit from the cell replacement therapy using iPS cells, because functional neurons are hardly renewable after being injured. Future efforts should be made to develop alternative reprogramming strategies that raise less safety concerns, such as using non-virus transduction methods. Further investigations are also needed to determine the long-term survival of transplanted iPS cell-derived neurons in pathogenic microenvironment that models CNS environment of affected individuals. The other scientific and/or clinical value of iPS cells lies in disease modeling. Patient-specific iPS cells offer an opportunity to directly investigate the disease phenotype of specific types of neurons from individual patient *in vitro*. It is of particular importance to study the multi-factorial diseases that affect the majority of neurodegenerative patients, because the iPS cells inherit the entire genetic background as well as epigenetic features of the host individual, which may contribute to the vulnerability of neurons to environmental pathogenic factors. In sum, the development in the studies on human iPS cells provides a promising future for revealing the underlying mechanisms of neurodegenerative diseases and developing efficient treatment strategies.

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诱导多能干细胞与神经退行性疾病

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摘要：神经退行性疾病，包括帕金森病、阿尔茨海默病和肌萎缩侧索硬化症等的共同特征是在中枢神经系统的不同部位发生特发性神经元丢失。这些神经元的丢失给病人造成了一系列相应的功能障碍。应用人类胚胎干细胞进行细胞替代治疗曾引起人们很大的兴趣，但是一些伦理学问题阻碍了该研究的发展。通过导入特定的转录因子，体细胞能够被诱导为具有胚胎干细胞特性的细胞，即诱导多能干细胞(induced pluripotent stem cells, iPS cells)。获取人类iPS细胞并不涉及明显的伦理问题，并且运用病人特异性的iPS细胞能使自体移植成为可能。因此，iPS细胞有可能成为细胞替代治疗中可靠的细胞来源。此外，利用iPS细胞，人们还能在体外直接研究病变神经细胞的表型以及神经细胞在特定致病因子作用下的疾病易感性，有助于揭示神经退行性疾病的内在机制。本文综述了iPS细胞用于神经退行性疾病细胞治疗的最新进展，并探讨了其在建立疾病的细胞模型中的潜在价值。

关键词：神经退行性疾病；诱导多能干细胞；干细胞；细胞模型